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Newly Created Hybrid Nanomaterial for Treatment of Lung Carcinoma

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Abstract

Deficient passage of therapeutic cargo into tumor bed is a bottleneck in cancer nanomedicine. Interest has been manifested in use of chitosan-based nanoparticles with utilizing metal oxide hybrid nanocomposite in nanomedicine. We synthesis, characterize, and investigate a hybrid nanomaterial (CHNM) anti-cancer activity. A developed CHNM of magnesium oxide nanoparticles coupled with cisplatin and coated with chitosan biopolymer were characterized by FTIR, X-ray diffraction, TEM and SEM. Anti-cancer effects were evaluated in A549 cell line. CHNM nanoparticles showed a diameter of ~240 nm with a negatively charged surface (−25.4 ± 3.75 mV) and mean particle size of 24.2 ± 7.89 nm. CHNM showed a high encapsulation efficiency (78%), drug loading efficiency (80%) and maximum cisplatin release (2- 6 h). CHNM showed improved anti-cancer activity on A549 cells (IC50=50.8 µg/ml). In conclusion, magnesium oxide nanoparticles coupled with cisplatin and coated with chitosan biopolymer could be used as promising lung cancer treatment system.

Keywords: Lung cancer; Cisplatin; hybrid nanomaterial; Chemotherapy.

Lung cancer is spreading rapidly due to global contamination and unhealthy, reckless activities. It has the greatest fatality rate of all malignancies because of its rapid spread, early metastasis, low sensitivity, and poor specificity in early diagnosis [1, 2]. Cancer is considered a deadliest disease, each year there are huge number of people identified with cancer illness, nearly half of them die. Regarding this serious health condition, scientists are doing their best to design biocompatible carriers for anticancer drugs [3].

Because of their biocompatibility, biodegradability, intrinsically, and exclusive bioactive qualities, biopolymers have been known and used as optimistic nominees in biomedical and biotechnological applications such as diagnosis, bioactive therapy, controlled drug delivery, and others. [4].

Nanotechnology is superior for the fast emerging of new healing and investigative perceptions in all areas of medicine [5] where polymer nanocomposites provide vast chances in various applications, including tissue engineering, antimicrobials, and nanocarriers. These novel collections of polymeric nanocomposites have gained significant research interest due to their exceptional properties, which are gained through the addition of nanoparticles. These unique materials have noteworthy perspective in disease theranostic [6]. Biocompatible polymeric nanocomposites are the most ideal select for use as anticancer mediators due to their uncommon helpful properties, most particularly heightened drug obtainability for extending the drug effects in tumor tissues [7].

Anticancer medicines essentially attack cancer cells to achieve an absorption required to apply active cancer assassination; definitely, suboptimal treatment concentrations exhibit weak anti-cancer activity with distinct concerns about drug resistance [8, 9]. Intravenous intake certainly causes a considerable percentage of chemotherapeutics to be broadly spread in numerous organs, leading to considerably low drug absorptions at cancerous spots. This requires the administration of high amounts to achieve therapeutically operative medicine absorptions at the diseased positions. Such high quantities could cause severe antagonistic effects,

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particularly at the places of hastily dividing cells as hair, liver, skin and spleen [8].

Chitosan, a natural compound, is a positively charged polymer carrier. The cell linkage and potential uptake of chitosan are most favorable due to their attraction to negatively charged cell membranes [10, 11]. Moreover, chitosan has shown high biocompatibility [12] as well as high ability to increase cell membrane permeability in vitro [11] and in vivo [13]. Among the various biopolymers, chitosan along with nanoparticles has been utilized as a stabilizing agent due to its excellent biocompatibility, non-toxicity, high permeability towards water, susceptibility to chemical modifications and cost-effectiveness [11].

Cisplatin, also known as cis-diamminedichloroplatinum(II), is a square planar metallic (platinum) synchronising compound. Under normal circumstances, it is water soluble and stable to some extent. It's particularly fascinating because it's shown antitumor activity in a variety of cancers. Though most cancers have now established a better estimate and, as a result, have become less life-threatening [14], remarkable challenges remain with respect to their cure. Likewise, because of drug resistance and substantial side effects, combined treatments of cisplatin with other anticancer drugs or designed materials have been studied as innovative therapeutic approaches for several types of human cancers [15].

