



Evaluation of antimycobacterial, antioxidant, and anticancer activities of CuO nanoparticles through cobalt doping

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Abstract

Here, we report the synthesis of cobalt-doped copper oxide nanoparticles (CuO–NPs) via combustion strategy with lime juice as a reductant at relatively low temperature of 600 °C and at shorter duration of 3 h. Powder X-ray diffraction (XRD) results revealed that, every compound was in monoclinic structure with space group C_{12}/C_1 (No. 15) and average particle size were found to be 18–21 nm. These NPs were used to evaluate the antimycobacterial activity against “*Mycobacterium tuberculosis H37Rv ATCC 27294*”, “*Mycobacterium abscessus ATCC 19977*”, “*Mycobacterium fortuitum ATCC 6841*”, “*Mycobacterium chelonae ATCC 35752*” and anticancer activity on *MDA-MB-231*. Antioxidant activity was evaluated by DPPH method. The results showed that, doping CuO with cobalt improved the antimycobacterial, anticancer and scavenging activities of CuO–NPs.

Keywords CuO–NPs · Cobalt doping · Antimycobacterial · Anticarcinogenic · Antioxidant

Introduction

Copper oxide (CuO) with a band gap of 1.6–2.2 eV is a highly promising material since it finds applicable in numerous fields (Kadiyala et al. 2012). It was revealed by many researchers that CuO–NPs exhibit anticancer activity against various cancer cell lines (Sathyananda et al. 2020), antimicrobial activity against several bacterial strains (Sathyananda et al. 2020; Ahamed et al. 2014) and also possess antioxidant activity (Sathyananda et al. 2020). Doping of transition metal ions introduces intensified properties in CuO (Chavan 2018). Studies have also shown that cobalt doping led to stable and efficient CuO NPs as catalyst for reduction reaction (Sharma et al. 2017).

Baturay et al. (2016) reported the electrical and optical properties of CuO thin films through nickel doping in their research. Manganese doped CuO NPs have been studied by Singh et al. (2020) for their morphological, optical, magnetic, photocatalytic properties and solar cell efficiency. An enhanced PVA/PEG cross-linked membrane that was loaded with silica nanoparticles have been formed and its characterization was studied by Dilshad et al. (2021) using cutting-edge analytical methods, and corresponding homogeneous dispersal of silica NPs over the membrane was also analyzed. Zinc-doped CuO has been studied by Goyal et al.

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(2020) for their structural, optical, and gas sensing properties. The optical and ferromagnetic properties of Fe-doped CuO has been reported by Mohamed Basith et al. (2013). There are merely very less reports on the biological response of Co–CuO–NPs. The antibacterial activity of synthesized Co-doped CuO nanoparticles was tested against bacteria such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* by Anu et al. (2020). Thakur et al. (2020) have investigated the antimicrobial nature of co-doped (Ag and Co) CuO–NPs. Moreover, the benefits of introducing Co into the metal oxide crystal lattice as far as bio-activities are concerned were also reported. The ways in curbing the disease agents together with the clinical conclusions of ivermectin, doxycycline, vitamin-D, vitamin-C, zinc, and cannabidiol, and the correlations of these molecules towards treating transmissible diseases have been explored by Chowdhury et al. (2021).

In the need of potential antimicrobials and anticancer agents, synthesis of CuO–NPs in different morphologies has gained much importance. Considering the available literature, this research work aims to establish an eco-friendly, and economical route to synthesize single phase pure CuO and Co–CuO–NPs by solution combustion synthesis/SCS making use of lime juice as reductant.

Various characterization techniques were used on the samples. Their antimycobacterial activity was tested against *Mycobacterium abscessus* (*M. abscessus*), *Mycobacterium fortuitum* (*M. fortuitum*), *Mycobacterium chelonae* (*M. chelonae*), *Mycobacterium tuberculosis H37Rv* (*M. tb H37Rv*) by Microplate Alamar blue dye assay (MABA). Cytotoxicity was tested by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Furthermore, the scavenging ability of these samples was measured by the 2, 2-diphenyl-1-picrylhydrazyl hydrate (DPPH) assay.

