TOPICAL REVIEW

Synthesis, microbial susceptibility and anti-cancerous properties of copper oxide nanoparticles: review

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Abstract

Use of Nanoparticles in the diagnosis of cancer and treatment of Cancer is being rapidly studied and developed. The present cancer chemotherapy agents are not much selective in differentiating between cancer cells and normal cells and often lead to development of drug resistance and severe side effects. This has prompted the need to study other potential anticancer agents like metallic oxide nanoparticles, with emphasis on their synthesis and application in the treatment of cancer by designing targeted delivery system to tumour and cancer cells [Vinardell and Mitjans 2015. Nanomaterials, 5, 1004–1021, Valodkar et al 2011. Mater Chem Phys, 128, 83–89]. In this review paper an attempt has been made to study various methods of preparation of Copper Oxide Nanoparticles, their characteristics and the detailed microbial activities and anti-cancerous properties of these differently synthesized Copper Oxide Nanoparticles.

Introduction

The metal nanoparticles earlier used to be most prevalent in material applications like fabrication of microelectronic circuits, sensors, photoelectric devices, fuel cells, coating of surfaces against corrosion, and catalyst. Today with the growth of nanotechnology, nanoparticles are being studied for their extensive use in biological applications like bio-sensing, imaging, drug delivery and antibiotics.

Of many nanoparticles under study, Copper Oxide Nanoparticles also referred to as Cupric Oxide Nanoparticles is the most prominent nanoparticles studied for its anti microbial and anti cancerous properties. This extensive studies and use may be attributed to its cheaper cost of synthesis as compared to Silver [1–3] or Gold [4, 5] nano-particles and longer shelf life or stability than nano-particles of other transition metal oxides like Cobalt [6], Zinc [7, 8], Chromium [9–11] and Cerium [12, 13]. Copper nanoparticles and it’s embedded form with Chotisan pluronic hydrogels have been synthesised and studied for antibacterial and antifungal properties [14–17] however Copper is easily oxidized to form Copper Oxide. It is the ease of oxidation of Copper which has led scientists to study either Copper Nanoparticles synthesized in presence of polymer or surfactant as stabilizer [18–20] or Copper Oxide Nanoparticles for its anti-bacterial and anti-cancerous properties. The latter route is often more appealing due to ease of synthesis and often better experimental results.

Copper Oxide is simplest member of the family of copper compounds and exhibits a range of potentially useful physical properties. The US environmental protection agency in the year 2008 approved copper alloy-based products in human use [21]. Copper Oxide Nanoparticles has been found to exhibit higher toxicity due to the smaller size and larger surface area [22]. Copper Oxide Nanoparticles have been characterized for its antimicrobial properties and was also found to be highly sensitive to prokaryotes, eukaryotes and aquatic fish than other metal nanoparticles [23–26].

Various studies are being carried out to study the effect of Copper Oxide Nanoparticles on pathogenic microorganisms i.e. (Antimicrobial efficacy [22–25,27]) and its cytotoxicity against cancer cell lines [27–31]. Copper Oxide being a transition metal oxide exhibits oxidative stress on cytoplasmic membrane which is the main reason for its cytotoxic property even in low dose. Copper Oxide Nanoparticles synthesized using various
methods exhibit different characteristics and have different impact on cell lines or we can say that they have different level of cytotoxicity on cancer cell lines [27–33].

Synthesis and characterization of copper oxide nanoparticles
Various methods have been adopted for preparation of Copper Oxide Nanoparticles, each yielding variation in characteristics and particle size. Copper Oxide Nanoparticles synthesised via precipitation method using Cupric acetate monohydrate as starting material and sodium hydroxide as reducing agent yielded leaf like structure at lower pH of 9–11 and needle like structure at higher pH of 12 and more [27]. Copper Oxide Nanoparticles of crystalline nature was obtained by reducing copper (II) acetate with sodium hydroxide as exhibited by XRD pattern and TEM and SEM images with particle size of 22 nm, 23 nm and 35 nm as confirmed by Siddiqui et al Maqsood Ahmad et al and Laha Et al respectively in different experiments [23, 30, 31]. Another method of thermal decomposition of the precursor Cu(SO_4)(OH)_6 (brochantite one of cupric sulphates) made by sonication of CuSO_4.5H_2O (Copper (II) sulphate pentahydrate) and Na_2CO_3 (Sodium carbonate) yielded Copper Oxide Nanoparticles of spherical shape with diameters ranging from 50 to 100 nm [22].