Regarding that, the current study intended to create a hybrid nanocomposite material (HNM) with anti-cancerous and biocompatible qualities in this regard. This hybrid nanocomposite material was created to overcome the drawbacks of utilizing anticancer medicines on their own. Cisplatin, the most commonly used chemotherapy medication, was grafted with magnesium oxide nanoparticles coated with chitosan and tested for anticancer efficacy on a lung cancer cell line.

1. Experimental

1.1. Chemicals

Highly pure chitosan (Cat. no. 9012-76-4) with MW 5 2.5 x 10^5Da and degree of deacetylation = 85% was purchased from Sigma Co. USA. Magnesium chloride, NaOH and all other reagents of high analytical grade were purchased from Al Gomhoria Co. Egypt. Cisplatin (cis-PtCl2 (NH3)2) (code: 5622539) with concentration 1mg/mL was obtained from Oncotec Pharma Produktion GmbH.

1.2. Hybrid Nanoparticles preparation

First of all, stock solutions of Chitosan; magnesium chloride and sodium hydroxide were prepared by dissolving appropriate amounts of each.

1.2.1. Preparation of Magnesium Oxide nanoparticles coated by Chitosan hybrid nanomaterial (HNM)

1% chitosan was obtained by dissolving 1gm chitosan in 1% acetic acid solution (1ml / 99ml H2O) with continuous stirring using magnetic stirrer until complete dissolution. 100 ml of 1 M magnesium chloride solutions and 100 ml of chitosan were mixed in a beaker by stirring for one hour, then 50 ml of sodium hydroxide solution (1M) were added drop by drop until a milky white suspension is obtained. The formed suspension is decanted by distilled water many times to get rid of excess sodium hydroxide after that the suspension completed to a volume of 100 ml with distilled water. The total solid content of the resulted HNM with magnesium oxide was evaluated to be 0.575 mg/ml.

1.2.2. Preparation of Cisplatin hybrid nanomaterial (CHNM)

To the HNM suspension prepared in the previous section (2.2.1), 20 ml of Cisplatin (1mg/ml) were added with continuous stirring for two hours. The CHNM milky white suspension then irradiated by gamma radiation at a dose of 20 kGy to successfully enhance the coating of cisplatin and magnesium oxide with chitosan chains. The highly suspended CHNM mixture then stored in a clean sealed bottle.

1.3. Characterizations of CHNM

The prepared CHNM before and after surface modifications were characterized for their particles size, and surface charge. The dynamic light scattering was performed using Nano series ZS instrument (Malvern, UK). The particles were suspended in PBS 7.4 and bath sonicated for 10 min prior to measurements.

Nearly 3 mg of dried chitosan, CHNM and HNM samples, were carefully combined with 150 mg of potassium bromide (KBr), to produce fixed and stable thick disks. The tested sample disks were further dried for 24 hrs. in an oven. Fourier-transform infrared spectroscopy (FTIR) was utilized to analyze the prepared samples for functional groups using Bruker 66 Spectrometer. Scanning electron microscopy (SEM) of CHNM and HNM solid powder samples was obtained with Carl Zeiss Sigma VP microscope (Japan). TEM, Philips CM 30 at an accelerating voltage of 200 eKV was used to evaluate the size and shape of the designed CHNM and HNM. The samples dispersion were deposited on an ultrathin carbon supported Cu grid, and dried in an oven for 24h to ensure removal of water and moisture. X-ray diffraction (XRD) data for HNM were collected using Rigaku 2550D/max VB/PC X-ray diffractometer supported with Cu Kα radiation (λ = 1.54056Å).

1.4. Encapsulation Efficiency and Loading capacity

Encapsulation efficiency is an expression of the amount of cisplatin incorporated into the HNM and is normally defined as the percentage of cisplatin

bound to HNM relative to the total amount of cisplatin used. Determination of this parameter generally requires analysis of the free and encapsulated cisplatin fractions on the HNM allowing calculation of encapsulation efficiency. The encapsulation efficiency of cisplatin and the loading capacity (LC) of the process was expressed as the percent of drug encapsulated and calculated using the following formula (1) and (2) indicated below:

$$\text{encapsolation \%} = \frac{\text{Total Cisplatin} - \text{Free Cisplatin}}{\text{Total Cisplatin}} \text{ x } 100$$

$$\text{Loading capacity \%} = \frac{\text{Total Cisplatin} - \text{Free Cisplatin}}{\text{HNM weight}} \text{ x } 100$$

1.5. In vitro Release Study

The *in vitro* release experiments were performed by suspending 200 mg of HNM loaded particles in 5 mL of release medium (PBS pH 7.4 or PBS pH 5.5). At predetermined time intervals 1 mL was taken out, and centrifuged (20,000 ×g for 5 min). The separated supernatant was monitored using UV-Vis spectroscopy. The volumes taken out at every time point were replaced with fresh buffer. The buffers used in this study were phosphonate buffers.

