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REVIEW

Copper nanoparticles and their oxides: optical, anticancer and antibacterial properties

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Abstract

The remarkable link between the strength and location of the Localized Surface Plasmon Resonance (LSPR) peak and the size, shape, and density of Cu NPs has been validated by numerous investigations on the optical properties of copper NPs. The prospect of attaining Cu NPs with tunable LSPR peak may be useful for developing catalysts, biosensors, optoelectronic devices, optical devices, etc. The diversity, complexity and heterogeneity of cancer and bacteria-causing diseases have placed them among the most disheartening infections that threaten the health of humans for so many years. Investigations on copper oxide's optical, anticancer, and antibacterial properties have been carried out on a number of occasions due to their fascinating properties, which have been discovered as a potential therapeutic agent for the treatment of both cancer and bacteria-causing illnesses. Despite these established investigations, little review research has been done on the antibacterial and anticancer properties of copper NPs and their oxides. The optical properties of copper NPs and their oxides are not known to have any recorded review information. The optical characteristics of copper NPs and their efficacy in treating cancer and bacterial infections are highlighted in this review as a result. The mechanism of action of CuO NPson cancer strains and bacterial strains, challenges, and recommendations in the clinical application of copper nanomedicine were also highlighted. The evaluated studies developed copper oxide nanoparticles with enhanced optical characteristics; however, the methods and conditions used in each study's synthesis varied from study to study. Outstanding anticancer and antibacterial properties were exhibited by the studied copper oxide nanoparticles. It is clear that most approaches are still unable to bring copper nanosystems loaded with anticancer and antibacterial agents to the clinic; thus, additional work must be done to solve the major issues of the cancer epidemic and antibiotic resistance.

Keywords Nanoparticles · Copper oxide · Anticancer · Antibacterial

Introduction

Many different fields, including chemistry, physics, nanomedicine, biology, electronics, and others, have shown a great deal of interest in nanoscale materials [1–5]. These structures can be explained by materials with at least one exterior dimension between one and one hundred nanometers [6–12]. Nanomaterials function at this scale as a connection between atomic, bulk, or molecule structures [10–13]. When compared to their bulk counterparts, nanostructured materials have been shown to have unique, distinctive, and interesting features because of their extremely small particle diameters, high diffusion rates, large surface areas with free dangling bonds, and higher reactivity [14, 15].

Metal nanoparticles (NPs), in particular nanostructured materials, frequently exhibit activity that differs from that of

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analogous bulk materials due to differences in size, shape, optical, catalytic, magnetic, electrochemical, thermodynamic, and other features that result in distinctive quantum properties [15–21]. These exceptional qualities have been used in a variety of industries, including construction, textiles, environmental protection, cosmetics, agriculture, aerospace, and others [18]. The biomedical component of these applications is strongly governed by the advancements in nanotechnology. Nanostructured materials have a wide range of applications, including biosensing, imaging, diagnostics, and therapy [19–22]. To improve the standard of living and the survival rate, there is constantly a push to offer adequate medical treatment at a fair price. Nanostructured materials, therefore, provide support to these attempts by setting a personalized platform with the potential of incorporating therapeutics and diagnosis into a single system [22].

Copper oxide nanoparticles (CuO NPs) are one of the most fascinating transition metal oxides with a narrow bandgap (~2.0 eV) and distinctive properties such as high-quality electrochemical activity, suitable redox potential, heightened optical properties, elevated specific surface area, and outstanding stability in solutions [23]. Among the many nanomaterials, copper nanoparticles (Cu NPs) have attracted a lot of attention. They have been studied in a wide range of fields, usually as catalysts in organic synthesis, agriculture, drug delivery, paint, catalysis, food preservation, electrochemistry, agrochemicals, sensors/biosensors, water treatment, energy storage, sensors, sintering additives, semiconducting compounds, in the metal–metal bonding process, capacitor materials, anti-fouling coating, nanometal lubricant additives, biocidal agents and construction materials, anticancer agent, antibacterial agent, etc. [23].

The advent of nanotechnology in the medical industry has enabled an astounding advancement in research efforts utilizing CuO nanoparticles. As a result of the potential to promote electron transfer processes at reduced over-potential and enhanced surface area, several investigations have established their use in the nonenzymatic responsiveness of medically significant analytes [23–25]. CuO nanoparticles have been demonstrated to exhibit pharmacological effect, particularly in the treatment of cancer and bacteria [23]. Because the US Environmental Protection Agency (EPA) has recognized CuO nanoparticles as antimicrobial agents, their use in biomedical devices to prevent bacterial infection has received a lot of interest [26]. From sensing to therapeutics, CuO NPs are being incorporated into all areas for the improvement of novel technologies and to enhance the accessible ones [23, 26].

Research on the optical features of CuO NPs has drawn so much awareness owing to their usefulness in technological applications [27–29]. The capacity of NPs to intensively interact with light can be utilized in amplifying stimulated fluorescence and Raman scattering. For instance,

Metal NPs particularly, copper NPs have been extensively utilized in the amplification of nonlinear optical properties of lithium niobate and fabrication of nonlinear optics devices [28]. Pang et al. generated embedded Cu NPs with spheroidal geometry via Cu^+ ion implantation in lithium tantalate ($LiTaO_3$) crystal [29]. Substantial optical absorption in the visible light band was observed in $LiTaO_3$ with embedded Cu NPs due to the localized surface plasmon resonance (LSPR) effect. The authors confirmed that the diameter of Cu NPs and the correlated linear optical responses could be tailored by adjusting the Cu^+ ion. A previous study has established that the sensitivity of brisant explosives to laser radiation can be heightened with the aid of aluminum NPs [28]. This observation has supported their usage in the generation of optical detonator capsules. In all the aforementioned investigations, the effectiveness of the system function was dependent on the nanoparticle's optical features based on their sizes, structures, radiation wavelengths and shapes. Novel copper NPs with exceptional optical features can be developed if these parameters are tuned.

The ongoing, unchecked multiplication of cancer cells is the basic defect that leads to the development of cancer [30]. Cancer cells proliferate and divide uncontrollably, infecting healthy tissues and organs, and eventually spreading throughout the body. They do this instead of adequately reacting to the signals that regulate normal cell behavior. As a result of accumulating aberrations in numerous cell regulatory systems, cancer cells demonstrate a broad loss of growth control that is reflected in a number of behaviors that set them apart from normal cells.

Studies on laboratory animals as well as epidemiological analyses of the cancer rates in human communities have both helped identify substances, known as carcinogens, that cause cancer (e.g., the high incidence of lung cancer among cigarette smokers) [31, 32]. It is unduly simplistic to speak about a single cause for the majority of cancers because the formation of malignancy is a complex multistep process, and numerous factors may increase the risk that cancer will develop. Nevertheless, it has been discovered that a wide range of substances, including radiation, chemicals, and viruses, can cause cancer in both experimental animals and people. Through DNA damage and mutations, radiation and many chemical carcinogens cause cancer. Since the generation of mutations in important target genes is believed to be the earliest event leading to cancer development, these carcinogens are commonly referred to as starting agents. Sunlight ultraviolet radiation, which is a key contributor to skin cancer, tobacco smoke's carcinogenic compounds, and aflatoxin are some of the primary causes of human cancer (a potent liver carcinogen produced by some molds that contaminate improperly stored supplies of peanuts and other grains) [32]. The main recognized causes of human cancer are

the carcinogens in tobacco smoke, which include nickel compounds, dimethylnitrosamine, and benzo(a)pyrene. In addition to being linked to cancers of the esophagus, oral cavity, pharynx, larynx, and other locations, smoking is the undeniable cause of 80–90% of lung cancers. A remarkable toll for a single carcinogenic agent, smoking is thought to be responsible for close to one-third of all cancer-related deaths overall [31].

Infection by bacteria can affect every organ in a human body [33]. There are specific organs that each type of bacteria prefers to infect over others. Neisseria meningitidis, for instance, can infect the lungs and cause pneumonia in addition to typically infecting the meninges, the protective covering over the central nervous system. Infection of the skin is not brought on by it, though. Staphylococcus aureus, which most individuals carry on their skin or mucous membranes, frequently causes skin and soft tissue infections but also easily travels throughout the body via the circulation and can infect the lungs, abdomen, heart valves, and nearly any other place.

Infection-related cell death brought on by a bacterium or an immune system reaction to an infection are two possible causes of disease [34]. When a disease's symptoms come from the body's efforts to get rid of the germs, antibiotics could be ineffective or even harmful. The systemic inflammatory response syndrome (SIRS), which is typically brought on by a bacterial infection, is an excessive inflammatory response to infection that manifests as the release of numerous cytokines and manifests both infection-related symptoms as well as early hemodynamic instability symptoms [34]. Patients with SIRS have the potential to escalate to sepsis, which can lead to multiorgan failure and death, if left untreated. Even the most potent antibiotics frequently fail to arrest this progression once the cascade of events gets going.

Copper oxide nanoparticles offer a viable alternative in the management of a number of bacterial infections and cancer diseases, especially those associated with multi-drug resistant. Nanoparticles can be used singly or combined with antibiotics providing excellent synergistic effects. There has not been much research on the antibacterial and anticancer activities of copper NPs and their oxides. There is no known review information about the optical characteristics of copper NPs and their oxides. This paper addresses the optical characteristics of copper NPs and their oxides using various synthetic techniques for the first time. A succinct description of some intriguing results from employing copper oxide nanostructures as a therapeutic agent to treat bacteria- and cancer-causing disorders is also provided. Additionally highlighted were the challenges and recommendations in the therapeutic application of copper nanomedicine, as well as the mechanism of action of CuO NPs on cancer strains and bacterial strains.

Optical properties of copper/copper oxide nanoparticles prepared by different approaches

The response a material exhibits to electromagnetic radiations, particularly visible light, is known as its optical property. When light strikes a medium, a number of phenomena, including refraction, reflection, scattering, and absorption take place [35]. In numerous aspects, NPs' optical characteristics are important [35]. Due to the confinement of their electrical properties, they cause a quantum effect, with the potential for variations in form, size, or type to change the color they create. The change in the optical energy band gap, which subsequently impacts the surface plasmon resonance of the nanomaterials, is what causes the size-dependent optical property of NPs [35, 36]. Particularly for the semiconductor-based nanoparticles, it has been demonstrated that the optical band gap generally rises with a decrease in particle diameter [36].

