

## Original Article

# Synergistic Redox Modulation by *Punica granatum*-Derived CeO<sub>2</sub>-CuO Nanocomposites in Colorectal Cancer Cells

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Nanotechnology has emerged as a promising field in cancer therapy, offering innovative solutions through the design of multifunctional nanomaterials. Among them, metal oxide nanocomposites are gaining attention due to their unique physicochemical properties and biomedical potential. However, conventional synthesis methods often involve toxic chemicals and generate environmental hazards. To overcome these challenges, green synthesis using plant-based extracts provides an eco-friendly, cost-effective, and sustainable alternative. Pomegranate (*Punica granatum*) peel, a rich source of polyphenols and antioxidants, has shown potential in nanoparticle synthesis by acting as a natural reducing and stabilizing agent. This study aimed to develop an eco-friendly synthesis approach for (CeO<sub>2</sub>)-(CuO) nanocomposites while investigating their physicochemical characteristics and therapeutic efficacy as an anticancer agent. The synthesis utilized *P. granatum* peel extract as a reducing and capping agent, combined with Cupric acetate monohydrate and Cerium nitrate. Characterization techniques such as Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and Transmission Electron Microscopy (TEM) were employed to analyze the nanocomposites' structural and morphological properties. The anticancer activity was evaluated using an MTT assay on HCT116 colorectal cancer cells, determining cell viability and IC<sub>50</sub> values. The FTIR analysis confirmed the successful integration of organic components from *P. granatum* peel with metal oxides in the nanocomposite. XRD analysis revealed well-defined crystalline structures, while TEM imaging showed spherical nanoparticles with an average size of 48 nm. The MTT assay demonstrated dose-dependent cytotoxicity, with the nanocomposite inducing significant apoptotic changes in HCT116 cells at higher concentrations. The green synthesis approach successfully produced a (CeO<sub>2</sub>)-(CuO) nanocomposite with potent anticancer activity, underscoring its potential as a sustainable therapeutic agent. The study highlights the benefits of utilizing agro-industrial waste and developing effective nanomaterials for biomedical applications. Future research should focus on in vivo validation and detailed mechanistic studies.

## Introduction

Nanotechnology has revolutionised numerous scientific disciplines, offering innovative solutions to longstanding challenges. One of its most promising applications lies in synthesizing nanocomposites for biological purposes, particularly in cancer therapy [1,2]. Nanocomposites, composed of two or more substances at the nanoscale, possess unique properties that make them ideal for a wide range of applications. The combination of cerium oxide (CeO<sub>2</sub>) and copper oxide (CuO) has garnered significant attention for its potential synergistic anticancer effects [3].

Plant-mediated nanoparticles (NPs), synthesised using plant extracts, have emerged as a promising frontier in developing innovative anticancer treatments. Bioactive compounds found in plants, including flavonoids, polyphenols, and alkaloids, play a pivotal role in nanoparticle synthesis, imparting superior biocompatibility and reduced toxicity [4,5]. These NPs are particularly notable for their ability to selectively target cancer cells, thereby minimising collateral damage to healthy tissues [6,7]. Among these, pomegranate (*Punica granatum* L.)—a fruit extensively cultivated in Asia—stands out as a rich reservoir of bioactive metabolites. Its peel, which constitutes nearly half of the fruit's weight, is rich in polyphenols, flavonoids, and other compounds known for their po-

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tent anticancer and antioxidant properties [8]. Leveraging pomegranate peel for nanoparticle synthesis not only provides a sustainable approach to utilising agro-industrial waste but also enhances the functional properties of the synthesised nanocomposites.

Cerium oxide ( $\text{CeO}_2$ ) nanoparticles, renowned for their unique properties such as reversible valence states and reactive oxygen species (ROS) scavenging, have shown great promise in biomedical applications [9]. Copper oxide (CuO) nanoparticles also exhibit antioxidant activity, ROS generation, and catalytic properties, thereby enhancing their cytotoxic potential against cancer cells [10-12]. To fully characterise these nanocomposites, techniques such as Fourier-transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) are employed to confirm the integration of organic components from *P. granatum* peel and the composite's crystalline structure.

Despite the promising potential of green-synthesized  $(\text{CeO}_2)$ -(CuO) nanocomposites, their antimicrobial and anticancer properties remain underexplored, particularly when derived from agro-industrial waste. This study seeks to bridge this gap by employing *P. granatum* peel extracts as capping agents for the synthesis of  $(\text{CeO}_2)$ -(CuO) nanoparticles. The primary focus is to evaluate the cytotoxic effects of these green-synthesised nanocomposites on HCT116 colorectal cancer cells, emphasising their potential as sustainable and effective anticancer agents.

