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Nanochitosan–Paracetamol Composite as a Potential Lung Cancer Inhibitor: Synthesis, Characterization, and Cytotoxicity Studies

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Abstract

Nanoparticles have been used in many areas of life, including medicine, due to the properties they possess that distinguish them from conventional particles. In the current study, nanochitosan-paracetamol composite was synthesized and the synthesized nanoparticles were characterized using FT-IR and 1H-NMR techniques. The drug complex developed utilizing various properties a variety of properties, and its anticancer properties against A549 lung cancer cell lines were investigated in vitro. The types of linkages between nanochitosan-paracetamol composite have been determined between amino acids and Nanochitosan medications. The results demonstrated the effectiveness of the formulation in inhibiting cancer cell proliferation. The effect of Nanochitosan on lung cancer cells (A549) was shown only with an IC50 = 137.87 µg/mL. However, the paracetamol-loaded Nanochitosan exhibited enhanced cytotoxic activity, with an IC50 = 109.49 µg/mL. The p53 gene expression level in the control group was (1.00 + 0.0, N =3). Upon exposure to nanochitosan alone, gene expression significantly increased to (2.933 + 0.2028, N =3); however, treatment with the prepared nanodrug further elevated the expression level to (4.100 + 0.1528, N =3). The rationale is the pressing There is a pressing need for the medication to maintain its therapeutic effect for an extended duration enabling it to reach specific target tissues more effectively without endangering healthy tissues" for improved academic tone and terminology. When the synthesis of nanochitosan-paracetamol composite was tested for biological activity, Furthermore, it was found to significantly inhibit the proliferation of lung cancer cells (A549) compared to the control group.

Keywords: Lung cancer; nanochitosan-paracetamol composite; Molecular docking; Cytotoxicity; p53 gene

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1. Introduction

Nanotechnology is defined as the process of separating and combining materials by manipulating a single atom or molecule. Nanotechnology is used in many fields such as science, engineering, medicine and technology [1-3]. The term "nano" is a Greek word meaning "dwarf" [4]. Nanomaterials typically range in size from 1 to 100 nm [5]. Nanomedicines have become of interest due to the use of nanostructures as drug encapsulation agents, or to bind and deliver therapeutic drugs to target tissues [6, 7] . Chitosan is a linear polysaccharide [8]. Chitosan contains three types of functional groups and has exceptional chemical and biological properties [9]. Lung cancer is the leading cause of death worldwide for all cancers and for both sexes in recent years [10-12]. Most lung cancers begin in the membrane that lines the airways or what forms around the lungs. Genes play a major and important role in arranging and coordinating the cell division cycle, as there are primary oncogenes responsible for this growth and tumor suppressor genes such as BRCA1, BRCA2, and *p53*, which are responsible for regulating cell growth inhibition [13, 14]. The *p53* gene is located on chromosome (17q13.1), and contains 393 amino acids [15], and has an important role in increasing the effectiveness of genes that play an important role in regulating the cell cycle that maintains the integrity of the genome, which works with some genes to prevent abnormal cell growth, so *p53* is the guardian of the genome [16]. The *p53* gene is one

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of the tumor suppressor genes that has a major role in DNA repair, programmed cell death, and controlling cell division. In addition, *p53* causes cell growth to stop and enter senescence [17]. Nanoparticle chitosan can be used as a carrier to deliver anticancer drugs directly to lung cancer cells [18], increasing treatment efficacy and reducing side effects. Nanoparticles help deliver drugs at high concentrations to tumor foci [19]. Paracetamol is used to relieve mild to moderate pain that may accompany some types of cancer or side effects of other treatments, such as chemotherapy or radiation [20]. Paracetamol is a chemical compound with wide uses, including (relieving minor pain - headache - side effects of colds - influenza), its chemical formula is [$C_8H_9NO_2$] [21]. It is also known as acetaminophen. Its molecular weight is 151.165 gm / mol. Its half-life in the body runs from one to four hours [22]. Binding energy represents the free energy required to separate the bound compound from the protein *p53* [23]. In general, binding energy values ranging (from -5 to -10) kcal/mol are considered indicators of good binding [24]. Negative values indicate a strong association, while positive values indicate a weak or unfavorable association [25]. This study aimed to link Nanochitosan with paracetamol. Also, to study some chemical properties of Nanochitosan composite linked with the drug such as: solubility and drug release. Linking and studying the molecular docking energy of Nanochitosan – paracetamol composite with amino acids. To know the effect of gene expression of (*p53*) gene.

