Nanotechnology-Enhanced Chemoradiotherapy Using Copper and Gold Nanoparticles for Esophageal Cancer

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Abstract

Background : Esophageal cancer is a severe malignancy originating from the cells of the esophagus, a long, hollow tube connecting the throat to the stomach. Current therapeutic and diagnostic approaches for esophageal cancer are insufficient, necessitating improved methods. Nanotechnology-enhanced chemoradiotherapy presents a promising avenue, with nanoparticle (NP) based delivery methods showing effectiveness in radiation, chemotherapy, and imaging. Methods: This study aimed to evaluate the efficacy of copper (Cu) and gold (Au) nanoparticles in enhancing patient outcomes, diagnostic accuracy, and therapeutic efficacy for esophageal cancer. The nanoparticles were prepared and characterized using Scanning Electron Microscopy (SEM). Their anti-esophageal cancer properties and in vitro cytotoxic effects were tested against three cancer cell lines: human Caucasian esophageal carcinoma (OE33), squamous cell carcinoma of the esophagus (KYSE-270), and esophageal junction adenocarcinoma (ESO26). The MTT assay was employed to assess cell viability, focusing on duration and concentration effects, while IC50 values were used to determine antioxidant activity. Results: Both Cu and Au nanoparticles demonstrated significant anti-esophageal cancer capabilities, reducing the viability of OE33, KYSE-270, and ESO26 cell lines in a dose- and time-dependent manner. Notably, Cu NPs exhibited higher antioxidant activity compared to Au NPs, as indicated by their IC50 values. This superior antioxidant activity is likely responsible for the enhanced efficacy of Cu NPs in preventing human esophageal cancer cell proliferation. Conclusion: The findings suggest that Cu and Au nanoparticles possess substantial anti-esophageal cancer properties, with Cu NPs showing higher antioxidant activity and greater potential in inhibiting cancer cell growth. The antioxidant qualities of these nanoparticles are crucial in their ability to prevent esophageal cancer, highlighting their promise as effective agents in nanotechnology-enhanced chemoradiotherapy for esophageal cancer treatment. Further research and clinical trials are warranted to explore their full therapeutic potential and application in clinical settings.

Keywords: Esophageal Cancer, Nanoparticles, Chemotherapy, Radiotherapy, Medical, Gold (Au) nanoparticles, Copper (Cu) nanoparticles

Significance | Nanotechnology might induce esophageal cancer treatment, enhancing patient outcomes with copper and gold nanoparticles boosting therapy efficacy and diagnostic precision.

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Introduction

Nanoparticle investigation and atomic, molecular, or macromolecular technological development are together referred to as nanotechnology. Developing tools, systems, and structures with practical features and capabilities is the goal of the field (Khan

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et al., 2022). In addition, it advances our knowledge of materials and behaviors at the nano-scale. Many medical issues have been resolved by the application of nanotechnology, such as smart nanostructures for targeted drug delivery, which has brought novel ideas to the cancer area (Zhao et al., 2022). These days, a lot of research is being done on nanotechnology to improve health care by controlling, treating, diagnosing, preventing, or monitoring medical conditions, including cancer (Gao et al., 2020). Numerous nanomaterials have been developed via extensive studies for the detection and treatment of cancer. Many cancer-related nanotechnologies are currently in growth, including injectable drug delivery nano-vectors, biologically targeted small magnetic resonance imaging (MRI) agents for during-surgery imaging, and techniques that use nanoparticles for incredibly precise proteins and DNA identification (Atwan & Al-Ogaidi, 2024). In addition to this, researchers are especially keen to find out how nanotechnology can help overcome the drawbacks of traditional radiation therapy for the therapy of cancer. Nanotechnology is frequently applied in cancer detection and treatment. While the majority of oncology research using nanotechnology focuses on the delivery of chemotherapeutics and diagnostics, there is also research being done on using nanotechnology to enhance radiation oncology treatments (Liang et al., 2022). Despite its widespread usage, clinical radiation therapy frequently falls short of the intended results when it comes to treating cancer due to a variety of limitations. A prospective area of study for cancer therapy is nanotechnology, a developing multidisciplinary scientific and technology discipline (Pedziwiatr-Werbicka et al., 2021). Nanoparticles have been used to overcome the resistance to radiation of malignant cells and increase the effectiveness of radiation therapy because of their special chemical and physical features (Buchman et al., 2019). Esophageal cancer is an ailment that starts in the tissue of the esophagus, which is the tube that links the neck and stomach (Klekotka et al., 2020). The two main forms are adenocarcinoma, which forms in the glandular cells of the lower esophagus, and squamous cell carcinoma, which originates in the lining of the upper and middle esophagus (Zhang et al., 2022). Risk factors encompass disorders such as Barrett's esophagus and GERD, as well as high alcohol intake and smoking (Gao et al., 2024). Chest discomfort, weight loss, and trouble swallowing are common symptoms (Didamson & Abrahamse, 2021). The standard course of treatment consists of medical procedures, chemotherapy, and radiation therapy. This strategy intends to minimize systemic toxicity while optimizing medication delivery, particularly to malignant areas, by utilizing the special qualities of nanoparticles (Zhuang et al., 2022). Targeted drug-release nanocarriers combined with chemotherapy and radiation therapy are intended to have synergistic effects that improve treatment effectiveness for esophageal cancers (Xiao et al., 2023). Researchers evaluate the potential of Au and Cu nanoparticles to enhance treatment results for patients with esophageal cancer (Deng et al., 2022; Moawad et al., 2024; Poellmann et al., 2023).

