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Curcumin-mediated synthesis of copper-doped TiO_2 nanocomposite for potentially promising antioxidant, wound healing, and anti-apoptosis

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Abstract

The paper provides a green, eco-friendly synthesis and analysis of a novel curcumin-based, copper-doped titanium dioxide nanocomposite (CuO/TiO_2 -Curcumin NC). Curcumin was also utilized as a green reducing agent and also capping agent thereby enhancing the biocompatibility and functional surface chemistry of the nanocomposite. Stability of the nanocomposite was established using various forms of analysis. The relative biological studies showed that the synthesized CuO/TiO_2 -Curcumin NC had a high antioxidant capacity compared to pure curcumin and ascorbic acid. It also exhibited a strong, dose-dependent cytotoxicity to the breast cancer cell line MDA-MB-231 that is aggressive. The nanocomposite caused remarkable tumor cell apoptosis which was mainly triggered by excess production of reactive oxygen species (ROS) that caused irreversible damage of mitochondria, and caspase-activation pathways. This nanocomposite showed a concentration-related ability to inhibit the migration and proliferation of cancer cells and thus highlighted its high anti-metastatic capacity. Besides, the copper -titanium nanocomposite (CuO/TiO_2-curcumin) had promising in vitro wound -healing effects. Taken together, the present results confirm the CuO/TiO_2 -curcumin nanocomposite to be a highly effective, multimodal therapeutic platform, and, therefore, holds a lot of potential in biomedical applications in the future, as an enhanced antioxidant, a powerful anticancer agent, and a scaffold to promote tissue repair and regenerative medicine.

Keywords: Curcumin, copper-titanium nanocomposite, green synthesis, anti-apoptosis

1. Introduction

The disease process of most chronic illnesses, including cancers, has a close interdependence with oxidative stress. The overproduction of the reactive oxygen species (ROS) in such situations overwhelms the existing antioxidant defenses [1]. Aberrant wound healing can occur in parallel with oxidative stress and inflammatory events, thereby prolonging tissue healing and triggering clinical outcomes [2]. Current therapeutic interventions fail to address these interrelated pathophysiological mechanisms that are interrelated, and thus, there is a need to implement new multitarget interventions [3]. The use of nanotechnology offers a new approach, enabling the fabrication of complex, multifunctional materials with new therapeutic value [4]. Curcumin is a biopolyphenolic compound of Curcuma longa, with strong reducing and stabilizing abilities, which makes it a promising biogenic nanoparticles development candidate [5-7]. Its phenolic hydroxyl groups donate electrons, reducing metal ions and facilitating nanoparticle formation while preventing spontaneous aggregation. Curcumin's roles as a reducing agent and its proven antioxidant, anti-inflammatory, and anticancer activities make it very promising for biomedical nanotechnology [8]. Separately, TiO_2 and Cu-based nanoparticles also provide valuable biomedical applications, such as antioxidant defense and anticancer therapy [9,10]. TiO_2 in particular is well-studied for its biocompatibility and photocatalytic properties [11]. Copper doping in TiO_2 increases its bioactivity and broadens its therapeutic uses [12]. However, curcumin alone has poor bioavailability and is quickly metabolized [13]. Combining curcumin with Cu-doped TiO_2 NC offers an intriguing way to address these limitations.

Research on TiO_2 and Cu-based nanoparticles is extensive, yet there is limited work using curcumin in green synthesis for co-synthesized nanocomposites. Few studies explore their combined antioxidant, anti-apoptotic, and wound-healing potential, though conditions like chronic wounds and ulcers are worsened by oxidative stress and apoptosis.

We contend that curcumin-capped Cu-TiO_2 NC serves as a potent multi-modal therapeutic platform by efficiently removing ROS, precisely modulating apoptotic signaling pathways, and actively participating in cellular processes. We contend that curcumin-capped Cu-TiO_2 NC is a multi-modal therapeutic platform that removes ROS to lower oxidative damage, modulates apoptotic signaling to pre-

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vent harmful cell loss, and stimulates fibroblast migration to speed up tissue repair. Combination of these synergistic effects brings some visible benefits in the management of oxidative stress-related pathology, enhancement of wound repair mechanisms, and adjunctive anticancer therapies.

The current research paper outlines a novel and green synthetic method of the synthesis of copper-doped TiO_2 nanocomposites through curcumin reduction and stabilization, which shows a high level of therapeutic efficiency compared to conventional synthetic methodologies. To confirm the integrity of the produced nanocomposite and determine its size distribution, a set of complementary analytical methods were used to examine the produced biocompatible nanocomposite, comprising Fourier Transform infrared spectroscopy (FTIR), ultraviolet-visible spectroscopy (UV-Vis), scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDX), X-ray diffraction (XRD), high-resolution transmission electron microscopy (HR-TEM), zeta potential analysis, dynamic light scattering. Critical evaluations showed a strong antioxidant activity, a marked reduction in wound- healing activity, and a great anti-apoptotic effect. The findings highlight the possibilities of the nanocomposite as a two-purpose therapeutic agent in the fields of medicine and pharmaceutics, specifically when applied in the settings of oxidative stress-related conditions and wound healing.