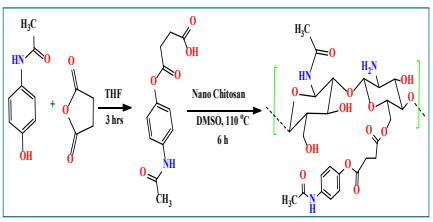
2. Experimental Section

2.1. Materials and Methods

All chemicals were used in this work of analytical grade. Note that nano-chitosan is supplied by the company (Shaanxi Sang herb Bio-Techlnc) / China. The size of the particles was equal to ≤ 80 nm, as in [26].

2.2. Synthesis of Nanochitosan–Paracetamol Composite

Paracetamol (4.53 gm, 3*10^{-2}mol) was dissolved in THF with (81mL, 1 mol) of succinic anhydride(81.09mL) with stirring and heating for 3 hours, then the precipitate was filtered. After that, the precipitate was dissolved in the solvent (DMSO) with the addition of intense hydrochloric acid droplets, then it was added to the Nanochitosan (5.0 gm) and then the heating process was carried out at 110 °C (with continuous stirring for 24 hours), and finally the precipitate was washed with a solution consisting of a ratio of (4:4) of diethyl ether and (2 M) sodium hydroxide and then left to dry for 15 hours at room temperature as in Equation (1) [27, 28].



Equation 1. Synthesis Nanochitosan–Paracetamol Composite)

2.3. Molecular docking

Based on previous studies, there are many proteins available on the website (PDB Protein Data Bank), but the proteins encoded by the gene (p^{53}) were chosen, and among these proteins found inside the cancer cell is (1tup), where the program (PyRx) was used, which links the ligand (drug) with the protein and also shows the strength of the bond between them. As for the binding sites, they were revealed in another program (Discovery Studio 2021 Client) which shows the binding of the drug to the important amino acids found in the proteins of the gene (p^{53}), and also shows the length and strength of the bonds between the drug and the proteins, while providing two-dimensional images of the binding sites between them [29, 30].

2.4 Cell culture maintenance

Lung cancer cell line A549 was maintained in RPMI-1640 medium, and the medium was supplemented to 10% by adding Fetal bovine serum with 100 µg/mL of penicillin and 100 µg/mL of streptomycin. The re-cultured cells were then passaged in the medium at 80% confluency using trypsin-EDTA twice a week, and incubated at (37) °C [31, 32].

2.5. Cytotoxicity Tests

To assess the cytotoxicity of pharmaceuticals (Nanochitosan only and Nanochitosan–Paracetamol Composite), MTT staining test was performed using a 96-well plate. Cells were cultured in cell\well (1×10^4) after 24 h a cohesive monolayer was formed and then these cells were treated with drugs (Nanochitosan and Nanochitosan–Paracetamol Composite) at varying concentrations. Cell viability was assessed after 48 hours of treatment by removing the medium, adding 28 µL of solution, and 2 mg/mL of MTT dye, followed by a 2.5-hour incubation of the cells. at a temperature of (37 °C). After removing the MTT stain, the remaining crystals in the wells were dissolved by adding (130 µL) of DMSO and incubated at a temperature of (37 °C) for (15 min) with shaking [13]. The absorbance was determined On (a microplate reader) at (492 nm), the assay was performed in triplicate. Then, the cell growth inhibition rate (percentage of cytotoxicity) was calculated using the following equation [19, 33]. Inhibition rate = (A-B)/A× 100 Under the inverted microscope, the shape of the cells was photographed when the cells were seeded in 24-well microtiter plates at a density of 1×10^5 cells mL^{-1}) and incubated for 24 h at a temperature of (37 °C), after which the cells were exposed to (Nanochitosan only and Nanochitosan–Paracetamol Composite) for a duration of 24 hours. After the exposure duration, bioactive polymers the plates were subjected to staining with crystal violet and incubated at 37°C for (10-15) minutes. The stain was eliminated by gently rinsing with tap water until fully eradicated. The cells were examined using an inverted microscope at 400x magnification, and photos were captured with a digital camera connected to the microscope [34, 35].