The generation of colloidal copper NPs with the enhanced optical property via pulsed Nd: YAG laser ablation in acetone and water was demonstrated by Tilaki et al. [37]. The optical features and morphology/size of the synthesized NPs were investigated using UV–visible spectrophotometry and transmission electron microscopy, respectively. The copper NPs were observed to be spherical with a mean diameter of 30 nm in water (Fig. 1) and 3 nm in acetone (Fig. 2). Optical extinction of the copper NPs obtained after the ablation exhibits surface plasmon resonance peaks at 575 nm and 626 nm in acetone and water, respectively (Fig. 3). Evaluation of the time evolution of the optical absorption showed a blue shift of the optical extinction maximum, linked to the transition of the particle size distribution. The copper NPs in acetone were stable and yellowish even after ten months. The blue–green-colored solution is transformed to brown–black in the water environment. Complete precipitation of copper NPs which oxidized to copper oxide (II) was confirmed by electron diffraction pattern and optical absorption measurements after two weeks. The oxidation of copper could be ascribed to the reaction of the colloidal particles with dissolved oxygen in the water. This investigation presents a route to regulate the composition and size of copper nanoparticles by adjusting the ablation medium. The authors inferred that the ablation of bulk copper in acetone and water is a flexible and physical approach for the generation of stable colloidal copper and oxidized copper NPs with improved optical properties.

A similar approach was employed by Sadrolhosseini et al. to synthesize copper nanoparticles (Cu NPs) in virgin coconut oil (VCO) via a laser ablation approach [38]. Nd: YAG laser at wavelengths of 532 nm for 5, 10, 20,

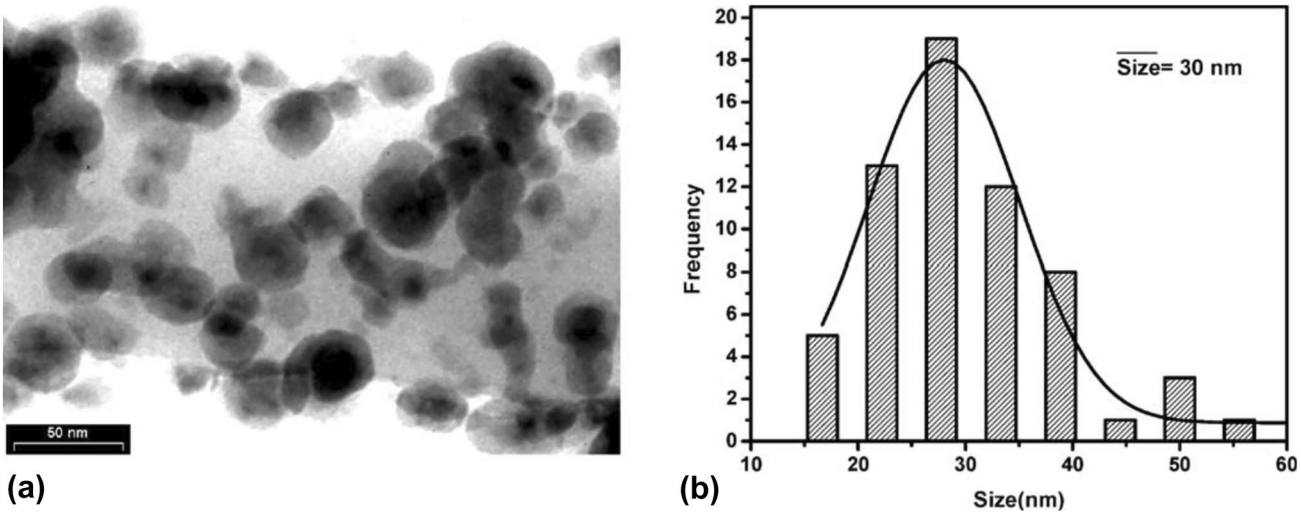

Fig. 1 **a** Typical TEM image and **b** size distribution of colloidal copper nanoparticles prepared in water [37]

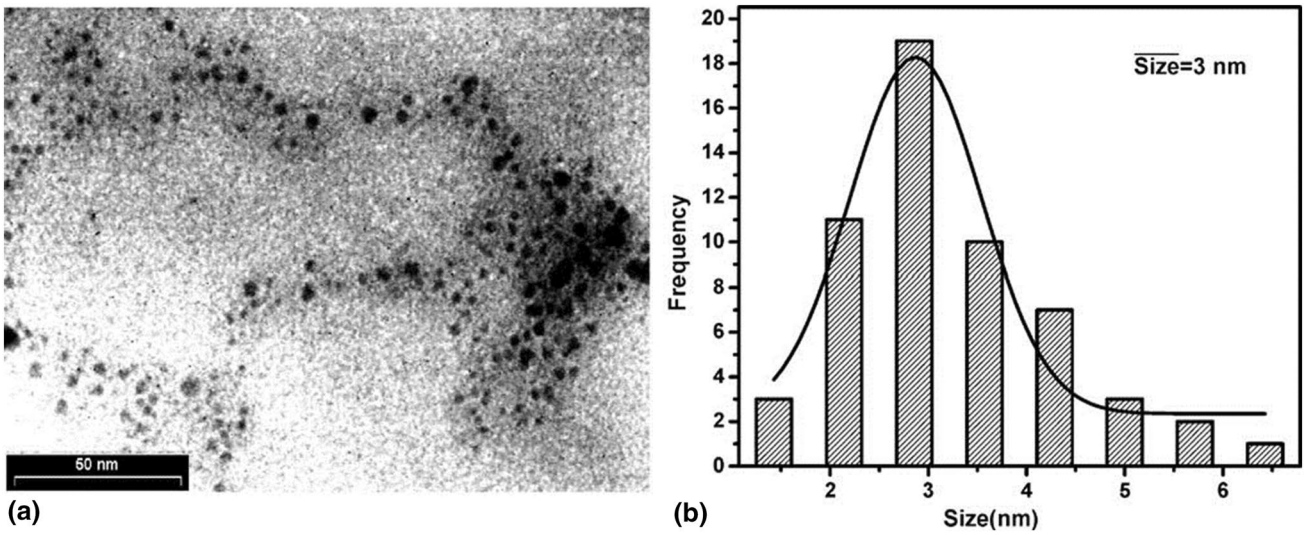

Fig. 2 **a** Typical TEM image and **b** size distribution of colloidal copper nanoparticles prepared in acetone [37]

and 30 min was used to induce irradiation of copper plate dipped in VCO. The TEM pattern and its depiction of the particle size and shape that were distributed in the VCO using the laser ablation technique are shown in Fig. 4. Cu NPs with a spherical shape could be seen on both non-agglomerated and dispersed TEM images. The average Cu NP size diameters for ablation times of 5, 10, 20, and 30 min are 11 nm, 10 nm, 7 nm, and 4 nm, respectively. The ablation time is increased from 5 to 30 min. The interaction between the laser beam and the VCO molecules that capped the nanoparticles determines how small the particles become. The copper cluster crystals were produced from liberated copper atoms, and VCO can cap Cu NPs. The NPs form during the laser ablation process by phase transition and nucleation. The NPs generated in the VCO environment averted the aggregation of Cu NPs. Increment in ablation time led to a corresponding increase in optical properties such as refractive index, absorption and nonlinearity effect. The concentration and volume fraction of copper nanofluid were also observed. Fourier transform infrared spectroscopy analysis confirmed the capping of the Cu NPs with oxygen from the VCO hydroxyl groups. The analysis of the surface plasmon resonance signals show refractive indices that raised from 1.44371 1 0.0034i to 1.44387 1 0.0142i (Fig. 5). Thus, laser ablation is an eco-friendly and green approach for the generation of Cu NPs in VCO.

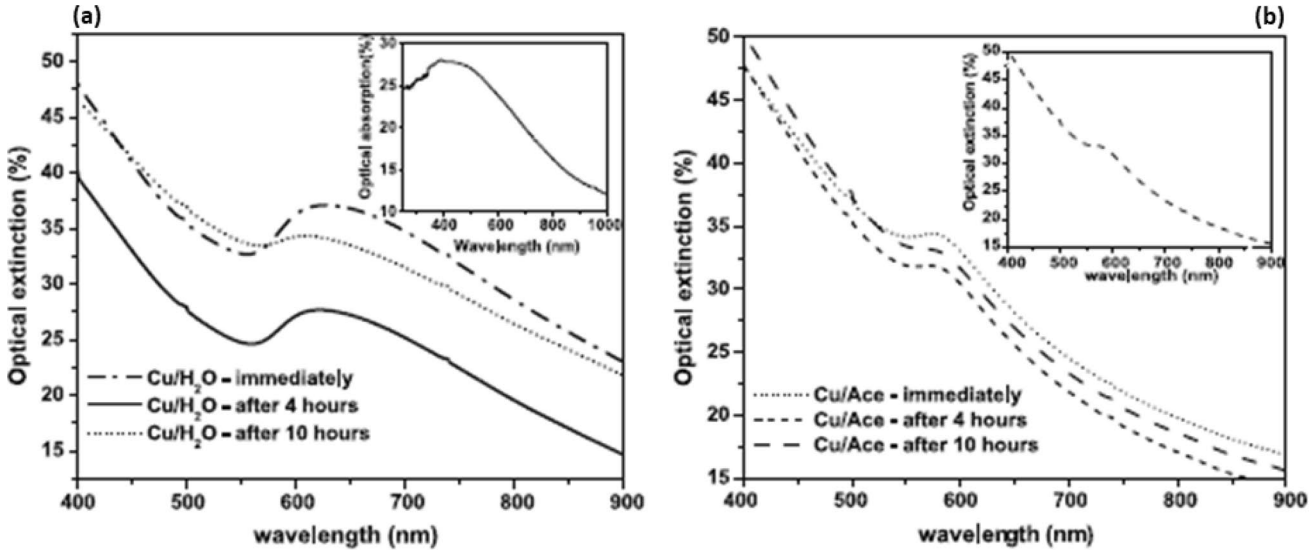

Fig. 3 Optical extinction spectra of colloidal copper nanoparticles synthesized in **a** water at different times; the inset is the optical absorption of the colloidal solution after 2 weeks **b** acetone at different times; the inset is the optical extinction of the colloidal solution after 2 weeks [37]

Another technique that has been used to generate copper or oxides of copper NPs is the liquid-phase reduction approach. Several studies have synthesized NPs with satisfactory stability to oxidation, variable shapes and dimensions, and comparatively lower cost when compared to other metals. The possibility of using copper NPs as additives to compositions for optical detonator capsules based on brisant explosives has been investigated by several studies owing to the aforementioned properties. The efficacy of heating NPs in the matrix of a labile material is controlled by the following features: the absorption efficiency factor of NPs, the laser pulse energy density, the initiating radiation wavelength and the special characteristics of light scattering in the sample [[28, 39, 40]. Kalenskii et al. calculated the spectral dependences of the light absorption, extinction, and scattering efficiency aspects of copper NPs with radii in the range of 400–1100 nm [28] (Figs. 6, 7). For the nanoparticle radii of 10–60 nm, the detection of plasmon maximum on the spectral dependence of the extinction efficiency factor was seen. The authors observed a shifting of the optimal absorption efficiency with an increasing radius of copper nanoparticles toward red wavelengths. The analyses of the results are based on the characteristics of the spectral dependence of the complex copper refractive index. The authors demonstrated that the placement of copper NPs with a radius of 35 nm into a translucent matrix that has a refractive index of 1.54 (secondary explosive pentaerythritol tetranitrate) exhibited an extremely high absorption efficiency factor (2.9) of the second harmonic of a neodymium laser. The studies of Kalenskii et al. imply that the copper NPs are prospective material for utilization in compositions for optical detonator capsules due to their improved optical features [28].