2. Materials and methods

2.1. Reagents

DPPH 1,1-diphenyl-2-picrylhydrazyl (DPPH - 97%) and ascorbic acid (99%) were purchased from Sigma-Aldrich (St. Louis, USA). Copper sulfate ($CuSO_4.5H_2O$, 99.97 PIOCHEM, laboratory chemicals); titanium isopropoxide (TTIP, CAS No. 546689, 97%, Sigma Aldrich, St. Louis, USA); curcumin ($C_{21}H_2O_6$, LAXNESS AG, Cologne, Germany, 95%); and ethanol (HPLC grade, EtOH, 90%).

2.2. Instruments

The properties of curcumin based copper-titanium nanocomposites were characterized by the application of a diverse array of analytical methods. First, the UV-visible and fourier-transform infrared (FTIR) spectroscopy were used to measure optical characteristics and functional groups. In order to explore the nature of particles further, hyperdeliveries of zeta-potential values were used to measure surface charge. This was followed by high-resolution transmission electron microscopy (HR-TEM) which was used to determine nanoparticle morphology and scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM-EDX) was used to give additional information about surface morphology and elemental composition. Also, X-ray diffraction (XRD) was used to measure the structure and spectrophotometry was used to measure antioxidant activity and determine phytochemical content, thus forming a full set of analyses.

2.3. Preparation of curcumin-mediated copper-titanium nanocomposite (Cu-Ti NC)

To prepare curcumin-mediated Cu-TiO_2 nanocomposites, tetraethyl orthosilicate (TTIP) was dissolved in ethanol and later combined with curcumin through vigorous stirring [6]. The mixture was heated to 60-70 °C in two hours, and this encouraged the development of TiO_2 nanoparticles. Then, copper(II) sulfate solution was introduced in dropwise and suspension was stirred in 60 o C and curcumin served as a reducing agent that transformed Cu^{2+} ions into copper oxide within TiO_2 framework.

Nanoparticle dispersion was improved with the help of ultrasonic treatment. The nanocomposites were eventually centrifuged, washed, dried and their characterization was done using X-ray diffraction (XRD), energy-dispersive X-ray spectroscopy (EDX) and scanning electron microscopy (SEM). The materials that were obtained were then tested on their biological activity.

2.4. Antioxidant Activity

2.4.1. DPPH Assay

The antioxidant ability of curcumin and curcumin-mediated Cu-TiO_2 nanocomposites was measured using the 2, 2 -diphenyl-1-picrylhydrazyl (DPPH) colourimetric method. As a reference standard, the use of ascorbic acid was accepted [6]. A serial dilution protocol was done on all samples that included mixing of an equivalent of sample and methanol. Each of the samples was then added to the DPPH working solution in equal portions (1.35mM). The mixtures were then kept at ambient temperature in darkness after the DPPH solution was added and after incubating them over a period of 30 minutes. The absorbance of every aliquot was then determined at 517nm. The proportion of undecomposed DPPH was estimated as Equation 1.

$$\% \text{ DPPH}^{\cdot} \text{ remaining} = [\text{DPPH}^{\cdot}]_T / [\text{DPPH}^{\cdot}]_{T=0} \times 100 \quad \text{Eq. (1)}$$

The percentages of DPPH most of the time were against the sample concentrations (mg/mL) using an exponential regression model. The analysis allowed establishing the effective concentration, which is referred to as IC_{50}. The 50 value is the number of antioxidants that is needed to lower the original DPPH 50 -concentration by 50 percent. By extension, reduced IC_{50} values indicate that the antioxidant capacity of the tested sample is high.

2.4.2. Ferric Reducing Power Assay

The FRAP analysis is determined by antioxidant reducing ability by measuring the reduction of ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}), which results in a measurable change in color, from blue to green [14]. First of all, the FRAP reagent is assembled by mixing 300 mM acetate buffer at pH 3.6 with 20mM ferric chloride ($FeCl_3$). Afterward, the hot FRAP reagent is poured in every test tube, and the test solution, i.e., ascorbic acid or curcumin, is put in. The mixture obtained is incubated at 37°C. Lastly, the record of the absorbance at 700 nm is recorded; this high absorbance is an indication of increased reducing power and hence increased antioxidant activity.

2.4.3. Cell Culture

Cells were supplied by ATCC and originated from the pleural effusion of a patient with invasive ductal carcinoma. MDA-MB-231 cells measure 18.9±0.4 μm and exhibit strong, spreadable traits. These cells were cultured in DMEM with 2 mM glutamine, 15% FBS, penicillin (100 IU/mL), and streptomycin (100 μg/mL) [15]. Embryos were incubated at 37°C in a humidified atmosphere of 5% CO_2. When cells reached confluency, usually every three days, the culture was passaged into another container with up to $1\text{-}3\times10^4$ cells/cm^2. All cell culture reagents were purchased from Gibco (Carlsbad, California).