2.6. Heterogeneity assay

Primers were selected for molecular detection of the *p53* gene, based on standard sequences obtained from the NCBI GenBank database and as shown in Table (1).

Table 1. Primers used in p53 gene and used in qRT-PCR assay

p53 gene	Forward	5′-CCG TCG CAA GCA ATG GAT G-3′
	Reverse	5′-GAA GAT GAC AGG GGC CAG GAG -3′

The primers were obtained from (USA) as a powder (lyophilized product) in different concentrations. The stock solution and working solution were prepared according to the manufacturer's instructions. The stock solution was prepared by adding deionized water to obtain the final concentration of the suspension (100 µM/µL). (50 µL) of this solution was taken and added to (150 µL) of deionized water to obtain the final concentration of the working solution (25 µM/µL) The primers were stored at 20 °C [36, 37].

2.7. Statistical analysis

The obtained data were statically analyzed using an unpaired t-test with Graph Pad Prism 6. The values were presented as the mean ± SD of triplicate measurements [38, 39].

3. Results and Discussions

3.1. Characterization of Nanochitosan–Paracetamol Composite

The FT-IR results, in Figure (1)**.** for compound Paracetamol showed the presence of several main absorption bands, as we notice an absorption band at 3323.35 cm^{-1} in which the hydroxyl groups (O–H) and the amine group (N-H) are integrated, and a band at 3030.17 cm^{-1} representing Aromatic (C–H) bond, The spectra also exhibited an absorption band at 2829.87 cm^{-1} representing the aliphatic (C–H) bond, and the spectrum showed an absorption band at 1714.72 cm^{-1} representing the ester group (O–C=O), as for the absorption band 1676.14cm^{-1} it represents the amide group (N–C=O), as for the (C–O) band, it appeared at 1271.09 cm^{-1} [35, 40].

As for the ^{1}H-NMR spectrum, in Figure (2) for compound Paracetamol, it showed a set of signals. A signal appeared at (9.5) ppm, which is due to the amid group in the chitosan Nano polymer, while the two signals that appeared at (8.72, 8.74) ppm indicate the two amid groups present in the drug. A set of signals (7.4 – 6.8 ppm) appeared for the hydrogen proton in the aromatic ring. In addition, a signal appeared at (4.4) ppm, indicating the presence of the hydroxyl group of the chitosan Nano polymer. As for the signal that appeared at (2.5) ppm, it is due to the solvent (DMSO-d6), and a signal appeared at (1.8)ppm for the C-H protons of the methylene in the atoms, a signaler appeared at (1.01) ppm for the methyl group in the chitosan Nano polymer [41-43].

Molecular docking studies

Table (2) shows the binding energy of the drug (Nanochitosan–Paracetamol Composite) with the amino acids present in the proteins of the *p*53 gene, as well as the minimum and maximum limits (RMSD). shows the association of the drug (Nanochitosan–Paracetamol Composite) with the amino acids contained in the *p*53 gene protein**.** Figure (3). illustrates the type and length of the connections connecting Nanochitosan and Paracetamol with the amino acids that make up the 1tup protein, where the two amino acids glycine (Gly) which carries the serial number (C:199) and threonine (Thr) which carries the serial number (B:211) are linked by a carbon-hydrogen bond (C–H) with a very light green color. As for the amino acids threonine (Thr) which carries the serial number (B:170), aspartic (Asp) which carries the serial number (C:186), asparagine (Asn) which carries the serial number (C:200), and the amino acid arginine (Arg) which carries the serial numbers & (C:196) (B:209), they are linked by a hydrogen bond and their color is dark green. The amino acid phenyl (Phe)