The study we conducted focused on enhancing chemo-radiotherapy for esophageal cancer, with a particular emphasis on the application of nanotechnology. By utilizing nanoparticles of copper (Cu), gold (Au), and silica, the research aimed to improve patient outcomes by increasing diagnostic precision and therapeutic efficacy. The study specifically examined esophageal tumors, including the OE33 cell line representing Caucasian esophageal cancer, the KYSE-270 cell line for human esophageal cancer, and the ESO26 cell line for gastric junction adenocarcinoma.The remainder of the paper is broken up into parts. In section 2, the relevant objective-based works are indicated. Section 3 explains the materials and techniques. The statistical analysis is found in section 4. Section 5 discussed the experimental results. Section 6 completed the paper.

2. Related work

An important problem with current cancer therapy regimens is the emergence of multidrug resistance (MDR) during cancer chemotherapy (Didamson & Abrahamse, 2021). Repair processes for Deoxyribonucleic Acid (DNA) were activated, and the ability to resist chemotherapy was caused by a variety of molecular processes, including enhanced drug efflux and avoidance of pharmaceutical-induced apoptosis. The broad and non-specific toxicity of conventional formulations has been significantly improved by the use of a carrier system in the research of esophageal cancer (EC), along with other disorders (Gao et al., 2024). Photodynamic therapy (PDT) and diagnostics were newer approaches to the diagnosis and treatment of esophageal cancer that include photo-sensitizers (PSs) (Zhuang et al., 2022). Nevertheless, a few shortcomings linked to the traditional PSs have restricted their use in healthcare settings. The MTT experiment demonstrated that the Cu NPs' anti-esophageal cancer characteristics could effectively eliminate the cancer cell lines KYSE-270, OE33, and ESO26 in a time- and concentration-dependent manner (Xiao et al., 2023). NP-based systems for delivery have demonstrated optimal effectiveness in chemotherapy, radiation, gene therapy, phototherapy, and live imaging for cancers (Deng et al., 2022). As a result, they have recently been widely designed as innovative therapeutic approaches. A frequent malignant tumor of the intestines that poses a major threat to human health is called gastrointestinal cancer (GIC) (Jun et al., 2020). The limited sensitivity of endoscopic and MRI diagnosis of GIC in clinical settings was a common issue because of the distinct organ structure of the digestive tract. The doxorubicin/silver nanoparticles (DOX-SNPs) that were created demonstrate significant cytotoxicity against tumor cells as well as robust light harvesting to raise temperature in vitro (Moawad et al.,