2.4.4. Cell Viability Assay (MTT)

CuO/TiO_2 nanoparticles combined with curcumin were evaluated for their effects on MDA-MB-231 breast cancer cell viability using the MTT assay [16]. In this protocol, 5×10^4 cells were seeded in a 96-well plate with 100 µL of culture medium and allowed to attach overnight. The next day, cells were treated with various concentrations of CuO/TiO_2-curcumin nanocomposites (62 to 2000 µg/mL). After treatment, 10 µL of MTT solution was added. Plates were incubated for 4 hours at 37°C in the dark. The medium was then removed, and 100 µL of DMSO was added to each well to dissolve the formazan crystals. Plates were gently agitated before measuring absorbance at 570 nm. Cell viability was normalized to the untreated control. A dose-response curve was then generated from the 24-hour data to calculate the IC_{50}.

2.4.5. Apoptosis Assay

We used 7-Aminoactinomycin D and Annexin V-FITC staining to assess apoptosis in breast cancer cells treated for 24 hours with CuO/TiO_2-Curcumin nanocomposite [17]. We stained cells with the BD Pharmingen FITC Annexin V Apoptosis Detection Kit I and analyzed them using a BD FACSCanto II flow cytometer and FACSDiva software. This process identified cells at different apoptotic stages (early apoptosis, late apoptosis, necrosis, alive, or dead) and allowed accurate assessment of apoptosis onset after nanocomposite exposure.

2.4.6. Wound Healing (Scratch) Assay

The wound healing property of CuO/TiO_2-Curcumin NC was evaluated using a standard in vitro scratch test [18]. MDA-MB-231 human breast carcinoma cells were plated in 6-well culture plates and incubated to ~90% confluence, forming a homogeneous monolayer. After a linear scratch was made across each well using a sterile 200 µL micropipette tip, damaged cells were immediately treated with CuO/TiO_2-Curcumin NC at IC25 (~60.5 µg/mL) and IC_{50} (~121.1 µg/mL) concentrations, as previously determined by an MTT assay. Control wells received no treatment.

Wound areas were imaged at 0 h (T_0) and after 24 h (T_{24}) under normal culture conditions (37 °C, 5% CO_2) using an inverted microscope connected with a calibrated imaging system. Wound areas were measured using the ImageJ software, and percentage wound closure was calculated after Eq. (2).

$$\text{Wound Closure (\%)} = (\text{Area } T_0 - \text{Area } T_{24})/(\text{Area } T_0) \times 100 \quad \text{Eq. (2)}$$

Each condition was examined with three replicates. The mean wound areas at T_0 and T_{24} were measured, and the percentage of wound closure was utilized as a marker of cellular migration and proliferation.

3. Results

3.1. Characterization of Nanocomposite

3.1.1. FTIR and UV-Visible Spectroscopy

FTIR spectroscopy confirmed curcumin's chemical interaction with CuO- TiO_2 NC (Figure 1a). The purified curcumin showed characteristic bands, while the nanocomposite showed metal-ligand complexation and participation of hydroxyl, carbonyl, and aromatic functional groups in bioreduction. New peaks at 939, 869, 643, 568, and 430 cm^{-1} confirm nanocomposite formation.

3.1.2. High-Resolution Transmission Electron Microscopy (HR-TEM)

The images of high-resolution transmission electron microscopy (HR-TEM) (Figure 2) suggest the inhomogeneous distribution of the nominal diameter (10-30 nm) CuO nanoparticles incorporated into the TiO_2 matrix. Curcumin was simultaneously a chemical reducing agent, which favours the reduction of precursor species, as well as a stabilizing ligand, which discourages the coalescence of the nanoparticles, and provides a well-defined interface between the two oxide phases.

3.1.3. Zeta Potential and DLS Analyses

The functionality of curcumin-functionalized CuO-TiO_2 nanocomposite was evaluated in terms of zeta potential and DLS (Figure 3a), which indicated moderate colloidal stability. Reduced electrostatic repulsion is compensated by curcumin biomolecules which are involved in steric stabilization. The positive surface charge that has resulted is a guarantee that proper measurements are obtained.

Dynamic light scattering (DLS) was 217.7 nm with polydispersity index (PDI) of 0.476, which is moderate polydispersity in the green synthesis procedure (Figure 3b). This is caused by the hydration shell around the nanoparticles and the capping of the curcumin resulting in the increased diameter.

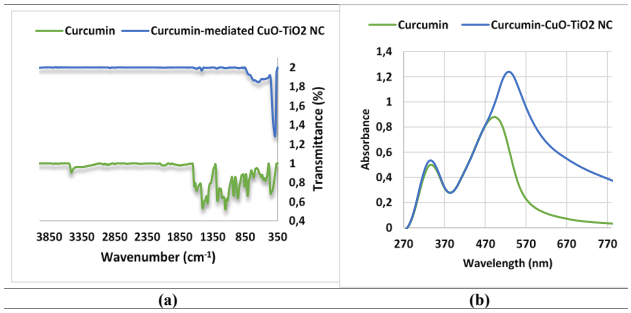

Fig. 1. FTIR spectral analysis (a) and UV-visible spectroscopy(b) of curcumin and curcumin-mediated CuO-TiO_2 NC.

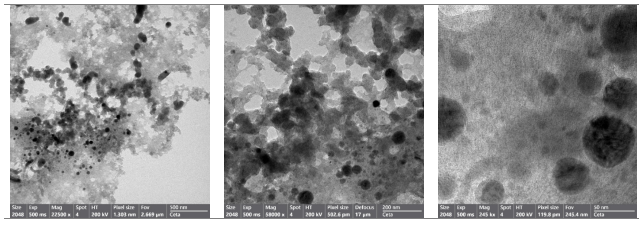

Fig. 2. HR-TEM micrographs of curcumin-mediated CuO-TiO_2 NC.