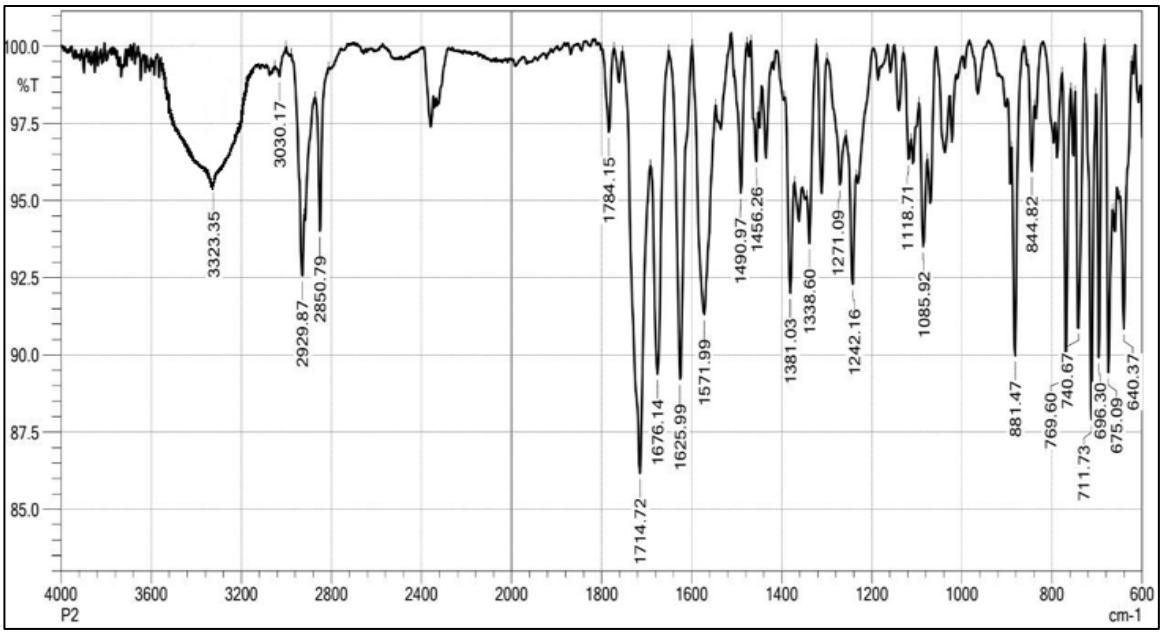


Figure 1. FT-IR of Nanochitosan–Paracetamol Composite

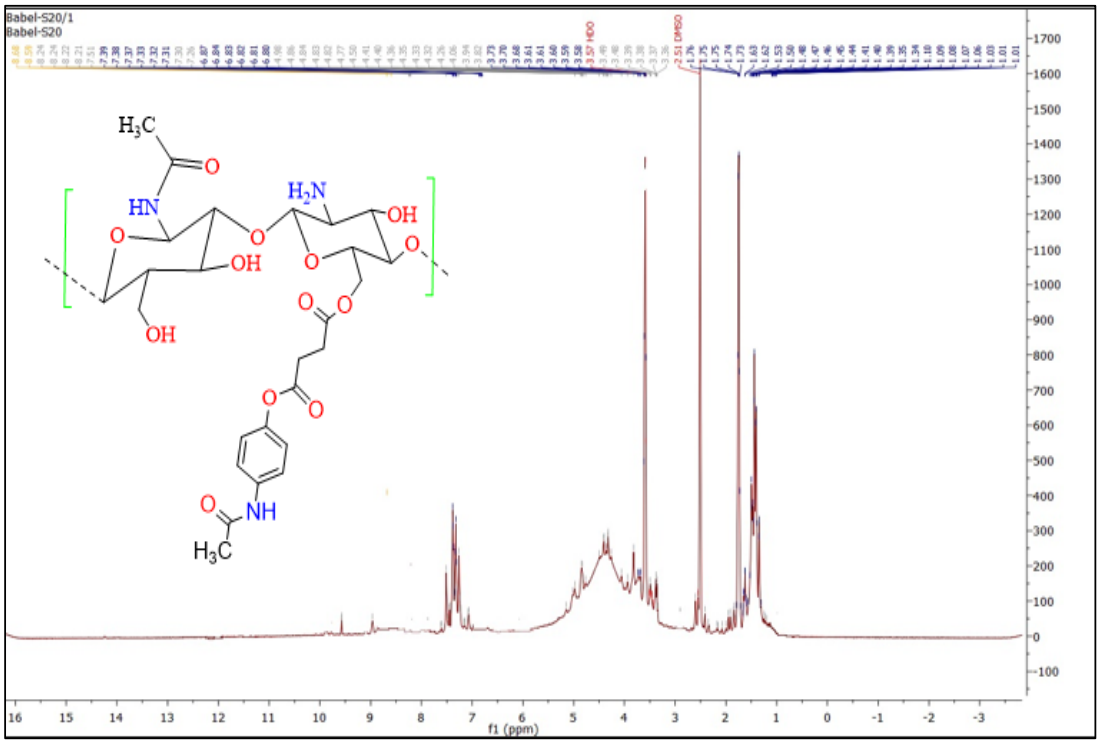


Figure 2. 1H-NMR Spectrum of Nanochitosan–Paracetamol Composite

Table 2. Shows the binding energy of the Nanochitosan–Paracetamol Composite

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
1tup_Fragment_uff_E=686.26	– 6.8	0	0.0	0.0
1tup_Fragment_uff_E=686.26	– 6.8	1	2.068	3.743
1tup_Fragment_uff_E=686.26	– 6.8	2	1.716	2.503
1tup_Fragment_uff_E=686.26	– 6.7	3	2.52	7.233
1tup_Fragment_uff_E=686.26	– 6.7	4	2.085	2.977
1tup_Fragment_uff_E=686.26	– 6.6	5	3.627	6.594
1tup_Fragment_uff_E=686.26	– 6.5	6	2.021	4.016