Significance of the research

For the first time, we report the antimycobacterial activity of pure and cobalt (Co) doped CuO–NPs (Co–CuO NPs). The samples were synthesized by low-cost SCS using lemon juice as biofuel instead of conventional fuels.

The samples exhibited anticancer activity against *MDA-MB-231*. Moreover, the antioxidant activity was found to be exhibited by the samples. Consequently, the experimental results clearly indicated enhanced antimycobacterial, anticancer and antioxidant activities of CuO–NPs upon cobalt doping.

The paper was organized as follows. A detailed introduction on CuO–NPs featuring on anticancer activity, antimicrobial activity, antioxidant activity along with their morphological, optical, magnetic, photocatalytic properties, etc., were elaborated in “Introduction” section. Moreover, the significance of this present research was also elaborated. The

experimental details encompassing the materials, preparation of pure CuO and Co–CuO–NPs, characterization, evaluation of antimycobacterial activity, anticancer activity and scavenging activity were discussed in “Experimental section” section. The attained results and their discussions with the help of structural studies, antimycobacterial response, anticancer response and scavenging response were discussed in “Results and discussions” section. Finally, “Conclusions” section gives the conclusion with few suggestions towards future research.

Experimental section

Materials

Copper nitrate hexahydrate [CuN₂O₉H₆, AR 99%, SD Fine], cobaltous nitrate [CoN₂O₁₂H₁₂, Fisher, AR 98% grade], dimethyl sulfoxide [DMSO, C₂H₆SO, AR 99% Merck], 3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide [MTT, C₁₈H₁₆BrN₅S, 97.5%, Sigma Aldrich], Dulbecco’s Modified Eagle’s medium [DMEM, Gibco], DPPH [C₁₈H₁₂N₅O₆, > 90% Merck], quercetin [C₁₅H₁₀O₇, 3,3’,4’,5,6-Pentahydroxyflavone, 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one, ≥ 95% Sigma], doxorubicin [Hydroxydaunorubicin hydrochloride, C₂₇H₂₉NO₁₁.HCl 98%, Sigma] were procured commercially and fresh lemons were purchased from the local market.

The cell line MDA-MB-231 used for cytotoxicity testing and *M. H37Rv* ATCC 27294, *M. abscessus* ATCC 19977, *M. fortuitum* ATCC 6841 and *M. chelonae* ATCC 35752 were procured from the American type culture collection (ATCC). Isoniazid, Rifampici, Ethambutol, Streptomycin and Levofloxacin were purchased from Sigma, USA. The cell line and the microbial strains were procured from ATCC.

Preparation of pure CuO and Co–CuO–NPs

Synthesis of was carried out as followed in our previous studies (Sathyananda et al. 2020; Prashanth et al. 2017, 2020). In brief, filtered lemon juice (9 mL) and 4.0 g of copper nitrate trihydrate [Cu(NO₃)₂.3H₂O] were taken in 40 mL of double distilled water and dissolved completely under stirring. The petri dish containing the mixture was placed in a preheated muffle furnace (375 ± 10 °C). Within a short while, the solution was boiled to form a gel followed by rapid combustion of the fuel lemon juice. Doped samples Cu_{1-x}Co_xO (x = 0.01, 0.03, 0.05, 0.07 and 0.09) were synthesized following the same procedure. All the samples were calcined at 600 °C for 3 h.

Characterization

All of the materials had their powder X-ray diffraction (PXRD) patterns recorded using a Panalytical X' Pert Pro MPD powder diffractometer with Ni-filtered Cu K radiation ($\lambda = 1.5418 \text{ \AA}$) as the X-ray source. Morphological and compositional studies were done on FE-SEM (Nova Nano SEM-450) coupled with an EDS detector for Elemental compositional analysis (EDAX).