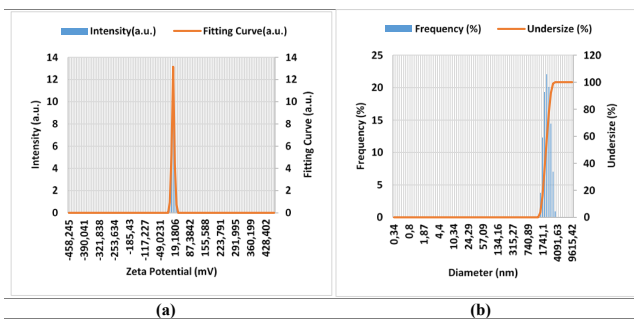

Fig. 3. Zeta potential (a) and dynamic light scattering (b) of curcumin mediated CuO TiO_2 nanocomposite.

3.1.4. Energy-dispersive X-ray spectroscopy (EDX)

The analysis of the energy concentration spectrum of the X-ray dispersers supported the existence of a curcumin-doped CuO-TiO_2 nanocomposites suggesting that titanium (Ti), copper (Cu) and oxygen (O) are the major element constituents. The most common element was Oxygen and the major dominant phase was the TiO_2 lattice. As shown in (Figure 4), culcurcumin was found to reduce Cu^{2+} ions.

3.1.5. Scanning Electron Microscopy (SEM)

SEM examination (Figure 5) indicated that curcumin-mediated CuO-TiO_2 NC consist of irregular large clusters alongside smaller dispersed particles, highlighting the distribution of the two oxides. The structure features porous-like areas with pockets and openings, while the overall morphology is heterogeneous, exhibiting particle sizes from fine specks to larger aggregates.

3.1.6. X-ray diffraction (XRD) analysis

XRD analysis of anatase TiO_2 reveals a main peak at $2\theta = 24.98°$, confirming the coexistence of TiO_2 and CuO phases, confirming nanocrystallinity, and supporting the successful synthesis of nanostructured TiO_2–CuO heterostructures (Figure 6).

3.2. Antioxidant Activity

The researchers compared antioxidant properties of curcumin, Curcumin-Cu-TiO_2 nanocomposite mediated curcumin, and ascorbic acid on the basis of DPPH free-radical scavenging assay. The scavenging activity of curcumin was the strongest, then it was followed by free curcumin and ascorbic acid (Figure 7).

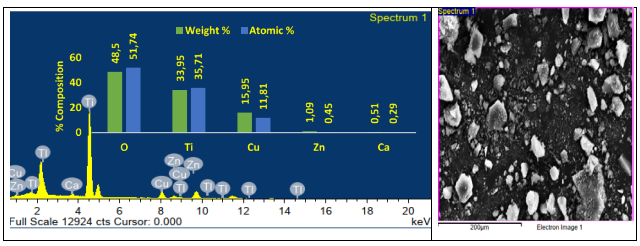

Fig. 4. EDX analysis of curcumin-mediated CuO-TiO_2 NC.

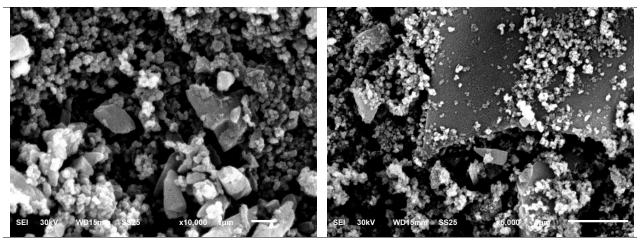

Fig. 5. SEM micrographs of curcumin-mediated CuO-TiO_2 NC.

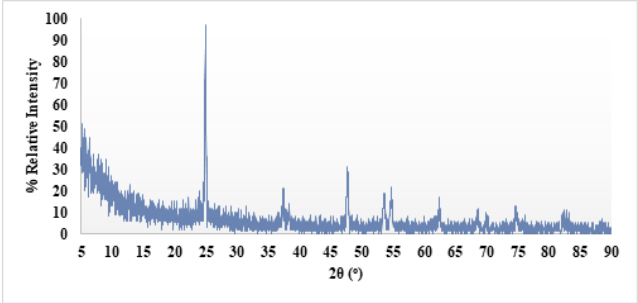

Fig. 6. XRD pattern of curcumin-mediated CuO-TiO_2 NC.

3.3. Anticancer activity

The MTT test indicated that the CuO/TiO_2 -Curcumin nanocomposite had a significant negative impact on the cell viability at an advanced concentration (Table 1). On the other hand, lower concentrations were linked to the enhancement of cell viability recovery, which was the great cytotoxic effect of the compound at high doses.

The resulting nanocomposite, which is an amalgamation of CuO and TiO_2 nanoparticles, exhibited considerable cytotoxic activity with a concentration of 121.1 µg / mL, thus, killing the cells at high concentration and mitigating the effect of cellular toxicity in low concentrations.