1tup_Fragment_uff_E=686.26	– 6.3	7	1.816	2.397
1tup_Fragment_uff_E=686.26	– 6.3	8	3.365	6.761

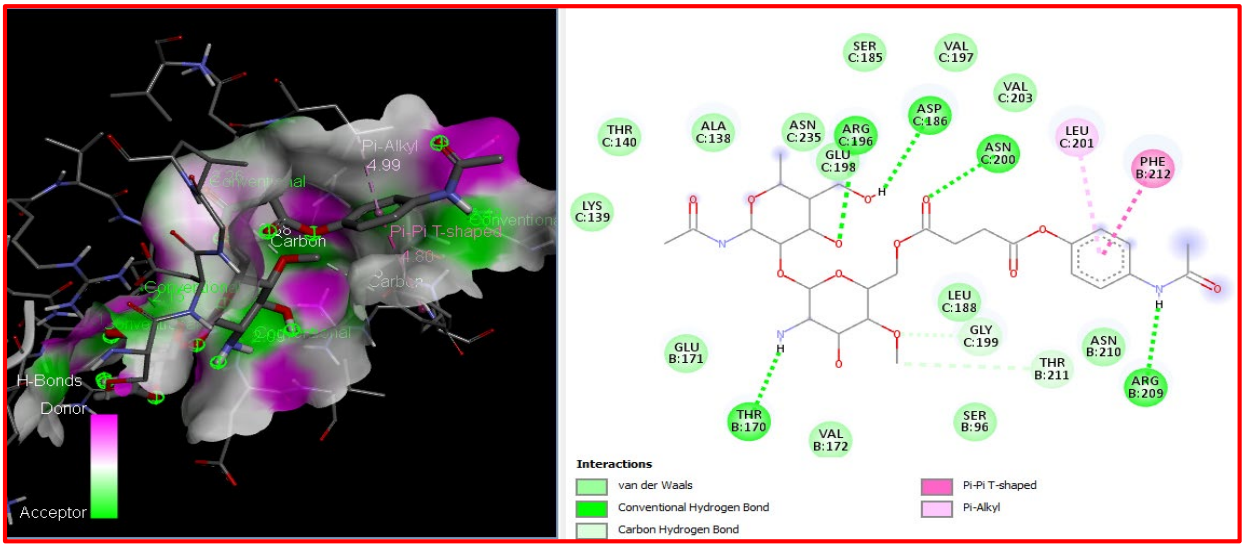


Figure 3. Illustrates the type and length of the bonds linking Nanochitosan–Paracetamol Composite to the amino acids constituting the 1tup protein

with the serial number (B:212) is linked by a dark pink (Pi-Pi-shaped) bond, as is the amino acid leucine (Leu) with the serial number (C:201) but is linked by a pink (Pi-Alkyl) bond. The remaining amino acids that appeared in the molecular bonding in the light green color are linked to the protein by van der Waals force and they are

(Glu – Leu – Lys – Thr – Ser – Asn – Ala – Val) [44].