Evaluation of antimycobacterial activity

Antimycobacterial activity of the samples compared to the pathogens mentioned above was assessed by the standard MABA method (Patil and Taranath 2016) with minor modifications. Minimum inhibitory concentration (MIC) was visually assessed based on the color change of Resazurin (from blue to pink), a weak fluorescent dye. A blue color was considered as no bacterial growth, and the pink color was recorded as growth.

Anticancer activity

Anticarcinogenic activity of the samples (ranging from 1 to 320 $\mu\text{g/mL}$) was tested against MDA-MB-231 as followed in the earlier reports (Prashanth et al. 2018; Prashanth et al. 2015; Krishna et al. 2016; Krishna et al. 2017). The percentage of inhibition shall be expressed as per the expression given in Eq. 1 below,

$$\% \text{ of inhibition} = \left(\frac{\text{OD}_{\text{Control}} - \text{OD}_{\text{sample}}}{\text{OD}_{\text{Control}}} \right) \times 100 \quad (1)$$

The percentage growth inhibition was thus calculated and IC50 values were determined accordingly.

Scavenging activity

Scavenging response was assessed by the standard DPPH assay as followed in the earlier work (Rajakumar 1994). DPPH scavenging activity (%) was calculated using Eq. 2 as given below,

$$\text{Scavenging response in } (\%) = \frac{1 - A_s}{A_c} \times 100 \quad (2)$$

where A_c and A_s corresponds to the intensity of peaks for control and supernatant DPPH respectively. Doxorubicin was used as the standard.

Results and discussions

Structural studies

Figure 1 exhibits the PXRD patterns of pure CuO and Co–CuO–NPs. The diffraction pattern clearly showed that all the diffraction peaks belong to JCPDS card No. 80–1268, indicating the monoclinic CuO phase. Further, trivalent cobalt ion ($r_{\text{Co}^{3+}} = 0.61 \text{ \AA}$) was substituted to divalent copper ($r_{\text{Cu}^{2+}} = 0.73 \text{ \AA}$) position in the CuO lattice. The ionic radius of Co^{3+} is smaller than that of the ionic radius of Cu^{2+} ions.

However, 9 mol % cobalt-doped sample showed small impurity line at around 2θ and 37° in the PXRD patterns corresponding to Co_3O_4 . The average crystallite sizes were calculated based on Scherrer equation and found to be in the range of 18–21 nm. Figure 2 shows the FESEM images of pure CuO and Co–CuO–NPs.

The particles were agglomerated in a spherical shape, as shown in these images. The EDS spectra (Fig. 3) revealed all predicted elements Cu, O, and Co along with no additional