The research article shows that increasing concentrations of CuO/TiO_2 curcumin nanocomposite have a significant negative impact on the viability of human cells, especially with higher concentrations, which could lead to suppression of cancer cell proliferation and cause cell death (Figure 8).

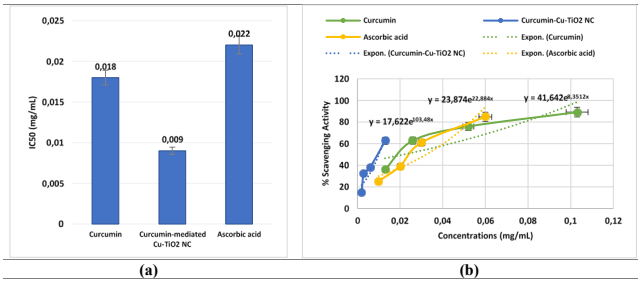

Fig. 7. The outcome of the DPPH test is the antioxidant. (a) IC_{50} values of the samples under test in comparison with ascorbic acid. (b) Plot of the scavenging activity (expressed as a percentage) vs sample concentration.

Table 1. Results of MTT assay of curcumin-mediated CuO-TiO_2 NC.

CuO/TiO_2-Curcumin NC / Dose µg/mL	O.D. (1)	O.D. (2)	MEAN	Cell viability% % (1)	Cell viability% % (2)	Mean Viability %	IC_{50} µg/mL
Control	1.491	1.472	1.4815	100 %	100 %	100 %	121.1
2000	0.123	0.135	0.129	8.3	6.88	7.59	
1000	0.092	0.091	0.0915	6.21	6.14	6.175	
500	0.096	0.089	0.0925	6.48	6.01	6.245	
250	0.147	0.144	0.1455	9.92	9.72	9.82	
125	0.773	0.776	0.7745	52.18	52.38	52.28	
62	1.173	1.191	1.182	79.18	80.39	79.785	

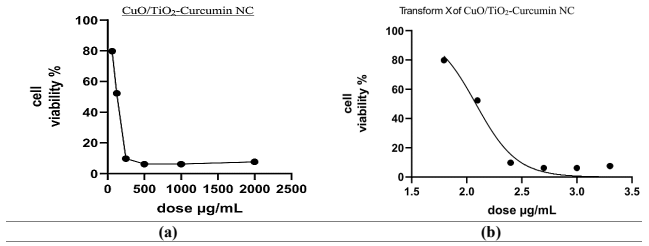

Fig. 8. (a) Dose-dependent action of CuO/TiO_2 -Curcumin nanocomposite on the viability of cells. (b) Representation of transformed dose-response curves that show the effect of CuO/TiO_2-Curcumin nanocomposite on cellular viability.

3.4. Flow Cytometry Analysis of Apoptosis.

The effects of CuO/TiO_2-Curcumin nanocomposites on the MDA-MB-231 breast carcinoma cells were determined by flow cytometry. The findings revealed that increasing concentration of the nanocomposite increased the presence of apoptotic activity. Precisely, an IC_{25} value provoked a premature apoptotic response, and an IC_{50} value provoked an early and late apoptotic subpopulation (Figure 9).

3.5. Wound Healing Potential of CuO/TiO_2-Curcumin NC

The current study examined the effect of the CuO/TiO_2 -Curcumin nanocomposite on cellular migration by use of an in vitro scratch assay. Findings obtained showed that cells in the untreated control exhibited vigorous migration, but on exposure to the nanocomposite, there was an increase in the wound area, which suggested that motility was inhibited (Figure 10).

The nanocomposite demonstrated anti-migratory effects even at 50% IC_{50} concentration, increasing wound area from 1,467,515 µm2 to 1,643,942 $µm^2$ at T24, indicating dose-dependency in cytotoxicity and anti-migratory effect.

4. Discussion

4.1. Characterization of Nanocomposite

4.1.1. FTIR and UV-Visible Spectroscopy

FTIR spectroscopy confirms curcumin's chemical interaction with the CuO- TiO_2 nanocomposite, leading to significant spectral changes and metal-ligand complexation. This confirms its role as a reducing and stabilizing agent in nanocomposite formation, as previously described by Papitha *et al*. [19] and Guo *et al*. [20].

Strong electronic interactions of curcumin, CuO, and TiO_2 contribute to the occurrence of a red -shift. These interactions, in turn, alter the band gap, the energy difference between the valence and conduction bands, facilitating $\pi \rightarrow \pi^*$ transitions (from bonding to antibonding π orbitals) and $n \rightarrow \pi^*$ transitions (non-bonding electron transitions to antibonding π orbitals) [20]. The increased absorbance is therefore an indication of amplified surface plasmon resonance and electron density, thus suggesting an efficient light-harvesting capacity and production of reactive oxygen species after illumination [21, 22]. These changes confirm that curcumin fortifies the nanocomposite, fine-tuning its electronic and optical characteristics. This, in turn, bolsters its potential for use in photocatalytic and biomedical fields.

4.1.2. High-Resolution Transmission Electron Microscopy (HR-TEM)

CuO nanoparticles with a TiO_2 matrix can be seen on HR-TEM imaging, and curcumin is used both as a chemical reducer and stabilizer, which increases surface area, electron flow, and reactivity. These physicochemical advances can be used to provide immense biomedical advantages.