Various attempts have been made to synthesize Copper Oxide Nanoparticles using green method [28, 29]. Ficus religiosa leaf extract [28] and black bean extract [29] have been used for reduction of Cupric Sulphate to yield Copper Oxide Nanoparticles of 37.6 nm and 26.2 nm spherical shaped particles respectively. In another green method, the extract of heart wood of P. Marsupium was used for phytogenic reduction of Copper sulphate to yield Copper Oxide Nanoparticles [24]. Pterocarpus Marsupium also called rasayana in Ayurveda system of medicine has been studied for its antibacterial properties [34]. The Copper Oxide Nanoparticles obtained by this green synthesis were found to be of spherical shape with diameters of 20 nm to 50 nm as analysed by TEM. Green synthesis of Copper Oxide Nanoparticles using CuCl_2.2H_2O (Cupric Chloride dihydrate) and aqueous leaf extract of Malva sylvestris along with sodium hydroxide yielded Copper Oxide Nanoparticles of 5 nm to 30 nm as analysed by SEM [25]. Floral extract of Magnolia champaca [26] and leaf extract of O. Sanctum [35] (Tulsi leaves) with Eugenol as capping and stabilizing agent was used to prepare Copper Oxide Nanoparticles from copper acetate as starting material. Copper Oxide Nanoparticles with average crystalline size of 35 ± 6 nm was obtained using the floral extract of Magnolia champaca [26] and were studied not only for its toxicity effect using DPPH ABST Test, but also evaluated for toxicity on aquatic life form using zebra fish embryos as study model [26]. Flower shaped Copper Oxide Nanoparticles with particle size of 250 nm were obtained using O. sanctum leaf extract and eugenol, with eugenol playing major role in obtaining flower shaped structure. The Copper Oxide Nanoparticles thus obtained were further studied for photocatalytic and antimicrobial activity [35]. P Yugandhar et al [36] in their green synthesis used S. alternifolium stem bark extract to prepare Copper Oxide Nanoparticles from Copper Sulfate. The Copper Oxide Nanoparticles obtained was spherical in shape as confirmed by TEM analysis with size ranging from 5 nm to 13 nm and average size of 17.2 nm as calculated using Debye–Scherrer formula from XRD analysis. The Copper Oxide Nanoparticles obtained were further studied for anti-microbial effect against seven bacterial and five fungal strains and its cytotoxic potential was studied using MDA-MD-231 Human breast cancer cell line.

Neran Ali Thamer & Nadia Tareq Barakat synthesized Copper Oxide Nanoparticles from leaves of cordia myxa L. To heated plant extract, CuSO_4.5H_2O solution was added and left at room temperature overnight. Change in colour to green from brown indicated the formation of Copper Oxide Nanoparticles which was further confirmed using various characterization techniques like XRD, UV–vis spectrometry, SEM, FTIR and Atomic force microscope [33].

Anti-microbial propensity and toxicity studies
The Copper Oxide Nanoparticles synthesised by various methods whether by regular chemical method or by green method did show anti-microbial properties. Anti-bacterial property is indicated by basic disc diffusion test against Shigella (gram −ve) and Listeria (gram +ve) of Copper Oxide Nanoparticles synthesised using Malva sylvestris [25]. The Copper Oxide Nanoparticles synthesised via green method using P. Marsupium showed antimicrobial property when tested against S. epidermidis, B. cereus, S. aureus and P. vulgaris indicative of resistance to both gram +ve and gram −ve bacteria [24]. Higher sensitivity was attributed to smaller size of the particle in addition to antibacterial properties of P Marsupium. MIC at concentration as low as 6 ug ml⁻¹ was observed against E. coli and K pneumoniae when tested with Copper Oxide Nanoparticles synthesized this way as compared to the antimicrobial studies used Copper Oxide Nanoparticles synthesized via precipitation method [23] which demonstrated MIC of E. coli at 31 ug ml⁻¹ and 250 ug ml⁻¹ for E. faecalis with least sensitivity to K pneumoniae [23]. Maqsood Ahmed et al [23] studied the anti-bacterial properties of Copper Oxide nanoparticles synthesised by precipitation method. Seven human gram negative bacteria Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Enterococcus faecalis, Shigella flexneri, Salmonella typhimurium, and Proteus vulgaris along with one human gram positive bacterium Staphylococcus aureus were used for
anti-microbial studies by well diffusion method and MIC using broth micro-dilution method. The zone of inhibition was highest for *E. coli* & *E faecalis* and lowest for *Klebsiella pneumonia* at all concentrations of Copper Oxide Nanoparticles of 150 ug, 250 ug, 500 ug and 750 ug. MIC studies too exhibited anti-bacterial property of Copper Oxide Nanoparticles in line with well diffusion method with MIC concentration of 31.5 ug ml<sup>-1</sup> for *E. coli* & *E faecalis* and 250 ug ml<sup>-1</sup> for *Klebsiella pneumonia*.