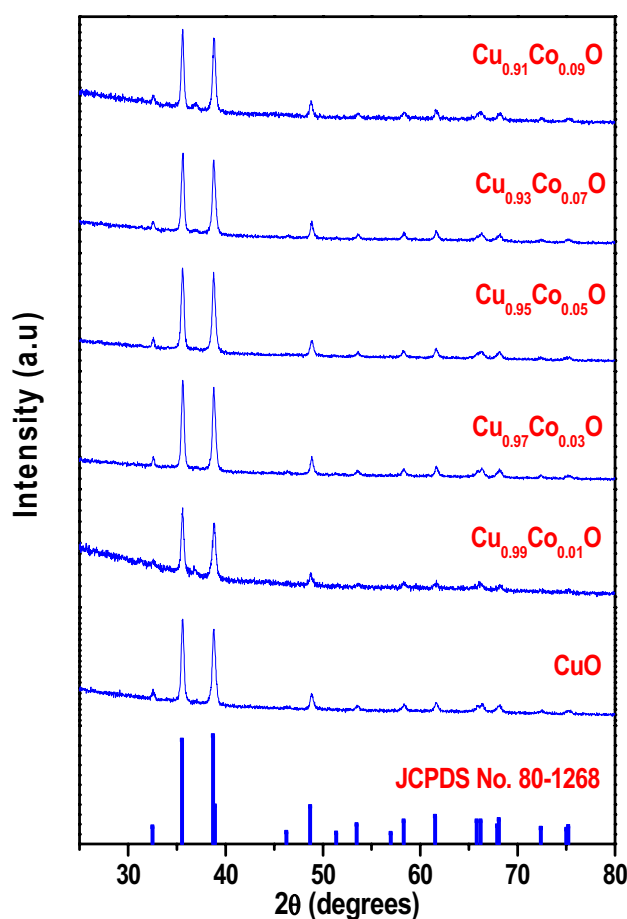


Fig. 1 PXRD patterns of the samples

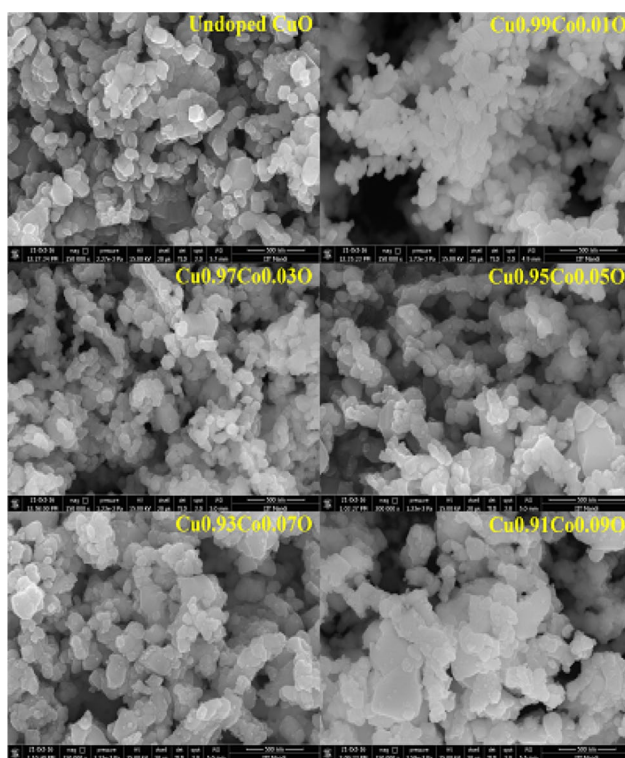


Fig. 2 SEM images of the samples

contaminants. The homogeneous distribution of elements Cu, O, and Co in the samples was clearly confirmed by element mapping as seen in Fig. 3.

Antimycobacterial response

The MIC values of antimycobacterial tests are given in Table 1. As visualized from the results, 9 mol % Co-doped CuO showed better activity than 1 mol % and undoped CuO on *M. fortuitum*. Interestingly, both 1 mol % and 9 mol % Co doped CuO–NPs exhibited quite lower MIC when compared to the undoped CuO on *M. chelonae*.

Though there are no existing reports on the antimycobacterial activity of CuO–NPs, the antibacterial studies suggest free radical generation behind the toxicity of CuO. They produce significant reactive oxygen species (ROS) in terms of superoxide (Meghana et al. 2015). These results indicated the improved activity of CuO NPs (8 µg/mL) against *M. tb H37Rv* when compared with reports of ZnO NPs against the same species (12.5 µg/mL) (Prashanth et al. 2017).

Anticancer response

The MTT results of the samples were presented in Fig. 4 and Table 2, respectively. The optical microscopic images

of MDA-MB-231 cells treated with pure CuO and Co–CuO NPs were given in Fig. 5.

The NPs can suppress and stifle cell viability by different mechanisms such as apoptosis and necrosis (Asha Rani et al. 2009). Apoptosis may be a cell suicide mechanism that controls cell numbers. The apoptotic cascade can be activated by means of outward and inherent pathways (Kumar et al. 2011). The induction of tumor cell apoptosis may be a significant mechanism for an anticancer compound (Frankfurt and Krishan 2003). Copper compounds were employed to treat cancer and several diseases over thousands of years (Hajra and Liu 2004).