Drugs containing nanoparticles can also be discovered at the active sites and are linked to certain amino acids that form proteins. Research has shown that hydrogen bonds affect protein stability, making their presence essential for the synthesis of proteins. In a similar vein, when a medication is loaded with nanoparticles, its affinity for amino acids increases with hydrogen bond strength [29, 45].

3.2. Cytotoxicity Assays

The effect of cytotoxicity on lung cancer cells (A549) was studied, and the cytotoxic activity and proliferation of cells were tested when exposed to nano-chitosan drugs, as we see in Figure (4), which shows the cytotoxicity of cancer cells (A549) when exposed to nano-chitosan only. Where the (X) axis represents drug concentration and the (Y) axis represents the toxicity of cancer cells, as we notice in the Figure With increasing the concentration of Nanochitosan drug, the toxicity of cancer cells in the lung cancer line (A549) decreases, it's spread decreases. At a Conc. of (12.50 µg/mL), the cell toxicity was at a rate and standard error of (90.00 + 1.732, N =3), and when the Conc. increased to (25 µg/mL), the cell toxicity decreased at a rate and standard error of (80.33 + 2.404, N =3), and with increasing the Conc. to (50 µg/mL), the toxicity became less at a rate and standard error of (67.67 + 2.333, N =3), the Conc. was increased to (100 µg/mL), the average Conc. of toxicity was (56.33 + 1.667, N =3), and at a Conc. of (200 µg/mL) The amount of toxicity decreased to (39.67 + 2.603, N = 3), toxicity appeared at a rate and standard error of (36.67 + 1.453, N = 3) at a Conc. of (400 µg/mL) and the value of IC_{50} = 137.87 µg/mL.

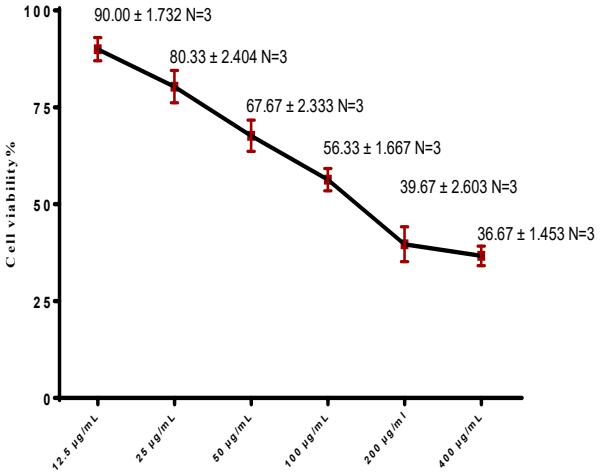


Figure 4. Effect of Nanochitosan drug only on the toxicity of lung cancer cell line cells type(A549) IC50 = 137.87 µg/mL

Figure (5) Illustrates the toxicity of the A549 lung cancer cell line. to the drug (Nanochitosan-Paracetamol Composite). When the lung cancer cell line (A549) was exposed to a Conc. of (12.50 µg/mL) of the drug, the toxicity rate was (90.33 + 2.186 N =3), and when the Conc. was increased to (25 µg/mL), the cell toxicity decreased (77.00 + 3.055, N =3), then the Conc. was increased to (50 µg/mL), the amount of toxicity became less by a standard rate (57.00 + 1.732, N =3), the Conc. was increased to (100 µg/mL), so the toxicity became (52.00 + 3.464, N =3), then the Conc. was increased to (200 µg/mL), so the toxicity rate appeared (36.67 + 1.856, N =3), and when using a Conc. of (400 µg/mL), the toxicity rate became The IC_{50} value was (28.67 + 2.186, N =3) = 109.49 µg/mL.

Figure (6) shows the lung cancer cell line (A549) before under an electron microscope at a power of (40X). It shows the shape of the cell before being exposed to any drug and the cells are in an abnormal division pattern and that each cell has two or more black dots inside it, each dot representing a single nucleus.