2024). To separate Circulating Tumor Cells (CTC) from mononuclear cells, the method combined dendrimer-mediated multivalent immune-capture at the nanoscale with biomimetic cell roll on synthetic E-selectin (Poellmann et al., 2023). Organometallic chemistry examinations, such as FE-SEM (Field Emission Scanning Electron Microscopy), FT-IR (Fourier Transformed Infrared Spectroscopy), and TEM (Transmission Electron Microscopy), were used to analyze gold nanoparticles (Liu et al., 2020). Based on a recent study, gold nanoparticles (GNPs) may find application as radio-sensitizing agents (Alhussan et al., 2021). Clinical trials have evaluated GNPs, and they have proven to be compatible. The main goal was to investigate what happens when other radio-sensitizing drugs, including cisplatin and DTX, were added to the GNP-RT system. The application of nanotechnology to medical research to find an advanced cancer treatment was known as nanomedicine. Several significant obstacles were posed by the traditional drug delivery systems (DDS) of chemotherapy medications, which were associated with their low specificity, sensitive toxicity, and lack of therapeutic effectiveness (Ahmed et al., 2022). PDT uses light triggers to produce reactive oxygen species (ROS) as a minimally or non-invasive cancer therapy approach (Liu et al., 2021). PDT can strengthen the immune system's ability to combat cancer, even if therapy cannot eradicate metastatic cancers.

3. Methods and materials

The chemo-radiotherapy approach for esophageal cancer that is improved by nanotechnology entails the synthesis of NPs such as Cu or Au and then tailors their characteristics for specific medication delivery. NP uptake and cytotoxicity are evaluated in vitro using esophageal cancer cell lines, while therapeutic effectiveness and bio-distribution are assessed in vivo using animal models. By combining NPs with chemotherapy and radiation therapy, the goal is to improve therapeutic results by making use of their capacity to improve medication delivery and sensitize cancer cells to radiation.

3.1. Materials

Copper (Cu): The Sigma-Aldrich business located in the United States provided the PBS (phosphate buffer solution), DMSO (dimethyl sulfoxide), MH (Mueller Hinton) Medium, Ehrlich solution, DMED (Dulbecco's-modified Eagle Medium), hydrolysate, decamplmaneh fetal bovine serum, antimitotic medication a solution borax-sulphuric acid mixture, Sabouraud Dextrose Medium, Sabouraud Dextrose Agar, Muller Hinton Agar. Gold (AU): KBr pellets were used to create the examples, and a Bruker VERTEX 80V apparatus was used to acquire the FT-IR spectra. Consequently, TESCAN MIRA3 and TSCAN microscopes were used to analyze the sizes, shapes, and elemental composition utilizing EDX and FESEM. Before the investigation, the specimens were physically scattered on a grid and wrapped in gold. At an accelerating voltage of 200 kV, TEM research was conducted with a Phillips CM10 microscope. The acetone-dispersed model was applied drop by drop on a carbon-coated Cu grid, let to dry, and then examined.

3.2. Green synthesis of Cu NPs

An earlier investigation was used to carry out the green synthesis of the Cu NPs. Thirty milliliters of a 40 mg/mL M. piperita extract water solution was combined with thirty milliliters of 0.3M $Cu(NO3)2.3H2O$. After that, the reaction mixture was agitated for 24 hours at 60 degrees Celsius. After three water washes, the precipitate was centrifuged for ten minutes at 15,000 rpm. Subsequently, the leftover precipitate was put in a 55°C oven. The dark brown, dried nanoparticles were stored in a container. Distilled water was used as the CuNPs' solution in the most recent study.

3.3. Preparation and extraction of aqueous extract

The procedures followed to produce the M. piperita aqueous extract are listed below. The first step involved powdering a hundred grams of dried plant material, which was then soaked in boiling water for three hours. The extract was filtered after soaking to remove any remaining solids. Afterward, evaporation was used to concentrate the contents of the filtered liquid extract. In the end, both the combined and crude extracts were freeze-dried to produce a concentrated black powder extract.

3.4. Procedure for antioxidant test

Copper (CU): Using this procedure, 1 mL of diphenyl-1-picrylhydrazyl (DPPH) (300$mmol/l$) and 1 mL of various nanoparticle concentrations (0–1000mg/mL) were added, and the ultimate volume of the mixture with methanol was 4000 mL. After being vortexed, the flying birds were left in the dark for sixty minutes. 517 nm was the wavelength that was measured. Using the following formula, the DPPH radical suppression percentage was determined.

$$Inhibition\ (\%) = \frac{Sample\ A}{Control\ A} \times 100 \quad (1)$$

Gold (AU): A material's capability to absorb the DPPH free radical is measured using the DPPH technique, which is commonly used to estimate an object's antioxidant capacity. Based on free radical salvaging, it is a well-known colorimetric technique. After mixing the experimental antioxidant material with the purple-colored DPPH alcoholic solution, the antimicrobial test's purple hue is quenched to a pale yellow by free electrons or atoms of hydrogen. The absorbance shift at 517 nm is measured using a spectrophotometer fitted with a UV-Vis. Equal amounts of DPPH in methanol at several concentrations were combined with the Au NP composite, with BHT serving as a reference. Subsequently, the outcomes were compared.

$$DPPH\ scavenging\ effect\ or\ inhibition(\%) = [(Ao - As)/Ao] \times 100 \quad (2)$$

Whereas As denotes the sample absorption and Ao denotes the original absorption.