Copper is a heavy metal that is toxic to mammalian cells. However, with the advancement of nanotechnology, the NPs can target specific cells with reduced side effects. Results of Nagajyothei et al. (2017) come to an agreement with that of the reports of Mariappan et al. (2011), which indicated that ZnO NPs kill human myeloblastic leukemia cells and are not as much of toxic to normal peripheral blood mononuclear cells.

Apoptosis process characterized by the morphological and biochemical changes and apoptosis of different cells in the same tissue does not occur at the same time. CuO NPs showed a clear cytotoxic effect on HeLa cells in sulforhodamine B assay (Nagajyothei et al. 2017). On MDA-MB-231 cells, our results showed the concentration dependent cytotoxicity and Co–CuO–NPs possessed better anticancer activity when compared with pure CuO–NPs. CuO–NPs' anticancer efficacy, particularly the mechanism of apoptosis in cancer cells induced by CuO–NPs, is still not known completely.

Scavenging response

The scavenging activity of the samples is presented in Fig. 6 and the IC₅₀ values were presented in Table 3. In DPPH, CuO–NPs can transmit their electron density to the free radical situated at the nitrogen atom (Das et al. 2013). These results very clearly demonstrate higher scavenging activity of Co doped CuO–NPs.

Conclusions

Pure CuO and Co–CuO–NPs were prepared by SCS. The physiochemical, structural, and biological characteristics of the produced NPs were assessed accordingly. The results clearly indicated that the doping of Co into CuO had beneficial effect on its antimycobacterial activity against *M. fortuitum*, *M. chelonae* and anticancer activity on MDA-MB-231. Similarly, DPPH scavenging results confirmed enhanced activity of Co doped CuO–NPs over undoped CuO–NPs.