A similar optical study involving the calculation of the Band Gap of the generated copper NPs in the wavelength range of 500 to 650 nm at room temperature was also examined by Mohindroo et al. [31]. The particles exhibited elevated absorption at 550 nm signifying their extraordinary absorptive features. This technique uses water as the medium for copper ions reduction to copper NPs. Starch was used as a stabilizer and reducing agent. The reaction mixture was heated using a microwave for approximately 5 min to achieve the necessary reaction temperature. The adjustment of the pH to alkaline was realized through a 5% NaOH solution. The generation of copper NPs was confirmed by the solution color transformation from blue to yellowish black supported by the UV absorption at 570 nm. Measurement of the stabilized copper NPs optical absorption was estimated at room temperature in the wavelength range of 520–650 nm. The nanoparticles generated from varying concentrations of copper ion revealed some level of absorbance disparity in the visible region, confirming their possible use in the fabrication of absorbing material. The authors observed that factors such as NPs size, NPs shape, and the effective masses of the electron and hole are influenced by the absorption of incident radiation. The optical absorption was seen to increase as the particle size of the copper NPs increased. The estimated Bandgap (1.98–2.02 eV) of the synthesized copper NPs is in line with previously reported values.

Wei and Liu (2017) proposed an effortless pathway for the fabrication of Cu NPs with tunable shape (hemisphere, cube and agglomerate), density and size (42–146 nm) via an electrochemical deposition approach using Na_3CA as a reducing/ capping agent and $CuSO_4$ as a precursor on ITO substrate [41]. The investigation of the synthesized copper

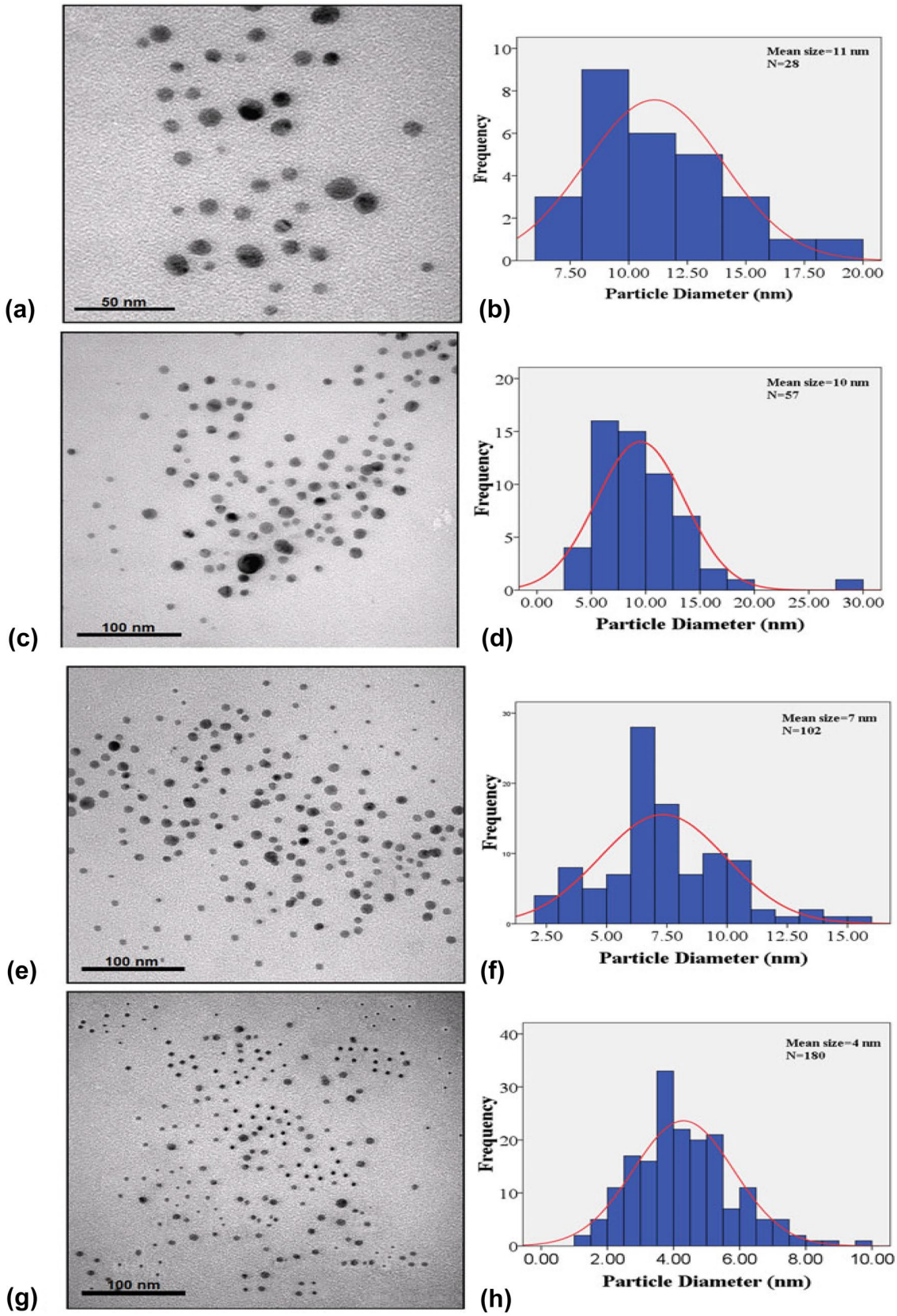

Fig. 4 TEM images and typical of statistical graphs for Cu NPs in VCO in different ablation times. [5 min (**a**, **b**), 10 min (**c**, **d**), 20 min (**e**, **f**), and 30 min (**g**, **h**)]. The particle sizes for 5, 10, 20, and 30 min are 11, 10, 7, and 4 nm, respectively (*N* is the number of particles) [38]

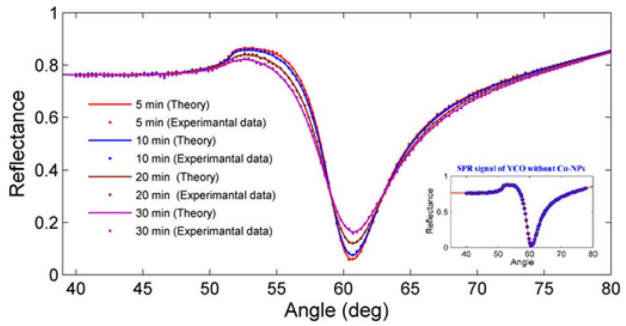

Fig. 5 SPR signal for different concentrations of nanofluid. Angles of resonance for 5 min, 10 min, 20 min, and 30 min are 60.646°, 60.662°, 60.702°, and 60.745°, respectively. The sub-figure shows the SPR signal for pure VCO and the resonance angle is 60.625° [38]

NPs was achieved using TEM, SEM, XRD, SAED, XAES and UV–vis spectrophotometry. The final morphology and composition of the nanoparticles were examined from vital parameters consisting of capping agent, applied potential, Cu^{2+} concentration and deposition time. The results are displayed in Fig. 8. The synthesis of pristine Cu NPs with decreased agglomeration was facilitated by sodium citrate which served as a capping and reducing agent. The slim presence of agglomerated Cu NPs resulted from the inadequate chelation between Cu^{2+} and Na_3CA. The existence of Na_3CA induced the transformation of Cu NPs from cubes to hemispheres because of the strong absorption of Na_3CA on Cu {111} facets, and Na_3CA also play a role in the generation of pristine Cu free from oxidation. Sodium citrate is selectively absorbed on Cu {111} faces rather than {100} faces, hence, influencing the thermodynamic equilibrium in crystal growth. Copper source, deposition time and applied potential influenced the dynamic process and resulted in a controlled growth rate and a number of nuclei. The optical features of the generated copper NPs examined via UV–visible absorption spectroscopy showed LSPR peak intensity and position that are intensely linked to the size, shape, and density of Cu NPs. The absorption band changes considerably based on the degree of agglomeration of the Cu NPs and whether there are copper oxides in the deposits. As the particle diameter increase, the intensity of LSPR peak red-shifts and heightens. Similarly, the intensity of the LSPR peak and promotion of absorption band red-shift can be reduced by the plasmon coupling generated by the decreased particle size. The authors concluded that Cu NPs with tunable LSPR peaks could be useful in designing catalysis, biosensors, optoelectronic devices, etc.