3.5. MTT assay protocol

Copper (CU): The first step in the process of getting cells ready for differentiation is to put them in a cell culture medium and expose them to certain hormones and growth factors. The cells undergo differentiation in response to this stimulation, which is how they change into distinct cells after chemicals attach to their corresponding membrane receptors, intracellular activities like as complex building, intracellular messaging, and signal transmission are carefully examined. A common technique in pharmacology and cell biology for determining cell viability and metabolic activity is the MTT test, which has a detailed methodology, as shown in Figure 1.

$$Cell\ viability\ (\%) = \frac{Sample\ A}{Control\ A} \times 100 \quad (3)$$

Gold (AU): The DPPH method is frequently employed to assess the antioxidant potential of a material. This method assesses the material's absorption capacity of the DPPH free radical. Radical scavenging is the foundation of a renowned colorimetric technique. An experiment antioxidant sample is added to the DPPH alcohol solution, which turns bright yellow due to the reduction of its purple hue by the release of electrons or free hydrogen. A $UV-V$is spectrophotometer is used to measure this shift in absorption at 517 nm. The Au NP nanocomposite's anti-esophageal cancer efficacy is shown in Figure 2.

4. Statistical analysis

Initially, Minitab software version 21 was used to verify if the data was normal. The abnormal data were then adjusted. Software from SPSS version 22 was used to analyze data variance, while Excel was used to create graphics. One-way analysis of variance (ANOVA) and the Duncan post-hoc test ($p<0.01$) were used by SPSS (version 20) software to analyze the acquired findings.

5. Result

By tackling major issues with the effectiveness of treatment and patient outcomes, nanotechnology has great potential to advance chemo-radiotherapy for esophageal cancer. To minimize systemic adverse effects and maximize therapeutic benefit, chemotherapeutic medications may currently be delivered specifically to cancer cells because of nanoparticles.

5.1 FE-SEM evaluation of Cu and Au nanoparticles

A UV-Vis spectrum for produced Cu NPs derived from an M. piperita extract is presented in Figure 3(a). The creation of Cu NPs is confirmed by the UV-Vis spectroscopy findings.

The biosynthetic Cu NPs are represented by the peak at 586 nm. This finding is rather consistent. The generated Au NP nanocomposite's dimensions, form, and composition were assessed using electron mechanical methods (FE-SEM and TEM). As seen in Figure 3 (b), the artificially created Au NPs have an average size of 25–30 nm and are quasi-spherical. The nanoparticle's outermost covering is quite rough due to the starch bimolecular coating of the Au NPs.

5.2 UV-V is an analysis of Au and Cu NPs

Figure 4 (a) shows the $UV-V$ spectrum of biosynthesized Cu NPs produced from an M. piperita extract. Results obtained from UV-V spectroscopy confirm that Cu NPs are produced. The synthetic Cu NPs are responsible for the peak at 586 nm. This outcome is in line with the earlier $UV-V$ investigation for Cu NPs that were biosynthesized. They were identified as a promising strategy regarding the bio-stimulated encapsulation of Au NPs using a range of cutting-edge analytical techniques. The comparison of Au and Cu NPs is analyzed using UV-V, and the result is copper, which is excellent. Figure 4(b) illustrates the color shift from yellow to a reddish brown that was seen when $HAuCl4$ and supersonic waves were mixed. By using $UV-V$ measurement, a color shift that mirrored the development of Au NPs was confirmed.

5.3 EDX investigation of Au and Cu NPs

Signals at 8.1 keV (for $Cu\ Ka$), 0.8 keV (for $CuLa$), and 8.9 keV (for $Cu\ Kb$) are detected by the EDX data. The green generation of NP is verified in Figure 5(a). Prior research has demonstrated that the ecologically safe combination of Cu NPs and plant extracts may generate copper oxide and the existence of oxygen in the Cu NPs is verified by the 0.5 keV peaks for OLa. EDX analysis was used to examine the elemental composition and quality of the generated Au NPs, as shown in Figure 5(b). It proves that the highest concentration of Cu is found in Au and Cu. These results showed that the targeted nanocomposite was made efficiently.