1.6. Cell culture study

The (A-549) human lung cancer cell line was purchased from the VACSERA's tissue culture unit in Giza, Egypt, and donated by the American Type Culture Collection (ATCC). Cell lines were grown in Dulbecco's Modified Eagle Medium (DMEM), which included 10% Fetal Bovine Serum (FBS), 0.2% sodium bicarbonate, and antibiotic/antimycotic solution (100x, 1 ml/100 ml medium). The cell line was kept at 37°C in a humidified environment with 5% CO_2. The vitality of the cells was assessed before starting the experiment. In this investigation, cells with a viability of more than 95% and passage numbers ranging from 20 to 22 were used.

1.7. In vitro study analysis

The cytotoxic impact of each of the tested treatments on A-549 cells was assessed using the MTT (3-[4,5-dimethylthiazol-2-yl]-2.5-diphenyl tetrazolium bromide) kit (Trevigen Inc., Gaithersburg, MD, USA) according to the manufacturer's instructions. Cells were seeded at a density of 10^3–10^5 cells per well in 96-well plates in the presence or absence of cisplatin (0.64 g/ml) or CHNM (5.75 g/ml) in an ultimate volume of 100 L of media and allowed to attach overnight. The MTT reagent (10 µl per well) is added, and the plate is incubated for 24 hours to allow the soluble yellow MTT to be reduced to the insoluble purple formazan dye. Before using a microplate reader to detect the absorbance of each sample at 550–600 nm, detergent reagent is added to each well to solubilize the formazan dye. The percentage of cell growth in each group (6 replicates) compared to untreated cancer cell line was used to calculate cell proliferation.

2. Results and discussion

Conventional chemotherapeutic agents grieve from poor cancer targeting and multidrug resistance of tumor cells that leads to weak antitumor efficiency in addition to cytotoxicity to normal tissues which causes failure of treatment. To overcome these existing complications in conservative drug treatment, nanodrug delivery system is being considered for accurate targeting delivery of drugs to cancer sites due to better internalization and reduced undesirable side effects by improved penetrability and retention effect (EPR) for passive targeting.

Nanoparticles have been used for chemotherapy delivery systems to enhance the effectiveness of conventional treatment agents counting, the absence of targeting ability, general poisonousness and short therapeutic index [16].

MgO NPs have been used as potential candidates in drug delivery [17]. MgO NPs may exhibit strong plasma distribution [18]. Enhanced chemical precipitation methods were employed to coat magnesium oxide nanoparticles with chitosan. Metal encapsulated nanoparticles were used by others in treatment of cancers [19, 20, 21]. Results showed that the copolymer chains successfully contained the hybrid nanomaterial, which may be utilized for medication distribution under mild circumstances.

3.1. Characterization of HNM and CHNM

3.1.1. DLS and Zeta potential of CHNM

Our CHNM were characterized by dynamic light scattering. DLS measures the hydrodynamic diameter, which is the diameter of the particle and surface associated ligands, ions, or molecules that travel along with the particle in colloidal solution, increasing the average particle size [22]. Surface charge was monitored by determining zeta potential of the CHNM in PBS (pH 7.4). The CHNM show a hydrodynamic diameter of 240 nm after encapsulation of cisplatin. The existence of negatively charged oxide on the surface of the magnesium oxide particle indicates a negative zeta potentiality, where oxygen is crucial to the formation of magnesium oxide that defines particle stability [23]. Our prepared CHNM shows zeta potential of −25.4 mV with 0.52 poly dispersity index (PDI) indicating the homogeneity and uniform dispersion of CHNM (Figure 1). PDI in the 0.2–0.6 range is appropriate because particle distribution is slightly polydisperse [24].