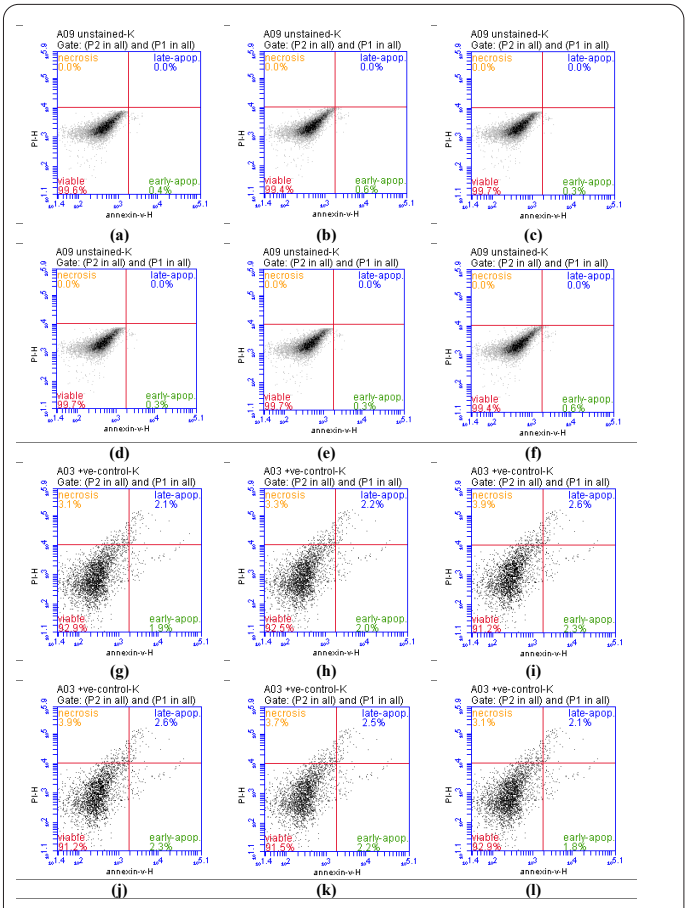

Fig. 9. Apoptosis of MDA-MB-231 cells after exposure to CuO/TiO_2-Curcumin nanocomposites after 24 hours, using Annexin V -FITC/7-AAD dual staining. The representative dot plots of different treatment conditions are given on panels (a–x). Panels a and b: Control cells (untreated) in which most of the cells are alive (Annexin V^-/7-AAD^-). Panels C -H: IC_{25}-treated cells, which demonstrates the rise in early apoptotic events (Annexin V^+/7-AAD^-). Panels I-N: In cells treated with IC50, both early and late apoptotic populations are significantly increased (Annexin V^+/7-AAD^+). Panels o -x: Additional replicates or time changes that demonstrate dose and time dependent apoptosis. The different cellular compartments are determined by each quadrant viable (lower left), early apoptotic (lower right), late apoptotic (upper right) and necrotic (upper left).

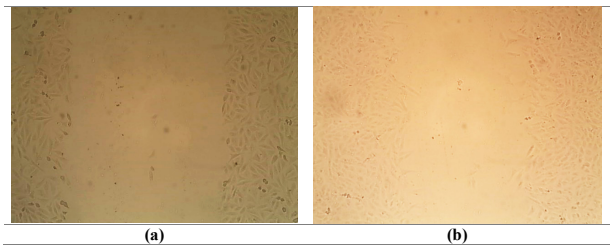

Fig. 10. Effects of CuO/TiO_2 -Curcumin nanocomposites on wound healing in MDA -MB -231 cells, as seen through a scratch assay. (a) Representative image of the wound area at 0 hours (T_0) in the untreated control group (control 0 t up L). (b) Wound area after 24 hours (T_{24}) in the same untreated control group (control 24 t up L2).

Francisco *et al*. [23] noted that there were CuO agglomerates on CeO_2 TiO_2 supports. On the contrary, our green-synthesized system exhibited significantly higher dispersion and stabilization of the CuO species. Xiaoyuan *et al*. [24] reported nonuniformly distributed clusters of CuO with lower phase separation as compared to discrete CuO and TiO_2 phases in conventional syntheses. The method achieves confined embedding and clear phase boundaries.

4.1.3. Zeta Potential and DLS Analyses

Curcumin-functionalized CuO- TiO_2 nanocomposite exhibits moderate stability and polydispersity in green synthesis, making it suitable for biomedical applications due to beneficial interactions at the biointerface, Martínez-Corona *et al*. [25] The study found that zeta potentials of -5.3 to -18.6 mV for bare TiO_2, CuO, and CuO/ TiO_2 synthesized via chemical means showed higher electrostatic repulsion but lacked steric stabilization by biomolecules, Simonin *et al.* [26] found that curcumin-mediated CuO- TiO_2 NC is moderately stable, with enhanced surface functionality and biocompatibility, compared to conventionally synthesized nanocomposites with lower PDIs.

4.1.4. Energy-dispersive X-ray spectroscopy (EDX)

The EDX results confirm balanced molecules and uniform elemental distribution, validating curcumin as an eco-friendly agent in green synthesis.