The effect of pH and shape of the Copper Oxide Nanoparticles crystals on microbial propensity was demonstrated when antibacterial activity test results of Copper Oxide Nanoparticles against Gram Positive (MRSA, B Subtilis) and Gram Negative (Salmonella paratyphi, K pneumonia, E aerogenes) indicated that only Copper Oxide Nanoparticles with pH 12 displayed antibacterial activity with a higher inhibition zone of 34 mm with Gram positive bacteria MRSA as compared with gram negative bacteria (*salmonella Paratyphi, K pneumonia, E. aerogenes*). The bactericidal effects of Copper Oxide Nanoparticles has been attributed to Cu<sup>2+</sup> ions released in the solution and binding of these ions to negatively charged cell wall leading to its rupture. Also, it was demonstrated that, the Gram positive bacteria have higher sensitivity to Copper Oxide Nanoparticles than Gram negative strains which may be due to difference in cell wall structure. Despite many studies demonstrating anti-microbial properties of Copper Oxide Nanoparticles a certain study has demonstrated minimal or no bactericidal effect of Copper Oxide Nanoparticles to inner layer. The effect of pH and shape of the Copper Oxide Nanoparticles crystals on microbial propensity was studied by Siddiqui et al. [35] using *O. sanctum* and eugenol as capping agent exhibited Anti-microbial propensity against *P vulgaris*, *P fluorescens*, *S. aureus* and *E. coli* via agar diffusion method. *E. coli* exhibited maximum propensity when subjected to different concentrations ranging from 25 ug ml<sup>-1</sup> to 100 ug ml<sup>-1</sup> of Copper Oxide nanostructures using agar diffusion method.

P Yugandhar et al. [36] studied the effect of their green synthesised Copper Oxide Nanoparticles using Copper sulfate as reducing agent and extract of *S. alternifolium* stem bark as reducing agent on seven bacterial strains and five fungal strains. The seven bacterial strains include Bacillus subtilis ATCC 6633, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and five fungal strains include *Alternaria solani*, *Aspergillus flavus*, *Aspergillus niger*, *Penicillium chrysogenum* and *Trichoderma harzianum*. The disc diffusion assay method and MIC studies were carried out on the selected strains. The results showed 20 ug ml<sup>-1</sup> of Copper Oxide Nanoparticles as minimum growth inhibition and 80 ug ml<sup>-1</sup> lethal to all the microorganisms under study. The highest zone of inhibition was observed in *E. coli* and *S. aureus* bacterial strains and *T. harzianum* fungal strain. The ZONE of inhibition was higher in bacterial strains as compared to Fungi strains which may be attributed to the cell wall structure of Fungi which is made of polysaccharides thus limiting the passage of Copper Oxide Nanoparticles to inner layer.