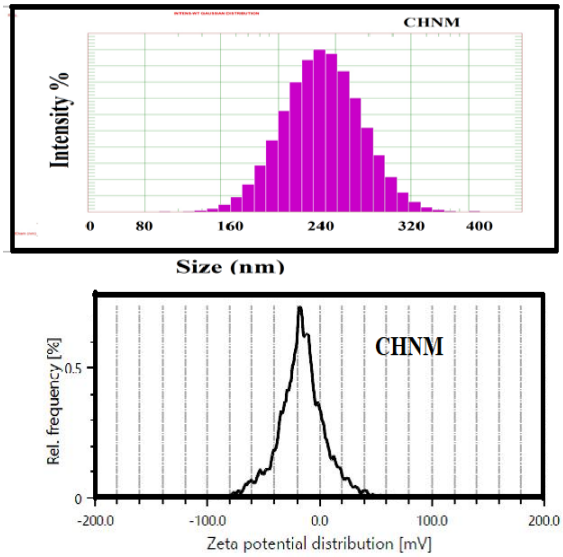

Fig. 1 Intensity mean values for CHNM (DLS) and zeta potential

3.1.2. *IR Spectrum of HNM and CHNM*

IR spectroscopy is a very important technique used to study the structural change due to physical or chemical interaction between materials. Figure 2 shows the IR spectra of the prepared HNM and CHNM. Examining the IR spectrum of the prepared HNM depicted the appearance of broad band with high intensity at 3321 cm^{-1} which attributed to the overlapping of the OH group resulted from chitosan and the adsorbed water molecules on magnesium oxide particles [25], also the bands at 2972 cm^{-1}, 1654 cm^{-1}, and at 1373 cm^{-1} due to the stretching vibration of OH, CH, NHCO, and CH_2 bending group respectively. The broad band at 599 cm^{-1} attributed to the Mg–O–Mg vibration [26].

The IR spectrum of the CHNM confirmed the presence of the bands due to grafted chitosan on magnesium oxide nanoparticles at 3701 cm^{-1}, 2966, 1436 cm^{-1}, 1053 cm^{-1} due to OH, CH, NHCO, and CH_2 bending group respectively which shifted to lower wave number due to high interaction of cisplatin and coated chitosan chains. The bands at the wave number range 885-528 cm-1 due to the Pt-O-Pt and Mg-O-Mg interactions**.** From FT-IR analysis of CIS solution, the main adsorption bands appeared are stretching vibrations of OH group at 3327.2 cm^{-1} due to water molecules and stretching vibration in the range 581.9 cm^{-1} to 603.6 due to Pt-O-Pt linkage [27, 28].

3.1.3. *X-Ray Diffraction Studies*

The XRD of the CHNM is shown in Figure 3. This figure displays the archetypal broad peak at 10-20^{O} due to the chitosan polymeric chains coated on the nanoparticles. The sharp peaks appeared at 2-Theta: at 22.8º, 27º, 38.0º, 46.41º, 47.9º and 56.6 º are owing to the platinum that contained in cisplatin chemical structure [29] while the sharp peaks at 2-Theta at 30,07º, 32.5º, 35.9º, 37º, 39.2º, 43.2º, 48.1º, 62.4º, 74º, 78º are corresponding o the magnesium oxide nanoparticles [30] present in the CHNM. Therefore, XRD results exposed that the cisplatin and magnesium nanoparticles are successfully encapsulated chitosan chains. Features of all constituents are given in the XRD spectra.