5.4 Antioxidant analysis of Cu and Au NPs

In the latest investigation, Figure 6 (a) displays the percentage inhibition of Cu NPs and BHT at varying doses for their scavenging properties.

Against DPPH free radicals, Cu NPs and BHT had IC50 values of 300 and $105mg/mL$, respectively, in the antioxidants tested. Antioxidant comparisons between Cu and Au NPs show that the cu particle produces better results. Mechanistically, the Au NP nanocomposite's free protons or electrons are snatched by the DPPH free radical and as predicted, the antioxidant material and the free radical combine. Figure 6(b) displays the matching outcomes.

5.5 Antioxidant effects of Cu and Au NPs

A well-known cytotoxicity assay, the MTT test, was used in our study to examine the effects of Cu NP treatment on normal and esophageal cancer cell lines during 72 hours (Figures 7 (a)–(b). In the MTT test, Cu NPs showed no toxicity against HUVEC cells. Comparing the antioxidant effects of Cu and NPs, the results indicate that Cu demonstrates better outcomes. The vitality of

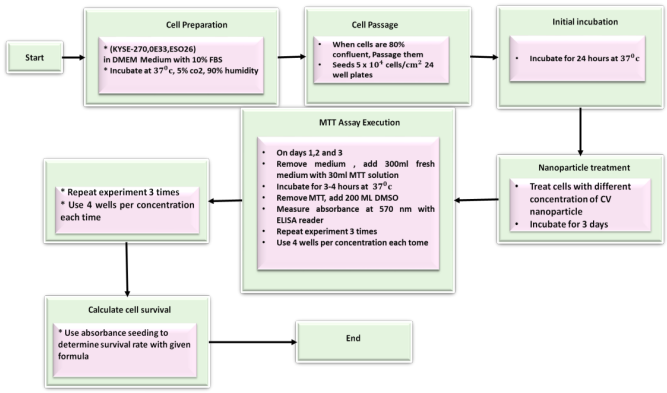

Figure 1 MTT assay protocol for Copper

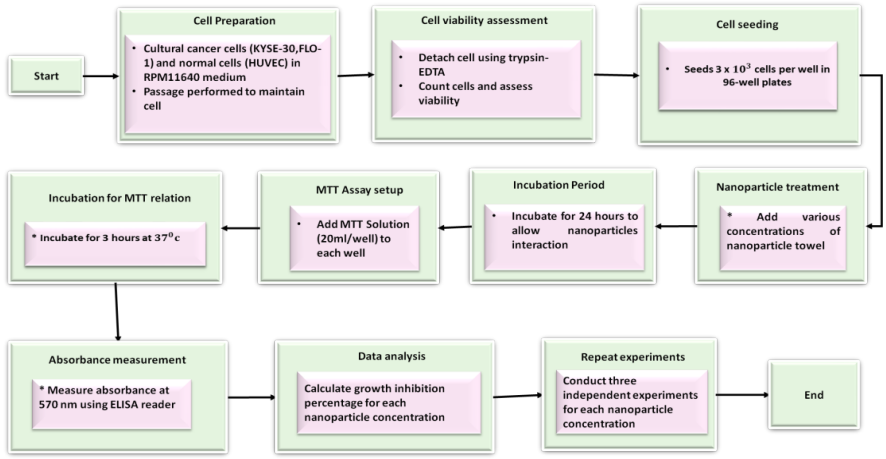

Figure 2 MTT assay protocol for Gold

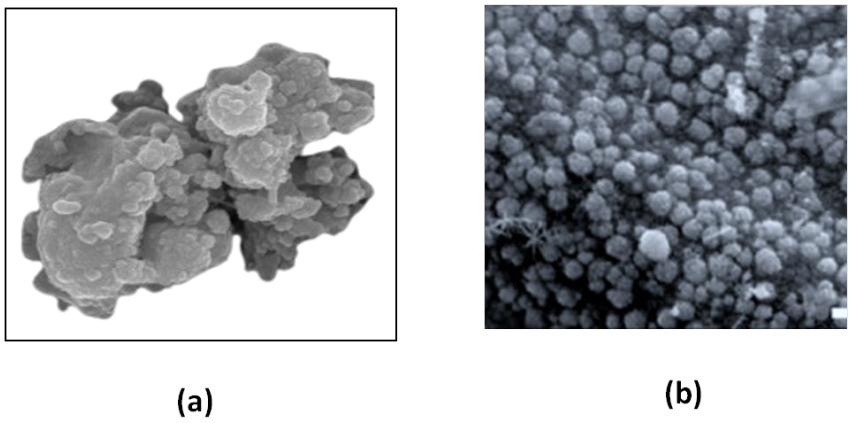

Figure 3 FE-SEM analysis (a) Cu NPs (b) Au NPs

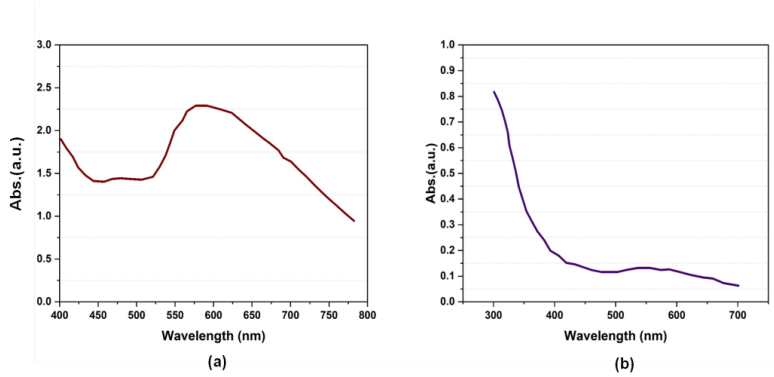

Figure 4 UV-Vis spectra analysis (a) *Cu* NPs (b) Au NPs

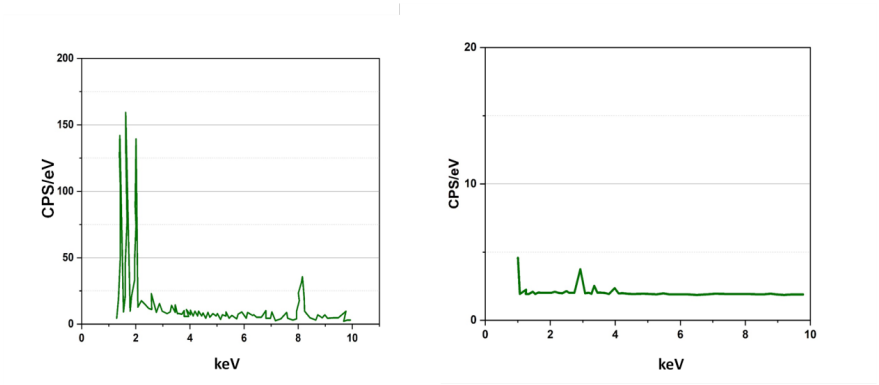

Figure 5 EDX analysis (a) Cu NPs (b) Au NPs

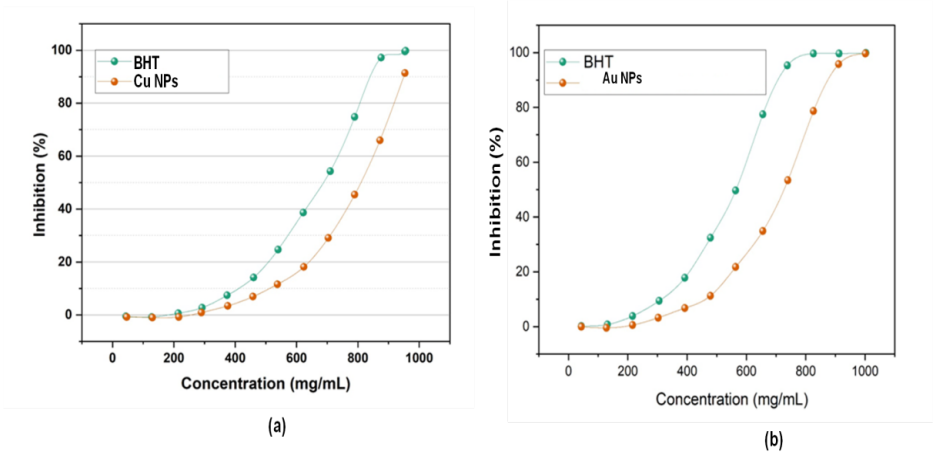

Figure 6 Antioxidant analysis (a) Cu NPs' (b) Au NPs with BHT's antioxidant properties