## Materials and Methods

Distilled water, Cupric acetate monohydrate, Cerium Nitrate, Ammonia solution and Sodium Borohydride Solution from Fisher Scientific, India, were used for the synthesis of  $(\text{CeO}_2)$ -(CuO) NPs in this study.

### Collection and Preparation of Plant Sample

*Punica granatum* peels were collected from various locations near Saveetha University in Chennai. The specimens were purified with distilled water to eliminate contaminants and subsequently dried in the shade to preserve their integrity. After the leaves were completely shade-dried, they were pulverised into a fine powder using a mortar and pestle. Afterwards, 10 grams of the powdered leaf material were combined with 200 ml of distilled water in a sterile conical flask. The mixture was then heated and stirred constantly for 24 hours. Subsequently, the extract obtained was passed through a filter paper of Whatman No. 1 to remove impurities [13].

### Synthesis of nanoparticles

Initially, the distilled water was added to a precisely calibrated solution of Cupric acetate monohydrate at a concentration of 0.4 M, along with the filtrate obtained from the plant extract. The mixture was stirred and heated at  $60^\circ\text{C}$  with a magnetic agitator. Simultaneously, 1 M Sodium borohydride solution and an ammonia solution were gradually added until a characteristic blackish-brown colour developed, indicating the formation of  $(\text{CeO}_2)$ -(CuO) NPs. The entire mixture was centrifuged at 5000 revolutions per minute for 15 minutes. After centrifugation, the liquid above the sediment, referred to as the supernatant, was gradually transferred into a Petri dish to begin removing water.

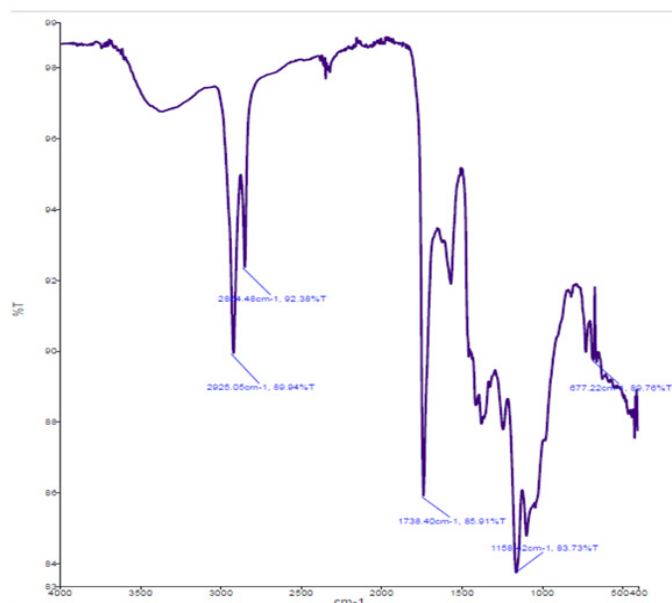
The nanoparticles were further dehydrated in a hot-air oven at  $100^\circ\text{C}$ , as described earlier [14]. A comprehensive study has been conducted to determine the characteristics of the  $(\text{CeO}_2)$ -(CuO) nanoparticles that were obtained using the *Punica granatum* extract.

### Characterisation of $(\text{CeO}_2)$ -(CuO) NPs

Spectral interpretation was performed by Fourier-transform infrared (FTIR) spectroscopy on a Bruker Alpha-II ATR instrument. The analysis was conducted within the wavelength range of  $4000\text{--}400\text{ cm}^{-1}$ . The SEM analysis was performed using Jeol JSM IT 800 Instrument, whereas TEM analysis was performed using G<sup>2</sup> 20 S – Twin TEM Instrument, revealing the presence of polydispersed  $(\text{CeO}_2)$ -(CuO) NPs.

### Anticancer activity

The MTT assay was carried out to determine the anticancer activity of biosynthesized  $(\text{CeO}_2)$ -(CuO) nanoparticles (NPs) in HCT116 cancer cell lines. After being cultured in the appropriate growth medium,



**Figure 1:** FTIR spectrum of the  $(\text{CeO}_2)$ -(CuO) nanocomposite synthesized using pomegranate peel extract

HCT116 cells were seeded into 96-well plates. Control samples and different concentrations of  $(\text{CeO}_2)$ -(CuO) NPs were introduced in multiple wells. The MTT reagent was applied to promote formazan crystal formation after incubation. To evaluate the vitality of the cells, absorbance readings were made. To establish the concentration at which 50% of cell viability was inhibited, the inhibitory concentration (IC<sub>50</sub>) was determined. Using HCT116 cancer cell lines, this approach extensively analyzes  $(\text{CeO}_2)$ -(CuO) NPs anticancer characteristics, exposing both their lethal effects and therapeutic potential [15].