Antimicrobial properties of Copper Oxide Nanoparticles obtained using various methods is summarized in Table 1:

**Study of anti cancerous activity**

Nanoparticles of Inorganic Copper have been studied for its anti-cancerous agent in its various inorganic forms like Cu<sub>2</sub>O (Copper (I) Oxide), CuO (Copper (II) Oxide), Cul (Copper (I) Iodide), Cu<sub>5</sub>(PO<sub>4</sub>)<sub>2</sub> (Copper (II) Phosphate), CuCO<sub>3</sub> (Copper (II) Carbonate), Cu<sub>2</sub>O (Copper Monosulfide), etc [23–25, 27–32, 38–41]. All these inorganic forms did show anti-cancerous properties as demonstrated by ROS, apoptosis and related experiments performed by various authors. In this section we shall be focussing on Copper Oxide Nanoparticles which has been of interest to scientists due to its ease of preparation, storage and toxicity to cancer cells.

Laha et al. [31] converted the Copper Oxide Nanoparticles to Folic Acid conjugated NP since they can bond with Folate receptors that are over expressed in tumour and can be passively absorbed. The Copper Oxide Nanoparticles synthesized by this method showed size of 35 ± 3 nm in FESEM. In their *in vivo* experiment they observed decrease in toxicity, significant increase in survivability of mice as compared to control group with decrease in tumor size of induced Daltons lymphoma. The *in vitro* study on MCF -7 cells of Copper Oxide Nanoparticles and Copper Oxide-FA NP demonstrated increased ROS activity of Copper Oxide-FA NP over Copper Oxide Nanoparticles leading to higher apoptosis. During another *in vitro* study on breast cancer MCF-7 cells and HepG2 cells by Jenima et al. [27] and Siddiqui et al. [30] respectively, the cytotoxic activities of Copper Oxide Nanoparticles was demonstrated by decrease in proliferation rate in a dose dependant characteristics with increase in concentration with IC<sub>50</sub> at 62.5 ug ml<sup>-1</sup> for MCF-7 cells and reduction in cell viability to 83%, 69%,
Table 1. A summary of synthesis pathway and antimicrobial testing of Copper Oxide nanoparticle.

| Authors                  | Method used for synthesis of copper oxide nanoparticles | Biological material/microbes tested                                                                 | Method used                                                                 | Result                  |
|--------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------|
| Maqsood Ahmed et al [23] | Precipitation method                                   | E. coli (gram − ve), P. aeruginosa (gram − ve), K. pneumonia (gram − ve), E. faecalis (gram − ve), Shigella flexneri (gram − ve), Salmonella typhimurium (gram − ve), and P. vulgaris (gram − ve) S. aureus (gram + ve) | Well diffusion method and MIC studies using broth dilution method            | Effective               |
| Rajgovind et al [24]     | Green synthesis using *P. Marsupium*                   | S. epidermidis (gram + ve), B. cereus (gram + ve), S. aureus (gram + ve), P. vulgaris (gram − ve), E. coli (gram − ve), K. pneumonia (gram − ve) | Well diffusion method and MIC study using broth dilution method             | Effective               |
| M Awwad et al [25]       | Green synthesis using *Malva Sylvestris* leaf extract   | Shigella (gram − ve) and Listeria (gram + ve)                                                    | Disc Diffusion method                                                      | Effective               |
| J Emima et al [27]       | Chemical synthesis using Precipitation method           | Methicillin-resistant S. aureus (gram + ve), S. aureus (gram + ve), B. subtilis (gram + ve), S. Paratyphi (gram − ve), K. pneumonia (gram − ve), and E. aerogenes (gram − ve) | Disk Diffusion test (Zone of Inhibition)                                   | Effective               |
| Jafari et al [37]        | Oxalate decomposition method                           | E. coli (gram − ve), S. gallinarum (gram − ve), S. aureus (gram + ve), *P. aeruginosa* (gram − ve), *P. vulgaris* (gram − ve), and *B. subtilis* (gram + ve) | Disk diffusion method (Zone of Inhibition) and MIC and MBC                 | Not Effective           |
| H. Siddiqui et al [35]   | Green synthesis using                                  | S. aureus (gram + ve), *P. aeruginosa* (gram − ve), *P. fluorescens* (gram − ve), S. aureus (gram + ve) and E. coli (gram − ve) | Well diffusion method (Zone of Inhibition)                                  | Effective               |
| P Yugandhar et al [36]   | Green Synthesis using *S. alternifolium* stem bark extract | S. aureus (gram + ve), E. coli (gram − ve), KI pneumonia (gram − ve), *P. vulgaris* (gram − ve), *P. aeruginosa* (gram − ve), *S. typhimurium* (gram − ve) | Disk Diffusion Method and MIC studies                                        | Effective               |