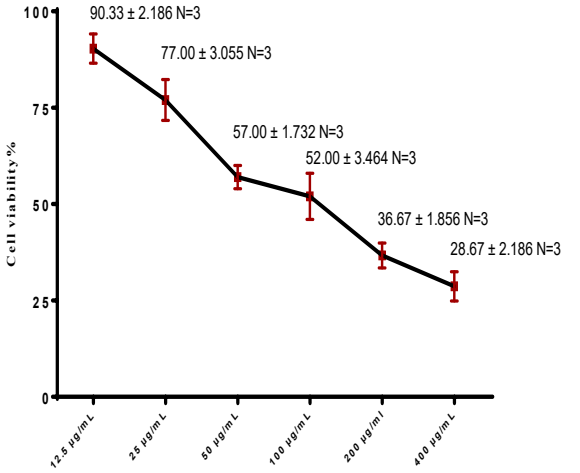


Figure 5. shows the effect of the drug (Nanochitosan–Paracetamol Composite) on the toxicity of lung cancer cell line cells type (A549) IC50 = 109.49 µg/mL

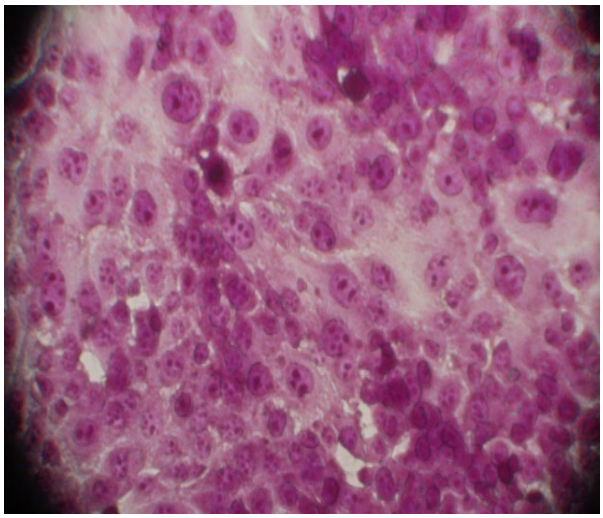


Figure 6. Shows a group of cancer cells before being exposed to any drug (control)

Figure (7). shows the morphological change of the cell in the lung cancer line (A549) after being treated with only chitosan nano drug, as it showed an effect on the cells as they began to swell and the presence of black dots indicating that the cancer cells swelled to more than their designated size and began to explode.

Figure (8). shows the morphological change in the lung cancer line (A549) when exposed to the drug paracetamol loaded on Nanochitosan, where the drug also gave good results such as black dots which are the remains of the exploded cells and the swollen cells.

Figure (6). for the lung cancer line (A549) showed that it is consistent with previous studies in which the cells fill the shape before treatment and their shapes are irregular and their number is large and they are not swollen [46]. Figures. (7) & (8) also agree with a previous study that the shapes of the cells after exposure to treatment are few in number and their shape is irregular in addition to the presence of swollen cells and the presence of black dots indicating the remains of the swollen cells that exploded after exposure to treatment [47].