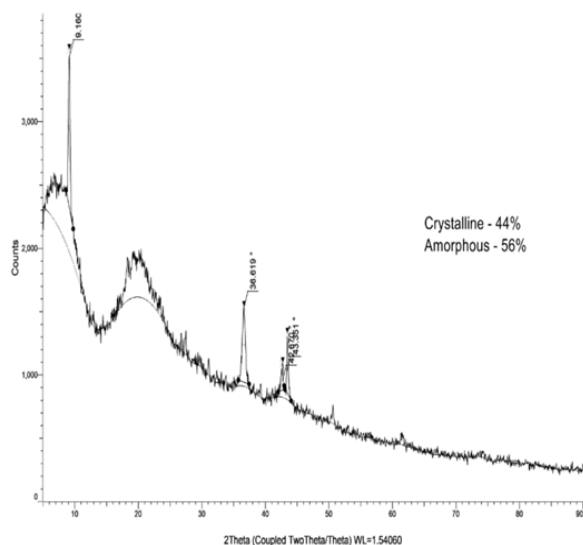
## Results

### FTIR Spectroscopy

The FTIR spectroscopy analysis (figure 1) confirmed the successful synthesis of the  $(\text{CeO}_2)$ -(CuO) nanocomposite derived from pomegranate peel by identifying distinct peaks corresponding to both organic and metal-oxide functional groups. The peaks at  $2925.05\text{ cm}^{-1}$  and  $2884.48\text{ cm}^{-1}$  are attributed to C-H stretching vibrations, indicating the presence of organic components and residual organic material from the pomegranate peel. A prominent peak at  $1738.40\text{ cm}^{-1}$  corresponds to C=O stretching vibrations, signifying carbonyl groups from organic constituents, while the peak at  $1158.42\text{ cm}^{-1}$  represents C-O stretching vibrations, characteristic of ether or alcohol groups. Additionally, the peak at  $677.22\text{ cm}^{-1}$  is assigned to metal-oxygen (M-O) stretching vibrations, confirming the presence of  $\text{CeO}_2$  and CuO in the nanocomposite. These spectral features collectively validate the incorporation of organic and inorganic components, highlighting the effectiveness of the green synthesis process.

### X-ray diffraction

X-ray diffraction (XRD) analysis was performed to investigate the crystalline structure and composition of the  $\text{CeO}_2$ -CuO nanocomposite synthesized using pomegranate peel extract. The XRD pattern (figure 2) revealed distinct peaks at  $9.160^\circ$ ,  $36.61^\circ$ ,  $42.67^\circ$ , and  $43.35^\circ$ , corresponding to specific lattice planes within the  $\text{CeO}_2$  and CuO crystal structures, as indexed by standard crystallographic data. These prominent, well-defined peaks confirm the successful synthesis of the  $\text{CeO}_2$ -CuO nanocomposite and highlight its crystalline nature. The results demonstrate the effectiveness of the green synthesis approach in producing nanocomposites with an organized crystal structure. The XRD diffrac-