The improvement and integration of Cu nanostructures in solar cells to heighten the solar cell proficiency over the

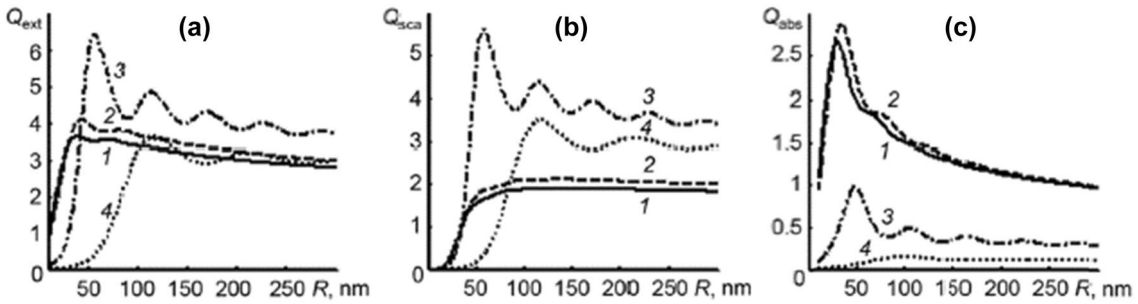

Fig. 6 Dependences of the light extinction (**a**), scattering (**b**) and absorption efficiency factors (**c**) on the radii of the copper nanoparticles calculated for wavelengths of 450 (curve 1), 532 (curve 2), 650 (curve 3), and 1064 nm (curve 4) [28]

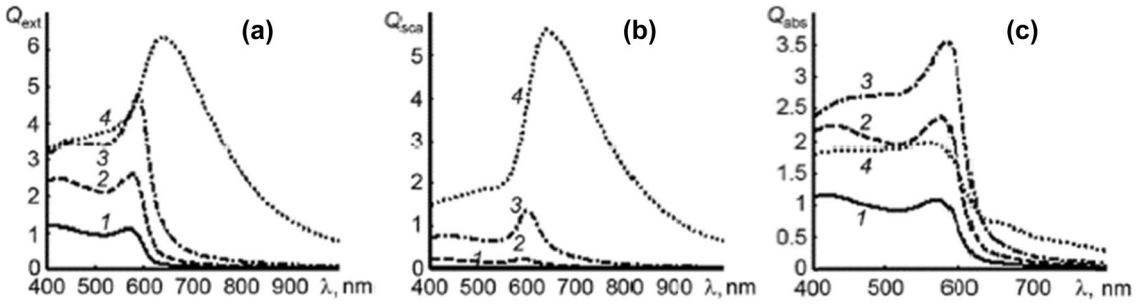

Fig. 7 Spectral dependences of the light extinction (**a**), scattering (**b**), and absorption efficiency factors (**c**) of copper nanoparticles with radii 10 (curve 1), 20 (curve 2), 30 (curve 3), and 60 nm (curve 4) in the medium with a refractive index of 1.54 [28]

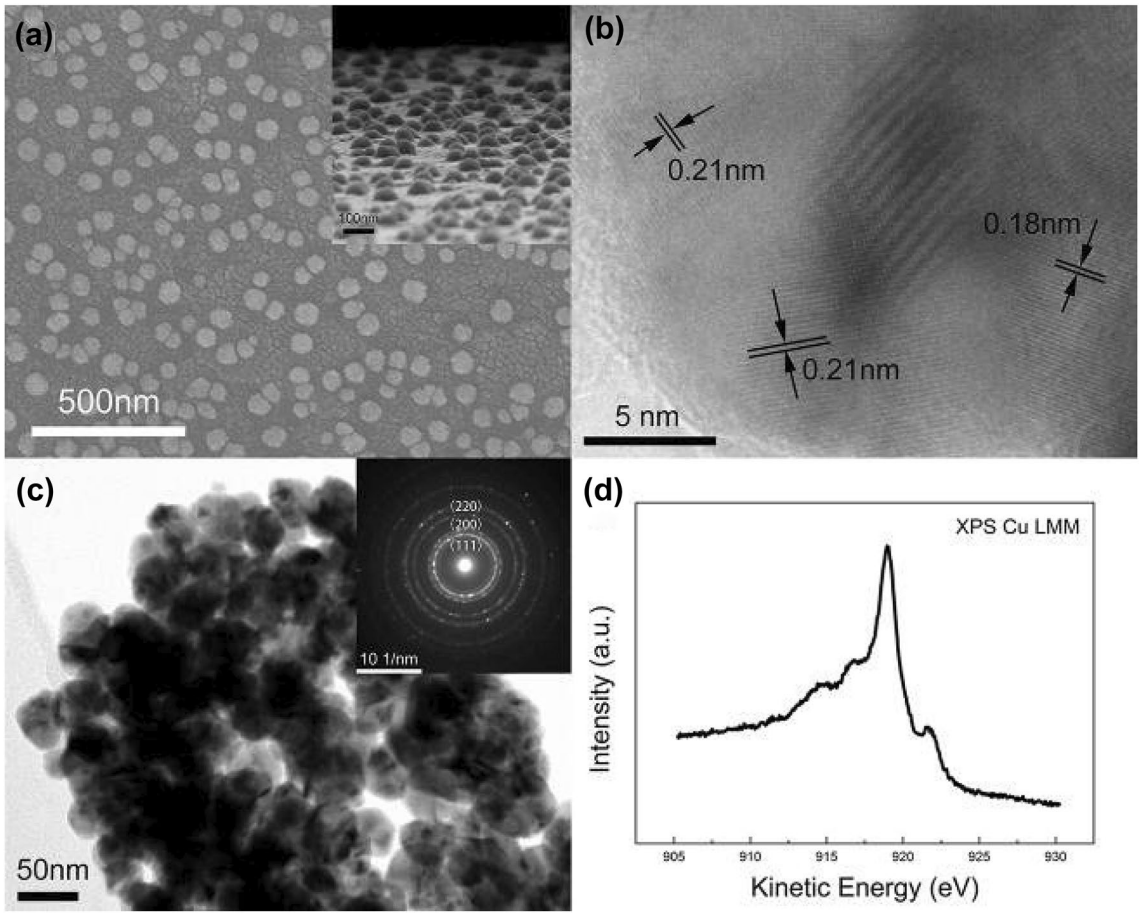

Fig. 8 **a** SEM images, **b** TEM and HRTEM images, **c** SAED image and **c** LMM Auger spectra of Cu hemispheres synthesized with potential of − 0.32 V vs. Ag/AgCl for 1000 s in electrolyte containing 2 mM CuSO4 and 10 mM Na_3CA [41].

entire NIR and visible spectrum are still very challenging. Cu nanostructures have been established as a system that can be effortlessly incorporated with solar cells, in such a way that, its electro-optical features, can be enhanced. Boscarino et al. fabricated copper nanostructures by ablating copper target or solid-state dewetting of 9 nm copper layer (dry) by means of a nanosecond pulsed laser at 1064 nm, in isopropyl alcohol and acetone (wet) [42]. The copper NPs are implanted in an aluminum-doped zinc oxide layer. Then, the optical, electrical and morphological characteristics of the two categories of systems were studied based on their synthesis conditions. The purpose is to correlate the two fabrication strategies and choose the primary requirements to attain the most suitable system for photovoltaic uses. The major disparities, shown by the dry and wet approaches were seen in the size and shape of the Cu NPs. Faceted nanoparticles, with an average particle size of below 150 nm resulted from dewetting in nitrogen, while smaller-sized spherical nanoparticles below 50 nm laser emanated from the ablation process (Figs. 9, 10). The copper NPs generated from the dry system via thermal annealing led to more improved electrical features when compared to the wet system (the obtained sheet resistance of the wet vs dry system is 103 vs. 106 Ω/sq, respectively). Ultimately, the dry system indicates a maximum transmittance of 89.7% at 697 nm when correlated to 88.4% at 647 nm for the wet system in acetone, in addition to 86.9% at 686 nm in isopropyl alcohol (Fig. 11). Also, wet systems demonstrate more heightened transmittance in NUV. The authors concluded that the outcome of this study can be harnessed to enhance the light-harvesting performance of photovoltaic devices.

Biomedical applications

The expansion of sophisticated analytical devices with heightened sensitivity, selectivity, and throughput, when compared to conventional bioanalytical approaches, has been made possible by the current advancement in the generation of nanomaterials with preferred features and biocompatible nature [43]. From diagnosis to therapeutics, nanomaterials can act as a system itself or can be incorporated into

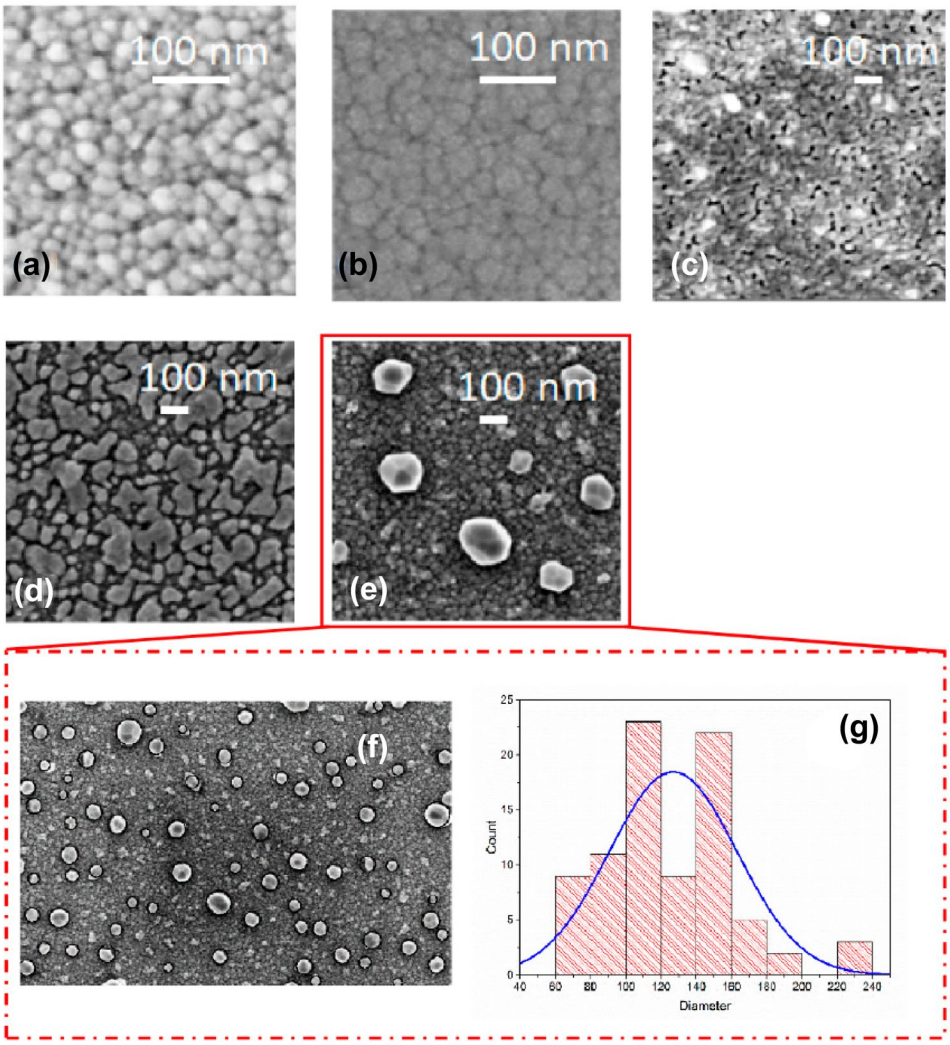

Fig. 9 SEM images of **a** as deposited AZO bottom layer surface; **b** the surface of as deposited Cu on AZO bottom layer; **c** glass substrate/AZO bottom/Cu stack after a thermal annealing at 300 Fig. 2. SEM images of **a** as deposited AZO bottom layer surface; **b** the surface of as deposited Cu on AZO bottom layer; **c** glass substrate/AZO bottom/Cu stack after a thermal annealing at 300 [42]