The superposition of weaker but distinct monoclinic CuO peaks (47.68°, 53.52°, 62.40°; JCPDS 00-037-0447) suggests successful integration of CuO into the TiO_2 matrix. Nguyen *et al*. [27] also observed co-existing anatase TiO_2 and CuO phases in CuO/ TiO_2 photocatalysts. However, their samples showed broader peak distributions and uneven intensity ratios with Cu loading. In contrast, Xiaoyuan *et al*. [24] noted sharper and stronger CuO reflections in thermally and precipitation-prepared composites, indicating greater phase separation and crystallite growth. The reported broadening of the peaks in the diffraction patterns with full-widths of half-maximum values of 0.27 to 0.47 degree indicate the existence of smaller size nanocrystalline domains and more strain in the lattices due to curcumin-medicated synthesis. Huang *et al*. [28] have noted that the effect of calcification on the phase crystallinity and the dynamics of particle growth are also affected. By contrast, our low-temperature, green synthesis provides mixed-phase nanocomposites with reduced crystallite sizes and enhanced oxide-oxide interactions, to form nanocrystalline CuO -TiO_2 nanocomposites that have potential biomedical applications.

4.1.5. Scanning Electron Microscopy (SEM)

Bi-functional properties of curcumin as a reducing agent and capping ligand play a vital role in controlling the nucleation and growth of nanoparticles to produce a less smooth and more heterogeneous surface morphology during green synthesis procedures [27]. The ability to interact with surfaces and successful interaction with copper oxide and titanium dioxide has made the nanocomposite to be promising in drug delivery and catalysis because of its high surface surface area and accessibility.

4.2. Antioxidant Activity

Curcumin also increases the antioxidant potential of the $CuTiO_2$ NC nanocomposite in a synergistic fashion by reacting with the $CuTiO_2$ catalyst that is effective in scavenging the reactive radicals and stabilizing the phenoxyl radicals [29]. This is due to high surface area and enhanced interfacial interaction of the composite [30], redox cycling of copper ions (Cu^+/Cu^{2+}) [31], and the semiconducting nature of TiO_2 that allow electron transfer [32]. Therefore, the composite has stronger radical scavenging activities and significantly lower IC_{50} than free curcumin and ascorbic acid with an IC_{50} of 0.009 mg/mL [33], polymer-grafted CuO/TiO_2 at 0.021 -1 mL -1 [34], curcumin-soybean polysaccharide/TiO_2 bio-nanocomposite at 0.025 mg/mL [35]. Even though previous reports have documented the increase in bioactivity of curcumin-metal oxide nanoformulations [37], Our FRAP assay showed significant reducing capacity (1.645 ± 1.13 at 2.2 mg/mL) compared to curcumin alone, indicating increased electron donation and redox potential from copper ions [38]. The FRAP assay confirmed curcumin's reducing capacity, increased electron donation and redox potential from copper ions, and validated the role of curcumin's phenolic groups in neutralizing radicals [39,40] and Cu- TiO_2's catalytic action; combined, they yield a nanocomposite possessing one of the highest reported antioxidant activities.

4.3. Anticancer activity

The research data reveal positive anticancer properties in curcumin-mediated CuO- TiO_2 NC mainly at elevated concentrations, alongside an adjustable cytotoxic response based on dosage amounts.

The cytotoxic effect of curcumin-functionalized CuO/ TiO_2 nanocomposite was also strong in the MDA-MB-231 breast carcinoma cell line with only about 10 -percent of the cells being alive at concentrations of 1,000-2,000 µg/mL. Later studies revealed that the same nanocomposite inhibited the growth of the MOLT-4 acute lymphoblastic leukemia cell line at a relative higher IC_{50}, indicating that there was an interaction between curcumin and the metal oxide constituents [41].

Besides this, Ahamed *et al*. [42] the protective property of curcumin against the cytotoxicity of CuO nanoparticle in human placental cell model. Their experiment showed that curcumin reduced the toxicity observed, and CuO nanoparticles used alone had high cytotoxic effects at lower concentrations, with an IC_{50} of about 160 µg/mL when used alone at low concentrations, without the addition of TiO_2.

As indicated in the study by Nemr *et al*. [34], the CuO/ TiO_2 -Curcumin nanocomposite synthesized in this case is found to possess stronger cytotoxic behavior in contrast to other nanocomposites analyzed, possibly due to the addition of curcumin. This supplemented activity can be attributed to the ROS modulation and interaction with mitochondrial pathways, thus making the nanocomposite a potential agent in the controlled cellular proliferation applications, including anticancer and antimicrobial therapy.

The cytotoxic action of curcumin-functionalized CuO/ TiO_2 nanocomposites has mainly been attributed to the processes that involve the generation of reactive oxygen species, leading to oxidative stress and eventual mitochondrial damage causing apoptosis [43]. These nanocomposites react with the cellular membranes and cause structural damage [44]. Curcumin has a lipophilic nature that allows it to be absorbed into the cell and increases treatment

efficacy [45]. However, it must also be acknowledged that the MTT assay only measures the activity of the mitochondria and thus fails to measure all forms of cell death.