Fungal Strains: *Alternaria solani, Aspergillus flavus, Aspergillus niger, Penicillium chrysogenum and Trichoderma harzianum
## Table 2. A summary of cytotoxic potential of Copper Oxide nanoparticle against different cancer cell lines.

| Authors | Method used for synthesis of copper oxide nanoparticles | Cancer cell lines tested | Method used | Result |
|---------|-------------------------------------------------------|--------------------------|-------------|--------|
| Dipranjan Laha et al[31] | Precipitation method by NaOH and Copper Oxide Nanoparticles - Folic Acid conjugated NP after EDC/NHS activation of FA | In vivo study on mice with induced tumor usingDaltons lymphoma. | Isolation of DL cells from mice and ROS Studies Estimation of intracellular glutathione Apoptosis and necrosis study using AO/EB MTT Assay | Increase survivability of Mice treated with Copper Oxide - Folic Acid conjugate Nanoparticles with evidence of increase uptake of CuO-FA NP than CuO NP |
| Siddiqui et al [30] | Precipitation method by NaOH | MCF-7 (Breast Cancer cell line) | MTT Assay | Decrease in proliferation rate |
| Jeemima Jeronsia et al [27] | Precipitation method by NaOH | MCF-7 (Breast Cancer cell line) | MTT Assay | Decrease in proliferation rate; |
| | | | NRU Assay | Decrease in mitochondrial membrane potential |
| | | | Rhodamine Fluorescence assay | Increase in membrane |
| | | | Lipid peroxidation assay | Lipid peroxidation & decrease in intracellular glutathione levels |
| | | | Intracellular glutathione assay | Production of ROS |
| | | | Intracellular ROS generations studies using DCFHDA | |
| | | | RNA isolation and RT PCR | Upregulation of tumour suppressor genes p53 and apoptotic genes bax & caspase-3 |
| Pandey et al [32] | Aqueous precipitation using NH₄OH | A549 (lung cancer cells) | Western Blot method & Protein estimation Apoptosis assay using Acridine Orange / Ethidium Bromide | ROS mediated Apoptosis |
| Nagajyothi et al [29] | Green Synthesis using balck bean extract | HeLa (cervical cancer cell Line) | ROS Studies using DCFHDA dye | Under hypoxic condition |
| | | | Mitochondrial fragmentation disruption assay | ROS mediated Apoptosis |
| | | | Clonogenic assay | Alteration in Mitochondrial structure |
| | | | Apoptosis assay using Acridine Orange / Ethidium Bromide | Inhibition of proliferation |
| | | | ROS Studies using DCFHDA dye | ROS mediated Apoptosis |
| Sankar et al [28] | Green synthesis using F. religiosa leaf extract | A549 (lung cancer cells) | Apoptosis assay using Acridine Orange / Ethidium Bromide | |
| Authors | Method used for synthesis of copper oxide nanoparticles | Cancer cell lines tested | Method used | Result |
|---------|--------------------------------------------------------|--------------------------|-------------|--------|
| Neran Ali Thamer and Nadia Tareq Barakat [33] | Green synthesis using leaf extract of *cordia myxa* L. | AMJ-13 and MCF-7 (Breast cancer cell lines) | MTT assay | Inhibition of Cell growth |
| P Yugandhar et al [36] | Green synthesis using extract of *S. alternifolium* stem bark | MDA-MB-231 (Breast Cancer cells) | MTT analysis | Inhibition of Cell growth |
52%, 34% and 28% when exposed to Copper Oxide Nanoparticles concentrations of 2 ug ml⁻¹, 10 ug ml⁻¹, 20 ug ml⁻¹, 25 ug ml⁻¹ and 50 ug ml⁻¹ respectively for HepG2 cells [27, 30].