the system to enhance the performance of the anticipated usage [23]. When compared to other metal nanostructures, copper-based nanomaterials are the most prospective material for application in biomedicine due to several exceptional properties [44]. For example, copper having variable oxidation states has made it extremely reactive, performing a multiplicity of catalytic reactions concerning one/two electronic mechanistic pathways [43]. This characteristic may be utilized to construct and design third-generation sensors for physiologically applicable electro-active analytes such as uric acid, glucose, ascorbic acid, dopamine and L-cysteine [23]. Copper has also been reported to possess inherent antifungal, antibacterial, and anti-inflammatory properties which make copper-based nanostructures an appropriate prospect for generating ointments, microbes-resistant medical devices and bandages. Furthermore, copper is a crucial trace element that is necessary as a cofactor for the standard performance of a range of metabolic enzymes [44]. This feature can be exploited in the synthesis anti-tumor formulations that cause the elimination of tumor/diseased cells by making alterations to the intracellular copper ions levels [45]. The small sizes of the nanoparticles have facilitated their ease of access to the micron-sized human cellular entity and interact readily with the biomolecules intracellularly and on the surface of the cell [45].

Cancer applications

Cancer is one of the principal reasons for the increased rate of mortality and morbidity globally, with roughly 70% of deaths occurring in middle and low-income countries according to the fact sheet of the World Health Organization (2017) [23]. Typical strategies for cancer remedy involve surgery, biopsy, chemotherapy, radiation and catheter application [45]. Chemotherapy is one of the most advocated approaches for cancer therapy, nevertheless, the non-explicitness of the concerned chemicals leads to harsh side effects such as anemia, metastasis, loss of appetite, and nausea with alopecia being the most frequent.

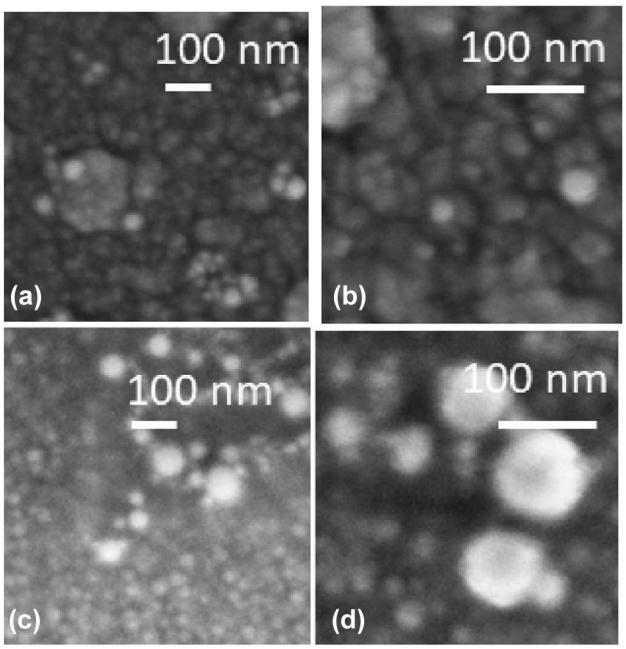

Fig. 10 SEM images, at two different magnifications of Cu nanoparticles produced in acetone (**a**, **b**) and in IPA (**c**, **d**) deposited on AZO bottom layer [42]

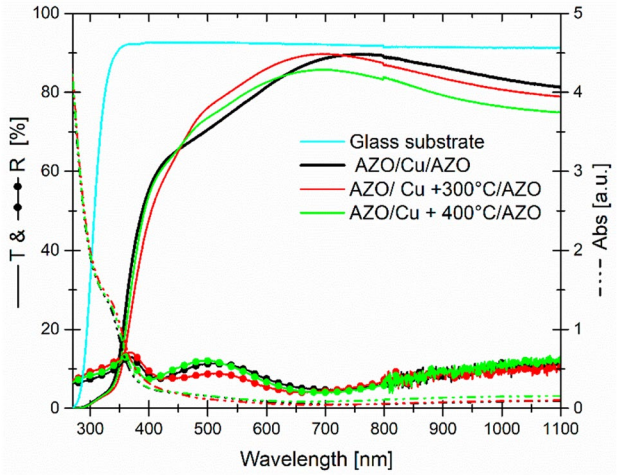

Fig. 11 Transmittance, reflectance, and absorbance curves of dry systems, as a function of the annealing temperature [42]

Besides, resistance to chemotherapeutics drugs which is a major setback develops with time [46]. In recent times, the use of nanomaterials in cancer therapy has sprung up as a substitute for chemotherapeutic treatment. Nanostructured materials have attracted an enormous significance owing to their toxic influence on human beings and other organisms; nonetheless, it is rather difficult for their activity to be restricted to the only tumor mass. CuO NPs have been established as a prospective curative agent that precisely inhibits the growth and metastasis of melanoma and stimulates apoptosis of tumor cells [47]. The anti-tumor feature of copper oxide NPs is due to the crucial function played by copper in regulating the typical endothelial cell growth and the lack of toxicity in copper that resulted from the system possessed by normal cells that help them to evade an elevated intracellular level of copper by means of cytosolic chaperones such as CCS and ATOX1 [48].

In addition, the existence of copper in several drugs has been shown to selectively possess an anti-tumor influence that enhances the suitability of CuO NPs as possible anti-tumor agents. In a matter of fact, chemically modified and unmodified CuO NPs have been utilized in the treatment of a broad variety of cancer variants such as lung, tumor of kidney, liver, brain, eye, breast, and prostate [23]. As soon as these NPs go into the nucleus or cell, it induces a cascade of reactions involving diverse genotoxic reactions such as the alternation of gene expression, mutations, DNA damage and mitochondrial localization [47]. CuO NPs have been reported to distinctively target the mitochondria within the cell and instigate the mitochondrion-mediated apoptosis signaling channel by generating oxidative stress environments in the cell. The investigation of the anti-tumor features of CuO NPs on metastatic lung tumors and subcutaneous melanoma showed that CuO NPs can hinder the metastatic growth of melanoma in tumor-bearing mice [48, 49].

Several studies have shown the possibility of using plant leaf extract as a reducing and stabilizing agent without the addition of any other capping agent. Chinnathambi et al. formulated a novel chemotherapeutic copper Cu NPs containing *Allium noeanum Reut. ex* Regel leaf for human endometrial cancer therapy [50]. The antioxidant activity was investigated using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) test. To compare the anti-human endometrial cancer properties of A. noeanum leaf aqueous extract, Cu $(NO_3)_2$ and copper nanoparticles, MTT analysis was carried out on human endometrial cancer (Ishikawa, HEC-1-A, HEC-1-B, and KLE) cell lines and normal (Human umbilical vein endothelial cells (HUVECs). Experimental results show that the studied copper NPs exhibited elevated anti-human endometrial cancer effects and cell death against HEC-1-A, Ishikawa, KLE and HEC-1-B cell lines. The IC50 of copper NPs and A. noeanum leaf aqueous extract against the HEC-1-B cell line were observed to be 331 mg/mL and 548 mg/mL, respectively; against the HEC-1-A cell line were 356 mg/mL and583 mg/mL, respectively; against KLE cell line were 411 mg/mL and 609 mg/mL, respectively; and against Ishikawa cell line were 357 mg/mL and 560 mg/mL, respectively. Out of the investigated cell lines, the best outcome of anti-human endometrial cancer features of copper NPs was obtained in the cell line of HEC-1-B. This examination demonstrated outstanding anti-human endometrial

cancer prospects of copper NPs containing A. noeanum in the in vitro condition.

The generation of intracellular emergence of reactive oxygen species such as hydroxyl radicals, superoxide anion and non-radical hydrogen peroxide in SKHep-1 and HepG2 cells by CuO NPs in a dose-reliant mode was established by an earlier examination [51]. The reduction of the mitochondrial membrane prospect, the prevailing glutathione formation instigated by the reactive oxygen species detoxification, and a considerable decline in the GSH/GSSG proportion at 10 µg ml^{-1} with both cell line types encountering a shift in the structural surface after the completion of 24 h incubation period was induced by copper nanoparticles (Fig. 12) [51]. Though the usage of NPs in vivo conditions is yet uncertain due to their adverse impact on characteristic cells, some investigators have established fewer levels of toxicity or the absence of toxicity while exploring the anticancer features of CuO NPs. For instance, in separate research, CuO NPs have been ascertained to judiciously incite apoptosis and autophagy in uveal melanoma cells and human renal cell carcinoma cells without impacting retinal pigment epithelium cells and human embryonic kidney cells [52]. The use of nanotechnology to specifically target cancer cells is an important stage of future biomedicines in which there is a singled-out NPs internalization for specifically targeted elimination of tumor cells without negatively affecting the normal cells. This discovery is meaningful because NPs may induce severe harm by penetrating unintended cells. To improve CuO NPs selectivity, an exceptional study was successfully carried out using polyethylene glycosylation NPs. This helps to improve their retention and permeation qualities and effortlessly infiltrates the leaky vasculature of tumor cells by bypassing tight normal cells vasculature. In a particular strategy, Folate receptors, which have been designated to be over-expressed in dissimilar cancers including breast, brain and kidney have been used for CuO NPs targeted delivery [53]. The rudimentary ambition was the conjugation of CuO NPs with folic acids to regularize the advancement of the binding of folic acid–folate receptor on the tumor cells merely as typical cells free from folate