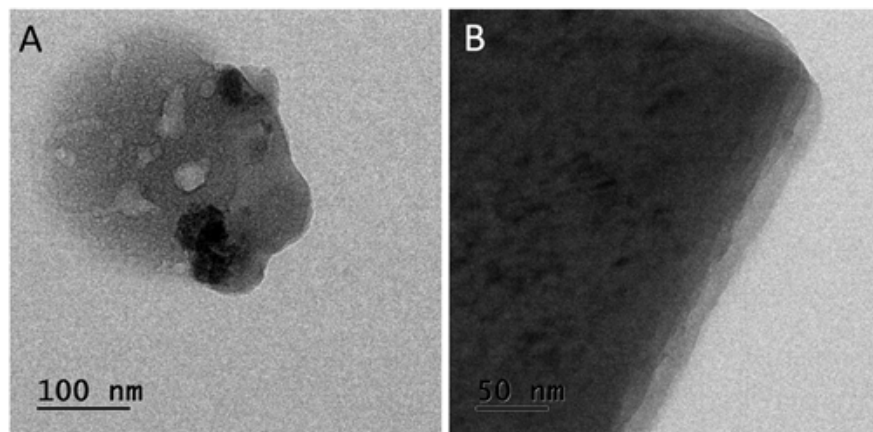


**Figure 2: XRD Analysis of the (CeO<sub>2</sub>)-(CuO) NPs synthesized from pomegranate peel**

tion peaks were used to estimate the crystallite size of the synthesized CeO<sub>2</sub>-CuO nanocomposite using the Scherrer equation,  $D = K\lambda/\beta\cos\theta$ , where  $D$  is the crystallite size,  $K$  is the shape factor (0.9),  $\lambda$  is the wavelength of the X-ray,  $\beta$  is the full width at half maximum (FWHM), and  $\theta$  is the Bragg angle. The determined crystallite size was found to be of the nanometer size range, and thus, it is consistent with the nanoscale morphology, as observed with TEM analysis, with an average particle size of about 48 nm. These findings are an affirmation that the nanocomposite synthesized has a crystal nanostructure that can be used in biomedical purposes.

#### Transmission electron microscopy

Transmission electron microscopy (TEM) was utilized to examine the morphology and structure of the (CeO<sub>2</sub>)-(CuO) nanocomposite synthesized from pomegranate peel. The TEM analysis (figure 3) revealed predominantly spherical nanoparticles with an average size of 48 nm, exhibiting a well-dispersed distribution. These high-resolution images confirm the nanoscale dimensions of the particles, which are critical for the effective application of the nanocomposite in various fields.



**Figure 3: TEM Analysis of CeO<sub>2</sub>/CuO NPs showed more dispersed spherical shaped NP at the average size 48nm**

#### Anti-cancer activity

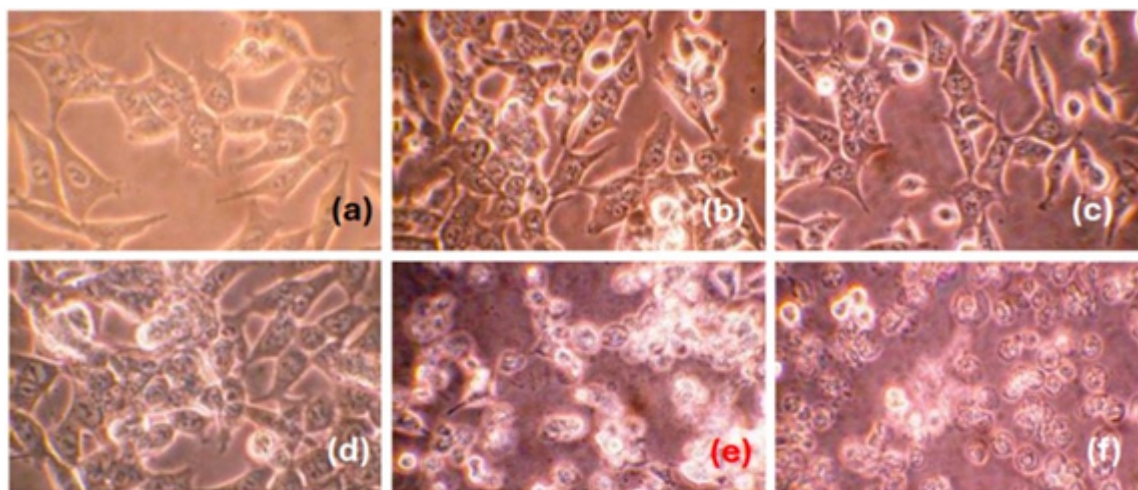
The morphological analysis of HCT116 cells treated with varying concentrations of the CeO<sub>2</sub>-CuO nanocomposite for 24 hours demonstrates a dose-dependent impact on cellular structure. Control cells (figure 4a) maintained a regular cobblestone-like epithelial morphology, characterized by distinct cell boundaries, uniform shape, and strong adherence to the culture plate, indicative of healthy cell status. In contrast, cells exposed to the nanocomposite exhibited significant morphological alterations. At lower concentrations (figure 4 b&c), initial signs of chromatin condensation and slight cell shrinkage became apparent, suggesting early apoptotic changes. With increasing concentrations (figure 4 d,e&f), these effects became more pronounced, with noticeable features such as further chromatin condensation, cell shrinkage, reduced adherence, and an increasing number of rounded cells. These changes are hallmarks of apoptosis.

At the highest concentrations, a substantial reduction in the number of cells with regular morphology was observed, alongside poorly adhered, rounded cells, underscoring the nanocomposite's potency in inducing apoptosis in HCT116 cancer cells. These findings highlight the potential anticancer efficacy of the CeO<sub>2</sub>-CuO nanocomposite.