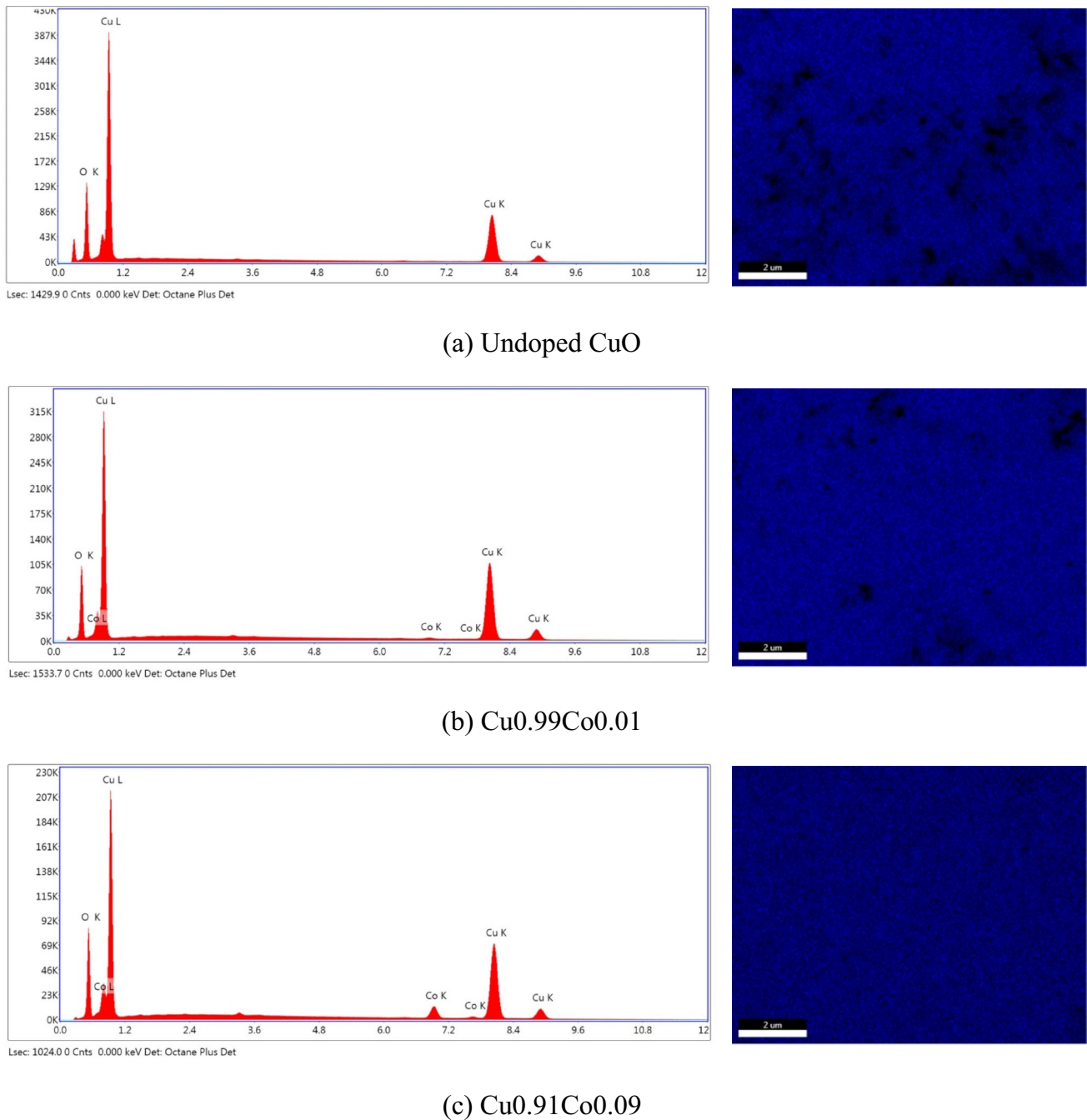


Fig. 3 EDS profile and elemental mapping of the samples

Hence, this study successfully demonstrated the increase in bioactivities of CuO nanostructures through Co doping.

The bacterial infectious diseases are currently one of the serious health problems that have drawn the public attention in worldwide as a human health threat, which extends to economic and social complications. Increased outbreaks and infections of pathogenic strains, bacterial antibiotic resistance, emergence of new bacterial mutations, lack of suitable vaccine in underdeveloped countries, and hospital-associated

infections, are global health hazard to human beings. The interaction of NPs with bio-molecules is an expanding area of research, which is still largely unexplored yet.

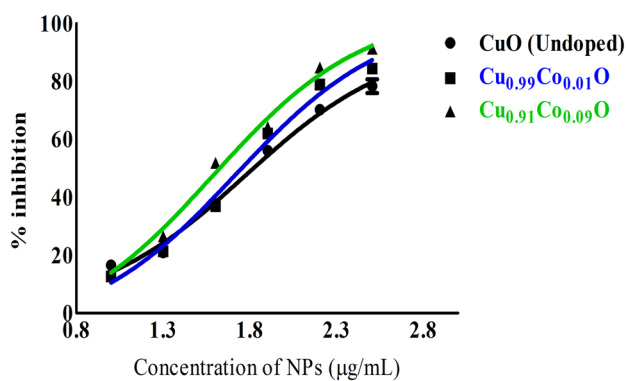
Thus, in the need of potential antimicrobials, and anticancer agents synthesis of metal oxides in different

Table 1 Antimycobacterial response of the samples

Sl. no.	Sample	MIC ($\mu\text{g/mL}$)			
		<i>M. tb H37Rv</i> ATCC 27294	<i>M. abscessus</i> ATCC 19977	<i>M. fortuitum</i> ATCC 6841	<i>M. chelonae</i> ATCC 35752
1	CuO	8	64	32	32
2	Cu _{0.99} Co _{0.01} O	8	64	32	8
3	Cu _{0.91} Co _{0.09} O	8	64	16	8
4	Isoniazid*	3×10^{-2}	NT	NT	NT
5	Rifampicin*	6×10^{-2}	NT	NT	NT
6	Ethambutol*	2	NT	NT	NT
7	Streptomycin*	1	NT	NT	NT
8	Levofloxacin*	0.5	2	0.06	0.06