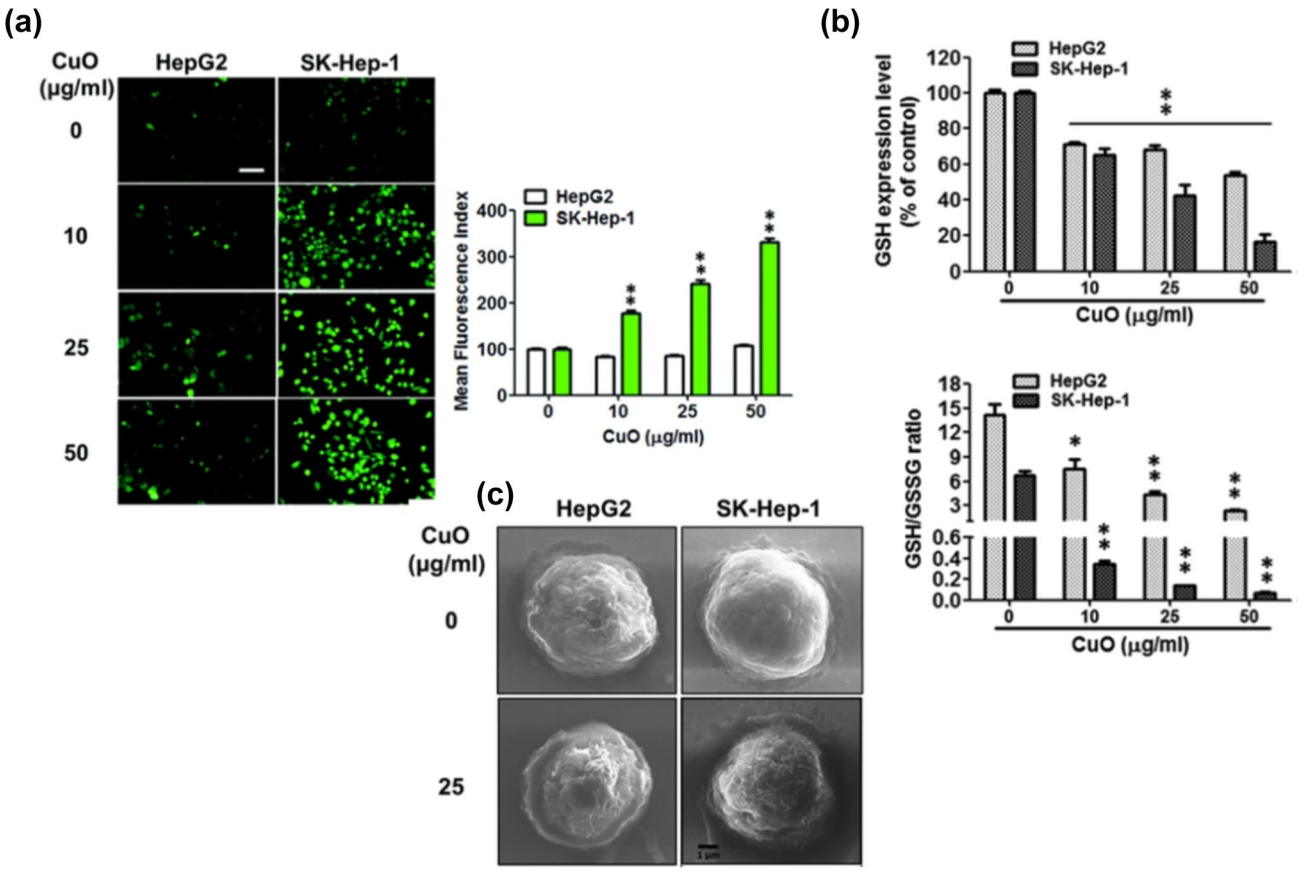

Fig. 12 **a** Fluorescent images of HepG2 and SK-Hep-1 cells after treatment with CuO nanoparticles for 24 h showing ROS generation and quantification of ROS by microplate reader with extinction and emission wavelength of 480 and 570 nm, respectively **b** GSH status analysis of HepG2 and SK-Hep-1 cells after treatment with varying concentrations of CuO nanoparticles for 24 h showing a decrement in the GSH/GSSG ratio. **c** SEM images of cells exposed to CuO nanoparticles for 24 h confirming a change in the cellular morphology of tumor cell [51]

receptors [53]. The in vivo examination shows that the life-cycle of the studied tumor-associated mice boosted up to 19 and 29 days after the injection of CuO and folic acid incorporated CuO NPs, respectively. Regardless, the emergence of tumor, its metastasis and reproduction are instigated by cancer stem cells.

Application as an antibacterial agent

In nations with inadequate socio-economic growth, an eruption of contagious infection is a severe problem in healthcare with a lot of monetary obligations. Most of the infections are induced by food /water/soil-borne pathogens such as viruses, bacteria, and parasites [54]. Distinguishable medications in the form of antibiotics have been produced but microbes typically form a characteristic of inherent resistance toward the diverse categories of antibiotics; therefore, a substitute antimicrobial medicinal agent is greatly needed [54].

The remarkable antimicrobial feature of CuO NPs has attracted substantial interest in manifold biomedical applications such as wound dressing bandages, topical antimicrobial ointments and antimicrobial coating of medical devices [55]. The US Environmental Protection Agency (EPA) has acknowledged copper and its associated compounds as active antimicrobial agents. They have been utilized extensively as possible antimicrobial agents against diverse strains of infectious microbes such as *Staphylococcus aureus, E. coli, Pseudomonas aeruginosa, Pseudomonas desmolyticum, Enterobacter aerogenes, Stenotrophomonas maltophila, Streptococcus faecalis* and *Candida albicans* [23]. Deterrence of biofilm formation and bacterial adhesion on medical instruments is a principal role of CuO NPs. In an investigation, CuO NPs were generated utilizing a liquid-phase chemical preparation technique to examine the effectiveness in thwarting biofilm generation. Heightened inhibitory outcomes on both Gram-negative and Gram-positive bacteria resulted from the addition of a little amount of CuO nanoparticles [56].

Nevertheless, the effectiveness of CuO NPs in eliminating bacteria is greatly dependent on diverse factors such as morphology, particle size, reaction pH and concentration. For example, CuO NPs were seen to be more effective at a pH of 5 in eliminating strains of *Staphylococcus aureus*, while its toxicity was reduced by a more elevated pH [57]. The observation was ascribed to the improved penetration capability of CuO NPs under an acidic environment. CuO NPs were documented to have more heightened toxicity against *L. brevis* and *E. coli* than their micro-scale NPs at a similar concentration in another examination [57]. More smallish sized CuO NPs have been associated with a considerable antibacterial property for the strains of Gram-negative and Gram-positive bacteria [56]. The morphology of the synthesized CuO NPs is one of the major factors that determine antimicrobial activity, although all the structural forms are generally bacteriostatic. The antibacterial features are heightened from all-around bacteriostatic to highly selective as the morphology metamorphoses from cubic to octahedral [58]. This disparity in toxicity is attributed to the CuO nanocrystal's surface facet's dissimilarity which eventually led to the formation of distinct adsorption and desorption propensities toward the bacteria. In a comparative analysis, the structure–function connection was demonstrated for CuO NPs as a function of antimicrobial property [59].

As a function of shape, including nanospheres and nanosheets, Gilbertson et al. established structural property–function (SPF) and structure property–hazard (SPH) connections for nano cupric oxide (n-CuO) [60]. Experimental samples, including filtered and unfiltered ones, were generated in the same way as for the cellular test to assess the interaction of bulk CuO, CuO nanopowder, and CuO nanosheets with E. coli. This was followed by a fixation procedure to preserve the samples for TEM imaging. For each CuO sample and a control sample devoid of CuO, TEM and STEM micrographs were made using meticulously constructed microtome layers (70 nm thick). The interaction of CuO with the bacterial cells (i.e., inside the cell, at the cell surface, and/or penetrating the cell wall) can be seen in Fig. 13 thanks to the use of STEM imaging in conjunction with electron energy loss elemental mapping. Differentiating between items made of copper and those made of other materials was made possible via elemental mapping. Phosphorus, osmium, and copper were each represented by a different color: green, blue, or red. The fixative contains the element osmium, which is present in the copper, which is the element of interest. Phosphorus defines the cell. Micrographs of the control microorganisms are shown in Figs. 13b, c (no CuO exposure). The NaCl salt that was used to make the biological media contains residual copper, which causes background copper readings in the control sample (seen as the red hue). TEM images of the CuO bulk, nanopowder, and nanosheets as they are preserved in the experimental sample are shown in Fig. 13d, g, and j. Individual or smaller aggregates on the nano size are seen in addition to massive aggregates of each substance. TEM images of bacteria exposed to CuO bulk, nanopowder, and nanosheets are shown in Figs. 13e, i and k, respectively. Figures 13f, h, and l show micrographs with the elements mapped to help identify the locations of the CuO materials. CuO is present inside the cell in each of the three exposure conditions, as indicated by the arrows. CuO nanosheets interact with the cell wall in Fig. 13k, with one sheet clearly displayed puncturing the cell wall (inset). Although the micrographs show potential CuO internalization for all of the samples examined here (bulk, nanopowder, and nanosheets), there are distinct differences in how each sample interacts with the bacterial cell. First,