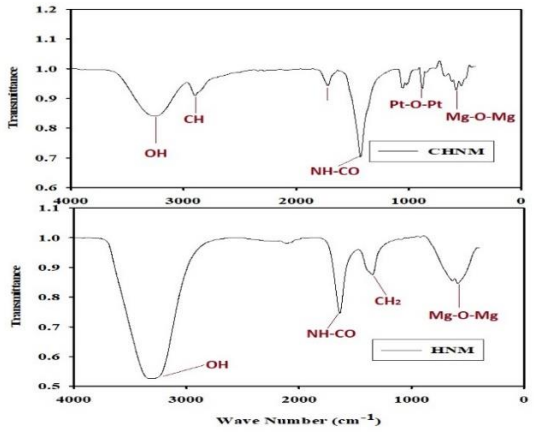

Fig. 2 IR spectra of the prepared HNM and CHNM

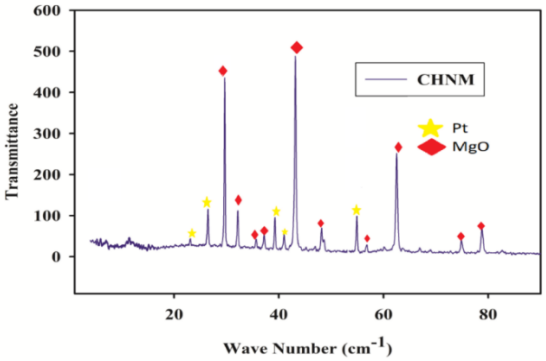

Fig. 3 XRD of the prepared CHNM

3.1.4. *Morphological study of HNM and CHNM*

Scanning Electron Microscopy (SEM) is a very helpful and important technique mainly used for morphological evaluation of the surface and cross-sectional area change that results from mixing more than one material. Transmission Electron Microscopy (TEM) is a highly specified technique for morphological evaluation of nanomaterial if present. Figure 4 represents the SEM and TEM images for the prepared HNM and CHNM.

It is clear from the SEM micrographs of the HNM and CHNM solid samples that the addition of cisplatin cause a great change in the morphology of the nanoparticles where in the SEM of HNM (Figure 4 a) the surface appeared very rough and a huge number of particles spread all over the surface related to the MgO nanoparticles. On the other hand, in the SEM

micrographs of the CHNM (Figure 4b) the surface became rougher with bulky structures due to the presence of Pt provided by Cisplatin molecules.

TEM images of the dispersions of HNM and CHNM shown in Figure (4 c & d respectively). TEM of HNM displayed that particles of magnesium oxide appeared spherical with particle size around 16.7 ± 10.02 nm. While, TEM of CHNM showed appearance of spherical particles with larger size due to addition of cisplatin where the average size was 24.2 ± 7.89 nm. Cancer cells invasion by nanoparticles is facilitated by their small size and invasive nature [31]. Also, a higher loading capacity was obtained upon using nanoparticles with high surface area [32].

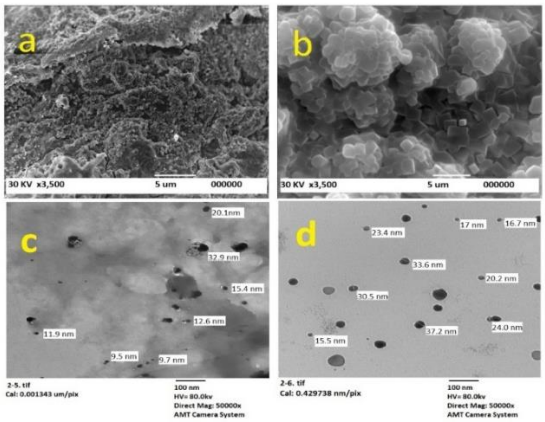

Fig. 4 Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) images for the prepared HNM and CHNM. (a): SEM of HNM, (b): SEM of CHNM, (c) TEM of HNM, (d) TEM of CHNM.

3.1.5. Cisplatin Loading %, Encapsulation Efficiency %, and release by HNM

The aim of this study is lung cancer treatment through anticancer-drug-loaded composites. Thus, the investigation of the CHNM loading capacity and releasing properties of the composite materials is very important in this regard. Figure 5 shows cisplatin loading percentage and encapsulation efficiency of HNM for cisplatin drug with variation in HNM concentration. It is obvious that as the concentration of the prepared HNM increase, both cisplatin loading % and encapsulation efficiency % increases due to the increased surface area of the prepared HNM. Drugs can be incorporated into polymeric micelles by physical entrapment or chemical conjugation [33].

The release of physically adsorbed drug from polymeric micelles is controlled by diffusion of drug from micellar core and the partition coefficient of the drug over micellar core and the aqueous phase. The *in vitro* release of cisplatin from functionalized prepared HNM is shown in Figure 6 as cumulative % release. At pH 7.4 free cisplatin release reached 79% after 60 minutes while it was released up to 90 % in first 2 h followed by gradual 100% release in 6 h from HNM at concentration 0.55 mg/ml with high encapsulation efficiency. In another publication, cisplatin was also loaded to chitosan nanoparticles with loading capacity around 50.44% encapsulation efficiency and showed burst release (84.84%) over a period of 10 days [34].