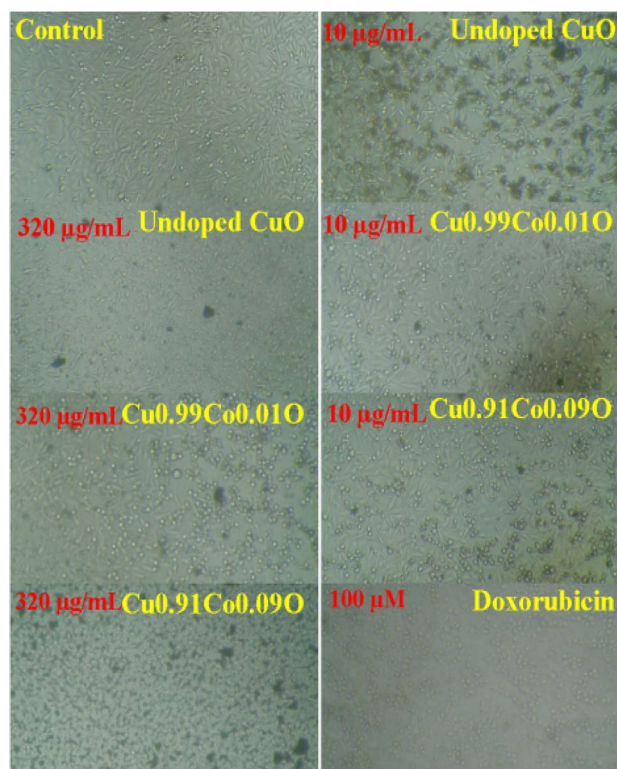
NT not tested

*Positive control

**Fig. 4** Determination of IC₅₀ values in MDA-MB-231 cells**Table 2** IC₅₀ values of the samples

S. No.	Sample	IC ₅₀ values
1	Undoped CuO	60.08 $\mu\text{g/mL}$
2	Cu _{0.99} Co _{0.01} O	52.61 $\mu\text{g/mL}$
3	Cu _{0.91} Co _{0.09} O	39.13 $\mu\text{g/mL}$
4	Doxorubicin (Standard)	19.71 μM

morphologies has gained much importance. Considering the available published literature, this formulated work aims to establish eco-friendly, and economical route of stable undoped and Co-doped CuO–NPs synthesis with wider range of application in medicinal domain. As the attained results are promising, further studies shall be conducted in vivo models to understand the efficacy of undoped/doped CuO–NPs as an anti-mycobacterial, anti-oxidant, and anti-cancer agent.

**Fig. 5** Optical microscopy images of MDA-MB-231 cells upon NPS and Doxorubicin treatment

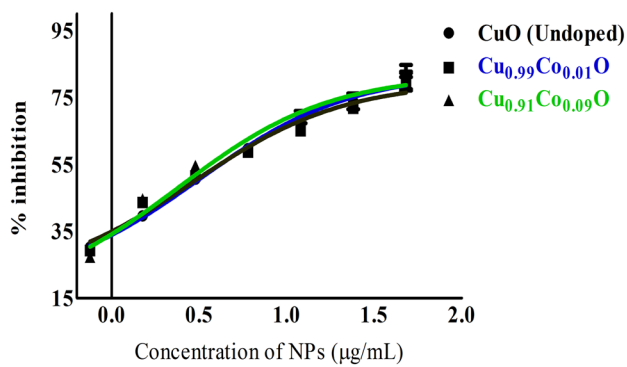


Fig. 6 IC₅₀ determination of DPPH assay of NPS

Table 3 DPPH scavenging activity of the samples

S. No.	Sample	IC ₅₀ values (µg/mL)
1	Undoped CuO	3.16
2	Cu _{0.99} Co _{0.01} O	2.9
3	Cu _{0.91} Co _{0.09} O	2.4
4	Quercetin (Positive control)	2.865

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Availability of data and materials The authors are willing to share the related data and material according to the relevant needs.

Declarations

Conflict of interest The authors declare no competing financial, professional and personal interests.

Consent for publication We consented for the publication of this research work.

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