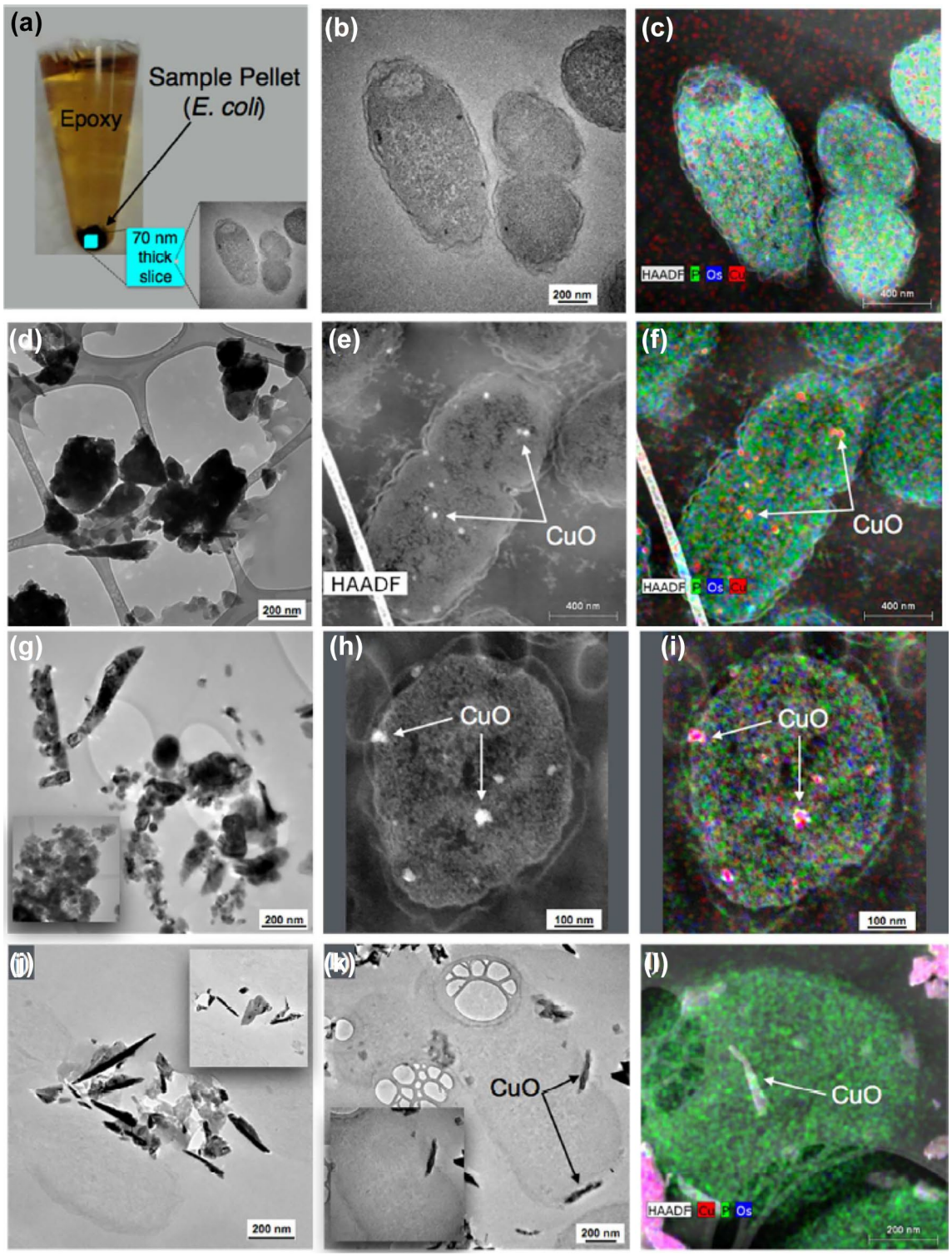

Fig. 13 **a** The experimental sample prepared for imaging of microtomed slices. The cells are pelleted, fixed, and cut into 70 nm thick slices using a microtome for imaging. TEM and STEMEELS micrographs of *E. coli* **b**, **c** control (no CuO exposure), **e**, **f** bulk CuO, **h**, **i** CuO nanopowder, and **k**, **l** CuO nanosheets. **d**, **g** and **j** show aggregates of bulk, nanopowder, and nanosheets, respectively. HAADF indicates the TEM mode used to collect the respective image. Green, red, and blue were used to differentiate between the cell (phosphorus), copper, and osmium (used in the fixative), respectively (**c**) [60]

absorbed material is either in the form of single particles or nanoscale aggregates. Larger aggregates and non-nano-sized particles do not enter the cell and instead remain outside. Second, rather than maintaining their sheet-like shape, the CuO nanosheets appear to be rolled up (this is supported by the Df ~ 1, which indicates a rod-like scattered aggregate morphology). The accumulation of n-CuO at the cell wall is also clearly demonstrated by strong evidence, as seen in Fig. 13k. Application of kinetic models to the toxicity data demonstrated that trends in observed reaction cannot be fully described by surface area alone, elucidating the underlying mechanisms of action to further explain the shape-dependent behavior. The combined results help to clarify additional steps toward the regulated design of ENMs.

A more heightened biochemical reactivity of the nanosheets was depicted by the chemical mechanistic pathways during the GSH oxidation assay. A better-improved oxidation propensity was displayed by the studied CuO nanosheets when correlated to the other two categories. The detailed mechanistic pathway involving basic facts about the toxic nature of the CuO NPs has not been explored thoroughly and is a matter of intense discussion. A previous analysis implied that the toxic feature of CuO NPs stems from the contact elimination pathway in which the discharge of copper ions sequentially induces the formation of reactive oxygen species and a corresponding disturbance of the cellular membrane [43, 61, 62]. The redox cycling between Cu (II) and Cu (I) assists in the inducement of the superoxide species that stimulate the biomolecule's degeneracy. CuO NPs react with endogenic hydrogen peroxide to develop hydroxyl radicals in a strategy comparable to the Fenton reaction [25]. Nevertheless, CuO NPs-mediated inactivation of certain cellular enzymes crucial for metabolic pathways have been documented [61]. The function of copper oxides in the contact-killing of bacteria has been examined comprehensively by a previous study [63]. A substantial disparity in the contact-killing behaviors existing between copper and its oxides has been ascribed to the distinct copper ions released per unit surface area. The observed discharged copper ions disparity was due to the antibacterial effectiveness seen for the optimal discharged pure copper followed by copper (ii) oxide and copper (i) oxide. Another study investigated the effectiveness of copper oxide NPs generated via Prunus africana bark extract (PAE) and Camellia sinensis extract (CSE) against carbapenem-resistant bacteria [63]. The agar well diffusion approach was used to examine the susceptibility of the CuO NPs. The green synthesized CuO NPs display the utmost expansion suppression zones of 30 mm with MIC between 30 and 125 µg/ml ranges against MDR bacteria.

Possible mechanism for anticancer activity of CuO NPs

On the use of CuO NPs, numerous studies have been published. However, it was unclear exactly how these NPs' activity was being controlled by signaling or other mechanisms. This is how the mechanism is summed up:

According to research, the main cause of cell death brought on by Cu/CuO NPs is the production of reactive oxygen species (ROS) (Fig. 14(1)). The hub of cellular signaling and energy metabolism is the mitochondria [65]. Reactive oxygen species (ROS) and nitric oxide (NO) buildup and oxidative stress are linked to the disruption of this organelle [64]. In response to black-bean-extract-mediated CuO NPs, HeLa cervical cancer cells showed altered mitochondrial structure together with a loss of membrane potential, indicating mitochondrial damage [66]. In addition, CuO NPs produced from black bean extract and the leaves of Ficus religiosa, E. globulus, and P. hexapetalum dramatically raised the intracellular ROS level [67]. In the case of A549 lung cancer cells, HeLa cervical cancer cells, and MCF-7 breast cancer cells, respectively, it was accompanied by the loss of mitochondrial membrane potential [66]. The uptake of CuO NPs increased the NO level in MCF-7 and HeLa cancer cells in addition to the generation of ROS [68]. On the other hand, research has indicated that cancer cells may have higher levels of ROS due to their high metabolic activity. Therefore, reducing the ROS level is a wise strategy in this regard. CuO NPs had an antioxidant function as demonstrated by their free radical scavenging ability [69] (Fig. 14(2)). According to a recent assessment, cancer cells' ROS levels were modestly elevated, which encouraged them to evolve antioxidant defenses that increased their sensitivity to outside stimuli [65]. This trait encourages the generation of ROS. Since the production of ROS is essential for the development of cancer, lowering its production might help prevent cellular transformation. To choose a CuO with the right properties, it is crucial to consider the role of ROS in disease states. Overly high levels of oxidative stress cause cell damage and death in living things. DNA damage, which is characterized by DNA fragmentation [65] (Fig. 14(3), can be brought on by a high intracellular ROS level. DNA fragmentation is thought to be the cause of the oxidative stress caused by A. indica leaf CuO NPs in cancer cells [70]. The results of a recent investigation that looked at the genotoxicity of commercial CuO NPs are consistent with this conclusion [71]. In contrast, it was discovered that the antioxidant-rich CuO NPs made from M. chamomilla flower extract interacted directly with the plasmid, which is thought to be involved in DNA breakage [69]. Tumor suppressor

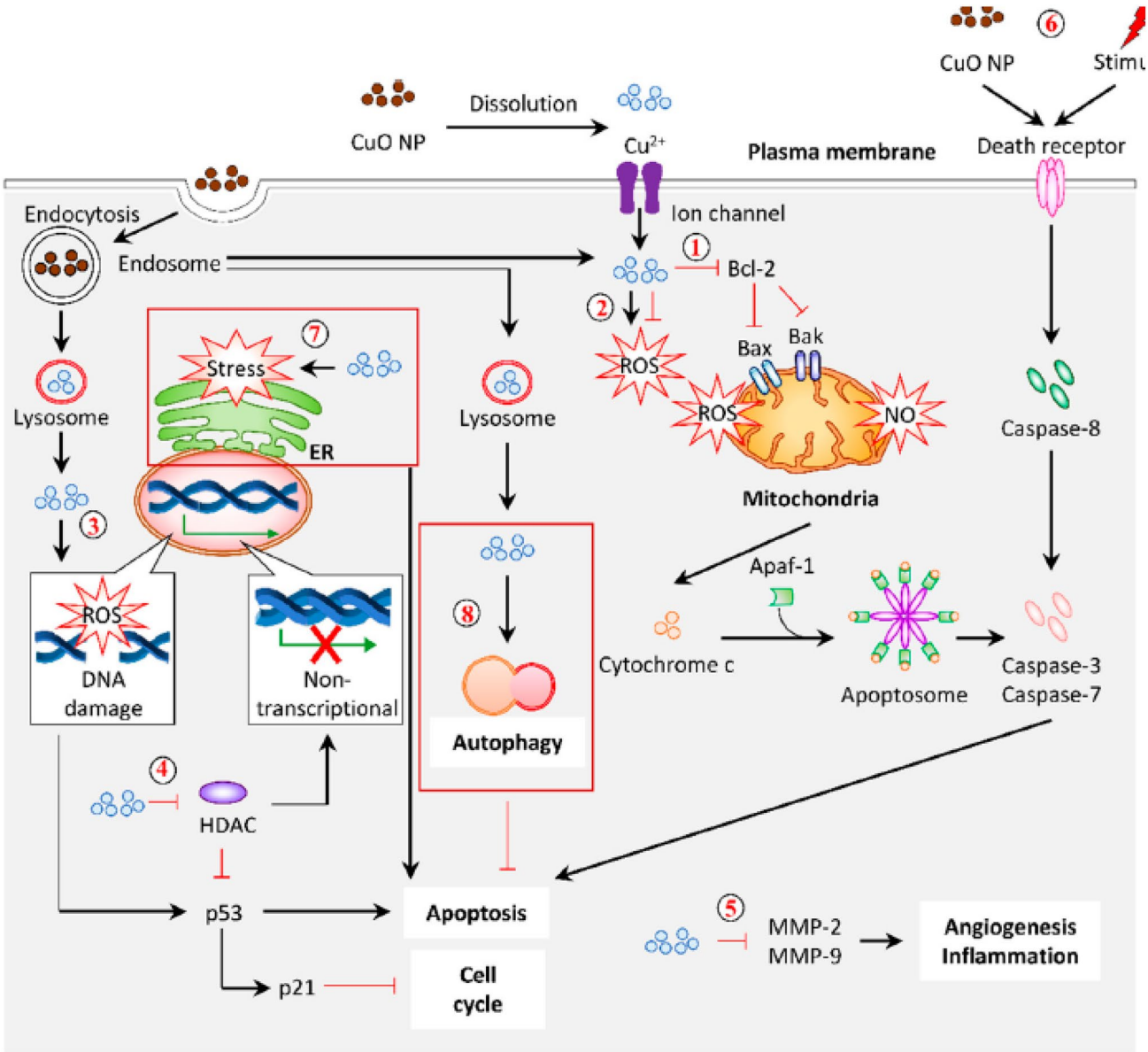

Fig. 14 Graphical representation of the proposed mechanism for anticancer activity in response to Cu Cu/CuO NPs O NPs [64]