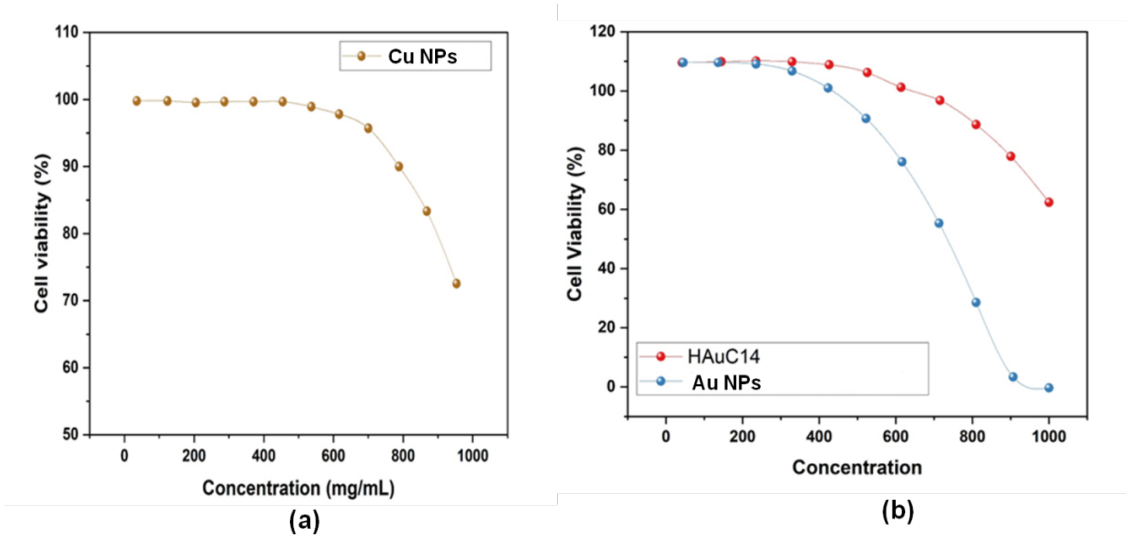

Figure 7 Cytotoxicity testing (a) *Cu* NPs' on the HUVEC cell line (b) *Au* nanocomposite and HAuCl4's cytotoxicity on normal (HUVEC) cells

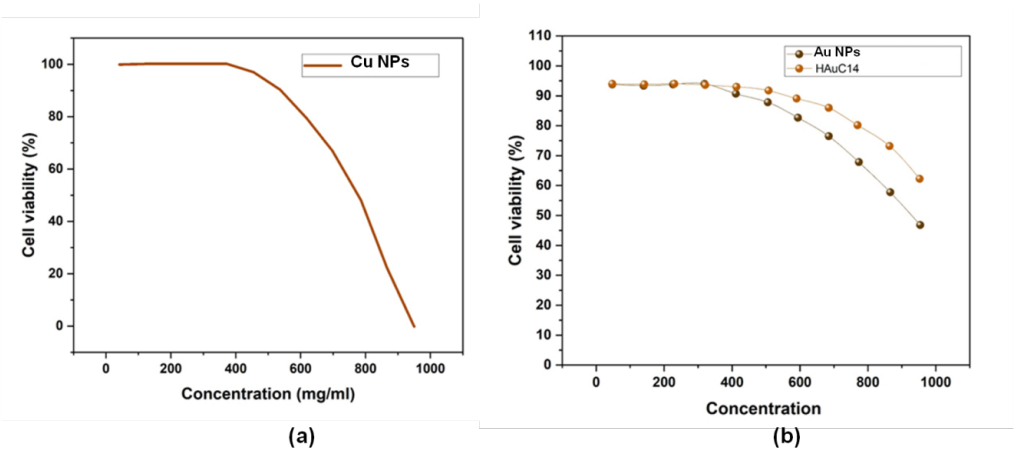

Figure 8 (a) Effects of cell line *Cu* NPs against KYSE-270 (b) KySE-30 and FLO-1 cells were tested with *Au* NP nanocomposite