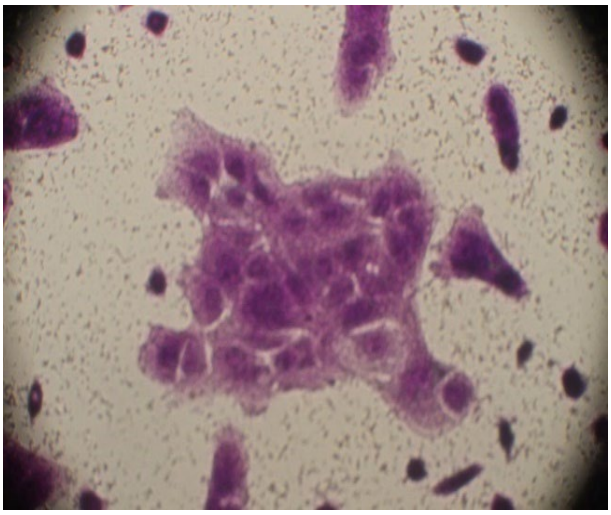


Figure 7. A group of cancer cells after being exposed to only Nanochitosan drug

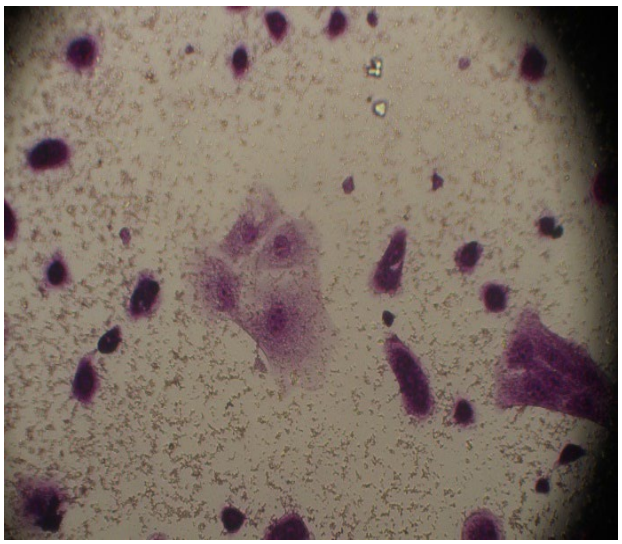


Figure 8. A group of cancer cells after exposure to the drug (Nanochitosan–Paracetamol Composite)

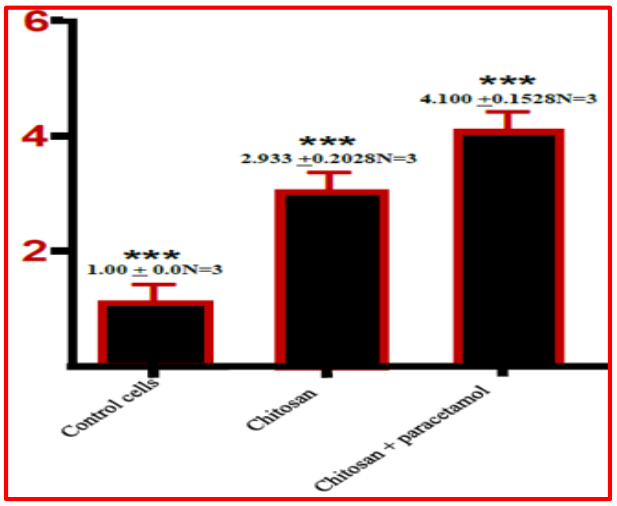


Figure 9. Gene expression of p53 gene when lung cancer cell line (A549) is exposed to the two drugs compared to the control group

3.3. Molecular diagnosis using (qRT-PCR)

Molecular detection of the p^{53} gene was performed using qRT-PCR technology to measure the extent of gene expression of this gene when the lung cancer cell line type (A549) was exposed to the drug paracetamol loaded on Nanochitosan in addition to the drug Nanochitosan only, where the results showed, as in Figure (9), significant differences in the level of gene expression of the p^{53} gene when exposed to the drug Nanochitosan (2.933 + 0.2028, N =3) compared to the amount of gene expression of the p^{53} gene in the control group (1.00 + 0.0, N =3), and the gene expression of the *p*53 gene appeared high when exposed to the drug paracetamol loaded on Nanochitosan by an amount of (4.100 + 0.1528, N =3) compared to its expression in the control group (1.00 + 0.0, N = 3).

When a cell's DNA is damaged, it also activates repair mechanisms. If the damage cannot be repaired, it induces programmed cell death to prevent the spread of damaged cells [48]. The *p53* gene plays a vital role in cancer prevention and is often known as the "guardian of the genome." The *p*53 gene acts as a tumor suppressor, helping to regulate the cell cycle, preventing cells from dividing too rapidly, and repairing damaged DNA [49]. Regulating stress response: *p53* responds to a variety of cellular stresses, such as hypoxia and oxidative stress. The drug's affinity for amino acids is enhanced by hydrogen bond strength, which increases the drug's efficacy when loaded with nanoparticles [26].

4. Conclusions

Paracetamol was linked to chitosan nanoparticles and was characterized using FT-IR and 1H-NMR spectroscopy techniques. Chitosan nanoparticles-paracetamol were also linked to amino acids in the tumor suppressor protein (1TUP) in cancer cells using molecular docking technique.

The cytotoxicity began to decrease when cancer cells were exposed to the drugs, i.e., the drug inhibition efficiency at the (IC50) point in the lung cancer cell line type (A549) was as follows: (chitosan nanoparticles only < Nanochitosan – Paracetamol Composite). The gene expression of *p53* gene increased when the lung cancer cell line type (A549) was exposed to the drugs compared to the amount of its gene expression before exposure to any drug.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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