Copper Oxide Nanoparticles synthesized using green methods by Nagajyothis et al [29] and Sankar et al [28] were tested against HeLa (cervical cancer) and A549 (lung cancer cells) demonstrated ROS mediated damage to the cell leading to Apoptosis [28, 29]. The apoptosis due to mitochondria damage in A549 cells is confirmed by reduced Rhodamine fluorescence of Copper Oxide Nanoparticles treated cells since fluorescence decay is directly proportional to loss of membrane potential. Improved cytotoxicity in A549 cells is attributed by Sankar et al [28] to bio-active molecules of F. religiosa leaf extract used for green synthesis of Copper Oxide Nanoparticles which resulted in decrease in viability of cells up to 70% even in low concentration as 50 ug ml⁻¹ and with increase in concentration up to 500 ug ml⁻¹ the viability further decreased to 6% with IC50 of 200 ug ml⁻¹.

Treatment of HeLa cells with Copper Oxide Nanoparticles also showed disruption of the mitochondrial membrane. The normal controls showed an extended lace like network of mitochondria whereas the Copper Oxide Nanoparticles treated HeLa cells showed altered morphology of mitochondria and have shown to exhibit condensed clump structures; Condensed nuclei and clumped structure of mitochondria of HeLa cells indicate apoptotic cells i.e. ROS mediated DNA and mitochondria damage leading to apoptosis [29].

A similar study on HepG2 cells [30] using Rhodamine 123 fluorescent indicator demonstrated decrease in Rhodamine fluorescence in dose dependant manner, which was indicative of reduction in membrane potential with increase in exposure to Copper Oxide Nanoparticles. Further confirmation of apoptosis in presence of Copper Oxide Nanoparticles was done using Quantitative RT-PCR where in the mRNA levels of apoptic genes in HepG2 cells exposed to Copper Oxide Nanoparticles were analyzed and the results confirmed altered expression levels of mRNA of the genes studied. The expressions were up-regulated of tumor suppressor genes i.e. p53, capase -3 and bax, whereas the expression was down regulated for anti-apoptotic gene bcl-2; the same was confirmed by examining the protein expression levels of these genes using western blotting method.

Additionally, the anti-oxidant properties of NAC (anti-oxidant N acetyl cystein) was studied and as confirmed by MTT studies NAC effectively prevented the ROS generation. ROS generation was reduced up to control level for Copper Oxide Nanoparticles in presence of NAC. ROS studies in presence and absence of NAC confirmed that NAC significantly preserved the viability of HepG2 cells caused by Copper Oxide Nanoparticles. Pandey et al [32], had shown that Copper Oxide Nanoparticles exhibit significant cytotoxicity and induce ROS mediated apoptosis against A549 lung cancer cells.

Nenan Ali Thamer and Nadia Tareq Barakat [33], demonstrated the toxic effect of the Copper Oxide Nanoparticles synthesised by green method from leaf extract of cordia myxa L., on breast cancer cell lines AMJ-13 and MCF -7. HBL-100 a normal cell line used for comparison in this study did not exhibit inhibition of cell growth indicating selective toxicity to cancerous cell lines. The cell lines were subjected to various concentration of Copper Oxide Nanoparticles and the rate of growth was monitored. Inhibition of 71.1% in MCF and 69.6% in AMJ-13 was observed after 24 h at concentration of 100 ug ml⁻¹. The normal cell line HBL-100 did not show any significant inhibition at same concentration and time period. P Yugandhar et al [36] green synthesised Copper Oxide Nanoparticles using Copper sulfate as reducing agent and extract of S. alternifolium stem bark as reducing agent and demonstrated cytotoxicity to MDA-MB-231 Breast Cancer cells using MTT analysis. A concentration of 50 ug ml⁻¹ was found to reduce the proliferation rate by 50% as compared to negative control used in the study. The cytotoxic potential of Copper Oxide nanoparticles against different cancer cell lines is summarised in Table 2.

Conclusion

In this article we have reviewed the work of various researchers who have studied antimicrobial and anticancer properties of Copper Oxide Nanoparticles and summarize that Copper Oxide Nanoparticles has great potential to be used in microbial infections as it exhibits anti-microbial propensity in not only gram negative and gram positive bacteria but also against certain fungal strains. Copper nanoparticles are also extremely promising in future cancer treatments, provided proper targeted vehicle is used like liposome or polymer in order to reduce its toxicity to normal cells. There is a huge scope for further researches in this area for development of next generation cost effective antimicrobial and anticancer drugs.

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