4.4. Flow Cytometry Analysis Apoptosis.

The use of cellular staining demonstrated specific stages of cell demise, with the exposure to IC_{25} raising the percentage of early apoptotic cell and IC_{50} concentrations raising the percentages of both early and late apoptotic cell populations. What these findings indicate is that the treatment facilitates apoptosis which is probably facilitated by mitochondrial impairment and plasma membrane disruption, hence the significant pro-apoptotic and anticancer effect.

CuO/TiO_2 nanocomposites functionalized with curcumin display a high-level cytotoxic activity, which may be explained by various mechanism pathways, with the main one being the production of reactive oxygen species (ROS) leading to oxidative stress, mitochondrial dysfunction, and induction of apoptotic processes [43]. Additionally, the nanostructures have the ability to perturb cellular membrane on a structural level [46]. This is due to the lipophilic properties of the curcumin that enable increased cellular uptake of the nanocomposite, which leads to increased cytotoxic ability [47]. Apoptosis induction, ROS, and assessment of the mitochondrial membrane potential are essential measures needed to outline the underlying cell death mechanisms [48].

CuO/TiO_2 -Curcumin nanocomposite triggers apoptosis by oxidative stress that causes DNA and protein damage, mitochondrial dysfunction, and caspases -9 and -3. It also suppresses the division of the breast cancer cells thus increasing treatment effects on breast cancer cells [49-53].

4.5. Wound Healing Potential of CuO/TiO_2-Curcumin NC

CuO/TiO_2 curcumin nanocomposite inhibits cell movement, growth, and expansion to cause an increased wound size and reduced cellular adhesion. Even though it exhibits anticancer properties, at highly toxic concentrations it loses its wound healing ability, which is due to the oxidative stress caused by the metal nanoparticles. [54]. Oxidative damage may be enhanced by Curcumin with pro-oxidant activity, which is controlled by metal-oxide nanoparticles. [55]. CuO/TiO_2 -curcumin nanocomposites can be helpful in dealing with aggressive neoplasms like triple-negative breast cancer but due to their nature, they cannot be useful in tissue regeneration and wound healing.

4.6. Mechanistic Understandings of the CuO/TiO_2-Curcumin NC-induced Cytotoxicity and Anti-Migratory Effects.

The cytotoxic and anti-migratory properties of CuO/TiO_2 -Curcumin nanocomposites are a result of interconnected molecular events. Both CuO and TiO_2 nanoparticles have the ability to produce reactive oxygen species (ROS) through a redox reaction or upon illumination [56]. In particular circumstances, curcumin can be involved in the production of ROS. Oxidative stress, therefore, impairs DNA, proteins and lipids, resulting in imbalanced cellular homeostasis and subsequent induction of apoptosis [57]. Radical homeostasis is especially vulnerable to cancer cells either through overabundance or deficit of free radicals [58].

Disordered function in mitochondria is a leading cause of cytotoxicity [59]. As ROS grows, it weakens the mitochondrial membrane and allows cytochrome c and other similar substances to enter the cytoplasm [60]. Activating caspase-9 and caspase-3 initiates the internal pathway that leads to apoptosis [61]. Together, curcumin and arsenic regulate the Bcl-2 family by shifting the balance, causing anti-apoptotic Bcl-2 protein levels to drop and pro-apoptotic Bax protein levels to rise, leading to cell death.

It has been reported that the cell cycle is interfered with by curcumin and metal oxide nanoparticles [37]. Curcumin in most cases causes G2/M checkpoint cell cycle arrest. At the same time, nanoparticles cause damage to DNA and distortion of normal checkpoint controls [62]. This type of arrest inhibits the process of cellular proliferation, hence making cells more susceptible to apoptosis. Thereby, we may explain impaired wound healing in groups treated through such proliferative inhibition [63]. The mechanism of action of the nanocomposite is also supported by the disruption of signaling pathways. Important migratory signals such as PI3K/Akt/mTOR, MAPK/ERK and FAK/Src are highly regulated [64]. The increases of reactive oxygen species and inhibition of these pathways by curcumin disrupts the organization of cytoskeleton, cell adhesion, and remodelling of the extracellular matrix [65]. Curcumin was demonstrated to inhibit matrix metalloproteinases MMP-2 and MMP-9, which are known to play a role in cell invasion in tumors and healing of wounds [66]. This repression also helps to explain the extreme anti-migratory response that is seen in the scratch assay. Further, the design of the nanocomposite is synergistic, which contributes to the increased uptake and bioactivity of cells [67]. The inclusion of nanoparticles enhances endocytic absorption, increases ROS generation with the aid of CuO and TiO_2 constituents, and stabilizes curcumin bioavailability and stability, which increases the biological response [68]. CuO/ TiO_2-Curcumin NC, through mechanisms like oxidative stress and mitochondrial injury, may aid cancer treatments but may limit wound healing due to cytotoxicity.

Conclusion

Curcumin-activated CuO/TiO_2 nanocomposite shows antioxidant, cytotoxic, and anti-migratory properties against breast cancer cells. It activates caspase pathway, regulates Bcl-2 and Bax, and inhibits cancer cell migration. Potential for selective anticancer agents, especially for aggressive triple-negative breast cancer.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request

Authors' contributions

Mustafa Taher Hatem: Research design and supervision; Saja Zubair Dhabian: Perform all laboratory procedures.

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