genes (p53 and p21) are expressed in response to DNA damage, and their overexpression stops the cell cycle and triggers apoptosis [72]. The exposure of NPs encourages DNA damage, which ultimately causes the cell cycle to stop. Cell cycle arrest at the G2/M phase was induced in MCF-7 breast cancer cells and A549 cancer cells, respectively, during the biofabrication of CuO NPs [73]. The expression of p53 was also increased [65]. According to a study, the various histone deacetylase (HDAC) enzymes, which create a non-transcriptional compact chromatin structure by removing the acetyl group on histones [74] (Fig. 14(5)), are responsible for controlling the level of tumor suppressor gene expression (p21 and p53) as well as the level of oncogene, MMP-2, and MMP-9 expression in response to plant-based CuO NPs. In reaction to cellular stress and DNA damage, apoptosis is a planned cell death mechanism controlled by a number of caspases [75]. Both intrinsic and extrinsic routes are capable of producing this cell death. The intrinsic pathway entails the mediation of proapoptotic proteins, the expression of Bak/Bax on mitochondria by an antiapoptotic protein, Bcl-2 to cause membrane permeabilization, and the release of cytochrome c to create the apoptosome with the Apaf-1 adaptor and pro-caspase-9 [76]. In terms of the extrinsic apoptotic pathway, the contact between the ligand and death receptor on the cell surface activates caspase-8.

Major executioner caspases like caspase-3 and caspase-7 will cleave as a result of both intrinsic and extrinsic apoptosis being activated [75]. CuO NP treatment significantly upregulates the expression of intrinsic apoptotic mRNA and protein, including Bax, cytochrome c, caspase-9, and caspase-7, according to studies [68].

In parallel, the CuO-NPs-treated cells expressed more caspase-8, indicating the capacity to start extrinsic apoptosis [68] (Fig. 14(6)). It appears that both intrinsic and extrinsic routes were used by the plant-mediated CuO NPs to trigger apoptosis. The elevation of ER-stress-related mRNA and protein expression, which implicates the numerous pathways involved in causing apoptosis [77], was recently found to be able to initiate commercial CuO-NP-induced apoptosis (Fig. 14(7)). Lipidomics was used in a prior study to show how the HCT-116 colon cancer cell line's lipid profile changed after being exposed to commercial CuO NP [78, 79]. Apoptosis, which may aid in cancer cell death, is interestingly not promoted by the CuO NP treatment but rather autophagy (Fig. 14(8)). In fact, this autophagy induction may serve as a cellular defense against the toxicity of CuO NPs, as CuO-NP-treated cells successfully undergo apoptosis when autophagy is inhibited pharmacologically or genetically [80]. Overall, the CuO NPs have shown to have anticancer effects through a variety of signaling pathways, including ROS production, antioxidant property, cell cycle arrest, apoptosis, and autophagy. Depending on the method and source of Cu/CuO NP synthesis as well as the cell line used, the mode of action of CuO NPs may change. Studies on NPs currently only pay attention to their use and outcomes, not their molecular mechanism or signaling. For instance, it has been shown that CuO NPs have an antiangiogenic effect on human breast tumors, but their molecular mechanism is yet unknown [81]. To further understand how these NPs function in various situations and cell types, it is essential to unravel their precise molecular mechanisms [82–85].

Antibacterial mechanism of action

Copper kills bacteria by a complex process that is still being studied. According to published research, copper interacts with microorganisms on various cellular levels, which all lead to cell death. These interactions include denaturing of nucleic acids, protein modification, and cell membrane permeabilization. A system that requires energy to function transports copper ions that have been released from the surface through the cell membrane. Once the intracellular concentration of copper ions reaches a critical level, the plasma membrane's barrier function starts to decline. Nucleotides, amino acids, and potassium leak from the membrane as it becomes more permeable [86, 87]; Warnes et al. [88] exhibited fast membrane depolarization and loss of membrane integrity upon exposure to metallic copper surfaces, resulting in cytoplasmic buildup of free radicals. Reactive oxygen species (ROS) are another way by which copper harms cell membranes (ROS). Due to their ability to give and take electrons, copper ions can undergo oxidation, changing from Cu+ to Cu2+. This causes oxidative stress to membrane lipids (lipid peroxidation), amino acids in proteins, and nucleic acids; catalyzes the generation of ROS like hydroxyl radicals (HO) and superoxide anions (O2); and causes oxidative deactivation of enzymes [88–94].

Coordination chemistry is a method used to ensure that essential metals are needed for appropriate protein activity [94, 95]. To catalyze cytotoxic processes, they serve as cofactors and are essential. Metallochaperoning proteins, membrane transporters, and metalloregulating proteins are among the proteins that regulate the activity of intracellular metal ions. Certain elements of protein complexes, such as oxygen (O), nitrogen (N), and sulfur (S), can bind to metal ions [96]. Proteins' atomic structure causes them to prefer certain metal ions for binding [97]. However, if metal homeostasis is disrupted, metal ions like Cu2+ can compete with other necessary metals like iron ions (Fe2+) and prevent proteins from associating with the correct cofactor, hence reducing protein activity [94]. When copper ions attach to the amino acid cysteine, for example, the HIV-1 protease is blocked [98]. One other illustration is the inhibition of protein tyrosine phosphatases by the oxidation of cysteine residues on the phosphatases by copper ions (74). The isopropylmalate dehydratase enzyme in *E. coli* is also rendered inactive through a process known as mismetallation, which involves the displacement of iron atoms from the enzyme's iron-sulfur clusters by copper ions [99, 100].

Clinical translation of copper nanomedicine: obstacles

Clinical translation of copper nanoparticles and other nanomedicine faces challenges, such as being time- and money-consuming. Clinical translation is hampered by biological difficulties, biocompatibility, regulatory issues, toxicity, legal and intellectual property (IP), and overall cost-effectiveness in comparison to conventional medicines [101]. Despite their efficacy, these barriers prevent copper nanoparticles from being widely used in the market today [102]. The clinical translation of copper nanomedicine should take a variety of factors into account. The first is the nanopharmaceutical design, which can be listed as follows: physical and chemical stability, biodegradability, complex formulation design, and administration route The difficulties associated with large-scale production, such as reproducibility and cost, should be addressed, as should the difficulties

associated with quality control assays for characterization, such as polydispersity, scalability complexities, incomplete contamination purification, consistency and storage stability of the final product, morphology, and charge [103, 104]. Preparation techniques are required to consistently produce high-quality, repeatable nanoparticulates in large, scalable amounts from batch to batch.

Recommendation

As it becomes evident that most methodologies still cannot translate anticancer and antibacterial-loaded copper nanosystems to the clinic, more research becomes necessary to address the enormous problem of antibiotic resistance. According to the Gawande et al. advice, the community currently has another responsibility, which is to "make more efforts for clinical translation of nanoparticles and takes their advantages in a more comprehensive way" [43]. An interdisciplinary approach to creating innovative protocols, tests, and infrastructure for large-scale manufacture of nanoparticulates is unquestionably necessary for successful clinical translation. We, therefore, call on all academic and pharmaceutical industry professionals with backgrounds in medicine, biology, pharmaceutics, toxicology, and engineering to make greater efforts to address these issues [105, 106].

The coordination of academic institutions, pharmaceutical manufacturing facilities, and research facilities that are highly skilled in analyzing nanoparticles platforms, conducting preclinical studies, and creating and executing clinical trials for nanoparticulate platforms are some potential strategies to expedite the transition of advantageous nanoparticles to clinical applications [68].

Conclusion

The development of innovative antimicrobial copper nanoparticles and their applications have been the subject of a number of recent studies, which have been covered in this chapter. Over the years, there has been a notable advancement in the biomedical application of nanostructured materials. CuO NPs contain a variety of distinctive physicochemical properties that can be modified at different levels to achieve previously unrecognized and desired particular qualities. This study's extensive literature evaluation demonstrates that local plasmon surface resonance gives copper nanoparticles (NPs) enhanced optical properties. Due to the close relationship between the size, shape, and density of Cu NPs and the intensity and location of the LSPR peak, it is possible to achieve Cu NPs with customizable LSPR. Numerous applications, including catalysts, biosensors, optoelectronic devices, optical devices, and nonlinear optical materials, have made use of these properties. This review also provided a brief summary of many studies that investigated the use of copper oxide nanostructures as a treatment for cancer and bacterial infections. CuO NPs have been proven to be a promising alternative for the treatment of bacteria- and cancer-causing cells. The potential and prospects for developing CuO NPs as a future medication in cancer and pathogenic therapy, are still highly promising. However, the clinical translation of copper nanoparticles and other nanomedicine faces challenges, such as being time- and money-consuming due to biological difficulties, biocompatibility, regulatory issues, toxicity, legal and intellectual property (IP), and overall cost-effectiveness in comparison to conventional medicines. To solve the aforementioned issues with antibiotic resistance, further research must be done.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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