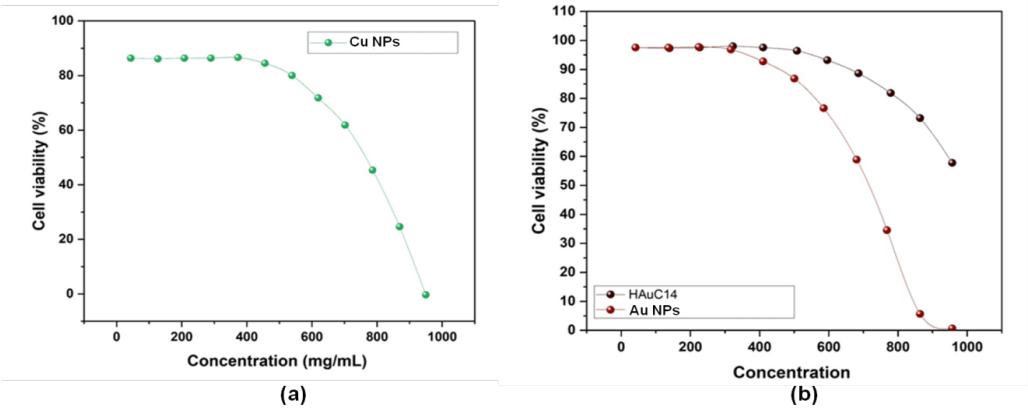

Figure 9 (a) Cu NPs' anti-esophageal cancer activities in the OE33 cell line (b) the anti-esophageal cancer characteristics of HAuCl4 (cell viability (%))

cancer cells of esophageal reduced in a dose-dependent way in the absence of Cu NPs.

Cells comparisons of KYSE-30 and FLO-1: The proportion of cell viability associated with the cytotoxic effect of Au NP nanocomposite when applied to FLO-1 and KYSE-30 cell lines is shown in Figures 8(a) and (b). The cytotoxic material Au NP composite exhibits a discernible reduction in cell viability as its concentration rises in all cell lines. Comparing cells KYSE-30 and FLO-1, Cu shows superior results compared to Au. When the substance was evaluated at a similar dose in the previous cell lines, a similar profile is seen in Figure 8(b).

Comparisons of OE33 and : The related IC50 values from the cancer research are displayed in Figures 9 (a) and 9 (b), where it was discovered that the example material concentrations needed to harm 50% of malignant cells were 125 and 176 $\mu g/mL$ for the FLO-1 and KYSE-30 cells, respectively. With the lowest IC50 value, the KYSE-30 cell line produced the best results, as the values show. In comparisons between Cu and Au, the Cu elements yielded superior results. Thus, the significant anti-proliferative impact of the Au NP nanocomposite on human esophageal cancer cells is demonstrated.

6. Conclusion

Utilizing chemical methods including EDX, UV-Vis, and FE-SEM, the produced NPs were examined. According to the findings, Cu NPs with sizes between 13.42 and 39.85 nm have a spherical shape. Cu NPs caused a dose-dependent decrease in the vitality of a cell line, severe in the esophageal. The OE33, ESO26, and cell lines were the targets of CuNPs, with corresponding IC50s of 241, 278, and 240mg/mL. In terms of antioxidant activity against DPPH, CuNPs exhibited the greatest results. BHT and Cu NPs had IC50s of 105 mg/mL and 300mg/mL, respectively, against DPPH. The generated Au NPs were discovered to be spherical and with a diameter of 10–20 nm using a FESEM. TEM and XRD analyses were performed to assess the particles' crystallinity. It is shown to have a significant capacity when compared to normal BHT molecules. After that, the substance underwent biological analysis to determine its cytotoxicity versus human esophagus cancer cells in vitro utilizing cells from the lines FLO-1 and KYSE-30.

Limitations and Future Study

The study focused on a limited group of esophageal cancer cell lines, including KYSE-270, ESO26, OE33, FLO-1, and KYSE-30. Future studies could employ a larger variety of cell lines to better reflect the diversity of esophageal cancer. Subsequent investigations may concentrate on refining the processes used in the manufacture of Au NP and Cu NP nanocomposites to maximize their bioavailability, stability, and efficacy in targeting cancer cells while reducing the likelihood of unintended consequences.

Author contributions

K.Z. conceived the study, developed the hypothesis, performed data analysis, and wrote the manuscript, including the introduction, methods, results, and discussion sections. K.Z. also collected data, conducted the literature review, and carried out the final revision. K.Z. read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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