The acidic intracellular lysosomes, endosomes, or cancerous tissues ease anti-cancer drug discharge which means that the nanoparticles might quicken the intracellular drug release after entering by endocytosis. This could decrease the undesirable effects of anti-cancer drugs on normal cells and reduce drug loss in blood transport [35] The cisplatin releasing mechanism of nanoparticles was typical means of DNA crosslinking that decrease the cisplatin toxicity through regulating drug release from nanocarrier [36].

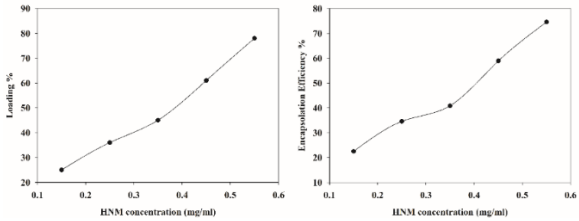

Fig. 5 Cisplatin Loading % and Encapsulation efficiency by HNM

3.2. In vitro examinations

Chitosan nanoparticles potentially cause apoptosis and cell death [37]. The antitumor activity of CHNM and pure cisplatin was evaluated using A-549 cell lines. The chemically structured materials CHNM and pure cisplatin were tested at various concentrations and the obtained outcomes were graphically illustrated in Fig (6). Figure 7 shows that the cisplatin IC_{50} was calculated to be 7.53 µg/ml while that for the CHNM IC_{50} was calculated to be 50.8 µg/ml. The cytotoxic effect of CHNM on A-549 human lung cancer cell line can be observed by morphological changes such as cell membrane damage, and non-adherence to the surface. The obtained results in this study are in line with results of Babu et al., 2014 [38] who studied the activity of cisplatin and chitosan nanoparticle on human ovarian cancer cells.

Our findings suggest that a drug-polymer nanocomposite can be utilized in a controlled release medication system to increase tumor tissue permeability and retention. The present work shows that *CHNM* have excellent anti-growth capabilities and are superior to cisplatin in lung cancer. The A549 cell line demonstrated that *CHNM* delivery systems can increase cytotoxicity in *vitro*.

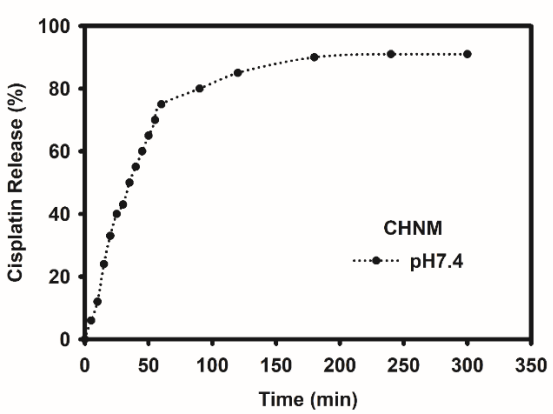

Fig. 6 Cisplatin release from HNM at concentration of 0.55 mg/ml

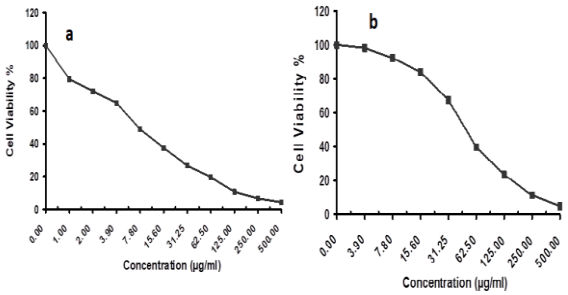

Fig. 7 Cytotoxic activity of (a) cisplatin (IC50= 7.53 µg/ml) and (b) CHNM (IC50=50.8 µg/ml) on A-549 cell line.

3. Conclusions

In conclusion, the CHNM could become an active chemotherapeutic way for lung cancer and could be superlative nominates for drugs inventio n in these nanoparticles. CHNM displayed a brilliant biocompatibility profile representing its appropriateness for targeting cancer. It can accumulate at the tumor cells and rise its permeability and retention focusing and accordingly decrease the required drug dose to accomplish higher anti-tumor effect and diminish toxicity. Besides, Chitosan is a hydrophilic polymer, which is why chitosan nanocomposites can be more extraversion and passive to extended circulation in blood. The capacity of Chitosan in tumor cell biodistribution and drug accumulation is connected to its use in our newly synthesized CHNM, which can demonstrate anticancer action**.**

4. Conflicts of interest

"There are no conflicts to declare".

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