#### Discussion

The findings of this study highlight the successful synthesis and characterization of a CeO<sub>2</sub>-CuO nanocomposite using pomegranate peel extract as a green synthesis approach. The FTIR and XRD analyses confirm the presence of both organic and inorganic components, as well as the crystalline structure of the nanocomposite. At the same time, TEM results demonstrate a uniform distribution of nanoparticles with an average size of 48 nm. Furthermore, the nanocomposite exhibits potent anticancer activity against HCT116 cells, inducing dose-dependent apoptosis.

Using pomegranate peel extract to synthesize nanocomposites offers a sustainable and eco-friendly alternative to conventional chemical methods. Previous studies have demonstrated the efficacy of various plant-based extracts, such as those from neem, tea leaves, and citrus fruits, in synthesizing metal oxide nanoparticles [16-21]. For instance, Jayakodi et al. reported the successful synthesis of CuO nanoparticles using neem extract, showcasing significant antimicrobial activity [22]. Similarly, Hasan et al. utilized tea extract to produce CeO<sub>2</sub> nanoparticles with notable antioxidant properties [23]. The results of our study align with these findings, further validating the use of plant-derived phytochemicals for nanoparticle synthesis. However, incorporating dual metal oxides (CeO<sub>2</sub>-CuO) in our study provides an added advantage, offering a synergistic effect that enhances the functional properties of



**Figure 5: Morphological analysis of HCT116 cells treated with varying concentrations of CeO<sub>2</sub>/CuO nanocomposite for 24 hours a) Control, b) 0.1 µg/ml, c) 0.5 µg/ml, d) 1 µg/ml, e) 5 µg/ml and f) 10 µg/ml**

the nanocomposite.

The crystalline structure of the CeO<sub>2</sub>-CuO nanocomposite, confirmed by XRD analysis, is consistent with earlier reports of metal oxide nanoparticles. For example, Khyrun et al. reported similar well-defined peaks in the XRD pattern of CeO<sub>2</sub>-CuO nanostructures, indicating high crystallinity and purity [24,25]. Additionally, the TEM analysis in this study revealed spherical nanoparticles with an average size of 48 nm, which is comparable to the findings of Guan et al., who synthesized CuO nanoparticles with an average size of 45 nm using a green synthesis method [26]. The uniform size and morphology observed in our study are critical for enhancing the nanocomposite's biological activity, as nanoparticle size plays a pivotal role in cellular uptake and interaction.

The dose-dependent induction of apoptosis in HCT116 cells observed in this study underscores the nanocomposite's potential as an anticancer agent. These findings are consistent with the results of earlier investigations, such as those by Hou et al., who reported significant apoptotic activity of CuO nanoparticles against colon cancer cells [27,28]. Similarly, Cerium oxide nanoparticles have been shown to induce oxidative stress and apoptosis in various cancer cell lines, as documented by Gu Z et al. [29,30]. The combined presence of CeO<sub>2</sub> and CuO in our nanocomposite likely contributes to a synergistic effect, enhancing its ability to disrupt cellular structures and induce apoptosis more effectively than single-metal nanoparticles.

The results are consistent with ROS-mediated cytotoxic reactions commonly reported in metal oxide nanomaterials, in which oxidative disequilibrium contributes to mitochondrial dysfunction and apoptosis [31]. The synergistic CeO<sub>2</sub>-CuO combination may enhance redox activity through catalytic surface interactions and redox cycling, thereby increasing intracellular oxidative stress and promoting cancer cell death [32]. Although reactive oxygen species (ROS) were not directly quantified, the observed apoptotic morphology and dose-dependent cytotoxicity suggest a redox-mediated mechanism, indicating that oxidative stress likely plays a central role in the nanocomposite's anticancer activity. Further confirmation is being pursued using assays such as DCFH-DA fluorescence and antioxidant enzyme analysis. Additionally, the present study did not include evaluation in normal (non-cancerous) cell lines to assess selective cytotoxicity; therefore, comparative testing in healthy cell models (e.g., fibroblast or epithelial lines) is planned to validate therapeutic selectivity.

Compared to chemically synthesized nanoparticles, the green synthesis method employed in this study offers reduced toxicity, cost-effectiveness, and environmental sustainability. Furthermore, the residual organic components from pomegranate peel, as indicated by FTIR analy-

sis, may provide additional bioactive compounds that enhance the nanocomposite's anticancer activity.

## Conclusion

This study successfully demonstrates the potential of the CeO<sub>2</sub>-CuO nanocomposite synthesized via a green approach as an effective anticancer agent. By comparing our findings with previous studies, we highlight the advantages of dual-metal nanocomposites, green synthesis methods, and the significant role of nanoparticle size and morphology in biological activity. Future research could focus on *in vivo* studies and mechanistic insights into the apoptotic pathways activated by the nanocomposite to further validate its therapeutic potential.

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