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A Perspective Study on Copper Oxide Nanoparticles and Their Role in Different Fields of Biomedical Sciences

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Abstract

Copper oxide is a p-type semiconductor that finds a large number of applications as an antioxidant, antibacterial and antitumor or anticancer agent. Copper oxide nanoparticle combines with the cell membrane and enters into the cell; generate reactive oxygen species (ROS) which cause oxidative stress in the cell. Oxidative stress leads to metastasis, cancer proliferation, apoptosis, DNA damage, cytotoxicity and unregulated cell signaling. Hydroxyl free radicals generated by nanoparticles, combined with DNA and yield 8-hydroxul-2-deoxyguanosine (8-OHdG), consequently DNA is damaged. CuO nanoparticle shows antibacterial activity on different bacterial strain such as Staphylococcus aureus, bacillus circulens BP2, Escherichia coli and P. aeruginosa. In recent times, CuO nanoparticles have applications in the detection of cholesterol, lactate biosensors, DNA sequencing of microbe, and analysis of the Anti-HIV drug. There are specialized CuO nanoparticles such as glucose sensor, hydrogen peroxide sensor, immunosensor, dopamine sensor for the detection of different biomolecules. ROS generated by CuO nanoparticles cause toxicity which leads to cell death.

Keywords: Copper oxide nanoparticles; ROS; cancer therapy; biomedical applications

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1.0 Introduction

Nanotechnology has wide applications in different areas liken biosensors, cosmetics, imaging and diagnosis and target drug delivery. Nanoparticles have great physiological properties due to which they got great attraction [1]. As the size of metal reduced from bulk to nanometer, properties like active surface area, hardness, electrical conductivities, biological activities and chemical reactivity, are also changed. Due to the high surface to volume ratio of metal nanoparticles, they have great applications in antibacterial activities. Metal nanoparticles can also be coated onto the polymer surface or combined with a polymer to achieve antimicrobial applications [2]. Copper oxide is of semiconductor nature and possesses a monoclinic structure. Copper oxide has wide application due to physical properties [3]. It is a p-type semiconductor, so used in many applications like field emission emitters, high-temperature superconductors, catalysis, sensors and batteries [4]. In recent times, CuO nanoparticles were observed for microbial activity and reach the respective organs by crossing biological membrane [5]. There has been the utility of copper for many years as a fungicidal agent. Freeform or complex form of copper has germicidal activity. In recent Studies, Copper nanoparticles are used in the paint industry as an antifouling coating. Copper has also been used as a copper nanocomposite to control fungi [6]. There is a fascinating area of research against tumors by the use of nanoparticles because of their antitumor nature. Metal nanoparticles exhibit anticancer activity due to physicochemical properties as antioxidant action or use of external stimuli. Free radicals which are produced by the metal nanoparticles kill cancer cells and also reduce the tumor environment. Metal nanoparticles reduced tumor development due to their antioxidant abilities [7]. Active or Passive process can be employed against cancer. There are merits of the passive process like Retention effect and permeability. Nanoparticles can easily passé into the cancerous cells and kill them. In the active process, nanoparticles are synthesized in a way to target the cancerous cell. A ligand used as a receptor to nanoparticles to specify target cancerous cell [8]. Apart from biomedical applications, CuO nanoparticles are found to be toxic for animal cells including mammalian cells due to more production of reactive oxygen species (ROS). Thus, oxidative stress is induced and increases the toxic effect which leads to damage of mitochondria and DNA [5, 9-11].

In this review article, our aim to represent CuO nanoparticle's mode of action i-e generation of Reactive oxygen species (ROS) and biomedical applications along with its toxicity toward the environment and animals including humans.

Reactive Oxygen Species (ROS)

It is a natural byproduct, result from cellular oxidative metabolism and play key a role in cell homeostasis [12]. ROS are produced by intracellular organelles like mitochondria, endoplasmic reticulum, etc. as shown in Fig. 2 [21, 22]. By contrast, extracellular ROS are produced by ROS inducing agents like nanoparticles, radiation and pollutants when exposed to cell [23] as shown in Fig. 1. It includes free radical and non-radical such as superoxide and hydrogen peroxide respectively [13]. It is oxygen free radical and short-lived specie, converted into hydrogen peroxide with the help of superoxide dismutase (SODs) [14]. Superoxide is produced by incomplete electron reduction of oxygen and then converted into hydrogen peroxide by SOD, which acts as antioxidant in cells for oxygen exposure. ROS are intermediate in cellular levels which are controlled by several enzymes like SOD, Catalase (CAT) and Glutathione (GPS) or by

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several antioxidants like Glutathione, Vitamin E, ascorbic acids and flavonoids [15]. The imbalance between ROS generation and its neutralization lead to harmful effects on cell signaling mechanisms or oxidative harm to biomolecules like nucleic acid, lipid and protein [16]. ROS generation promotes signaling molecule activation that leads to cell death [17-20]. The generation and consequences of ROS on human cell has been shown in Fig.3.

Mechanism of Reactive Oxygen Species (ROS) CuO nanoparticles act as catalysts and enhance ROS formation through Fenton reactions or Haber-Weiss reaction which produce hydroxyl radical [21, 22] while hydroxyl free radical is formed by the reaction of oxidized metal ion and hydrogen peroxide in Haber-Weiss reaction [23, 24]. Nanoparticles interact with membrane and invade the cell. Ultimately transported into cell by the endocytosis. Nanoparticle starts intracellular ROS generation by catalysis of free radical reaction in mitochondria. The mitochondrial membrane is depolarized and NADPH enzyme activation due to interference in the electron transport chain by nanoparticles [25]. CuO nanoparticles block the electron transport chain and increase oxygen free radicals which lead to oxidative stress in cells. Moreover, in ROS dependent mechanism, immune cells activated by exposure of nanoparticles via NADPH oxidase (NOX) activation [26]. Free radical produced by nanoparticles, reduced the Glutathione (GSH) into Glutathione disulfide which leads to the oxidative stress in cells [27, 28]. Cell experience showed antioxidant defense when exposed to the low levels of CuO nanoparticles and oxidative stress is overcome. In contrast, antioxidant system is overwhelmed by the exposure to a high level of CuO nanoparticle which leads to inflammation and cytotoxicity. Oxidative stress leads to metastasis, cancer proliferation, apoptosis, DNA damage, cytotoxicity and unregulated cell signaling [29-31].

Cytotoxicity and DNA Damage

Hydroxyl free radical generated by nanoparticles, combined with DNA and yield 8-hydroxul-2-deoxyguanosine (8-OHdG), resultantly DNA is damaged [32]. Polyunsaturated fatty acids also oxidize and lipid peroxide is produced at the start of ROS generation. Nanoparticle genotoxicity caused by mutation lipid peroxidation [33, 34]. Nanoparticle induced ROS cause toxicity in several biological systems like tumor cell, human erythrocytes and skin fibroblasts [35].

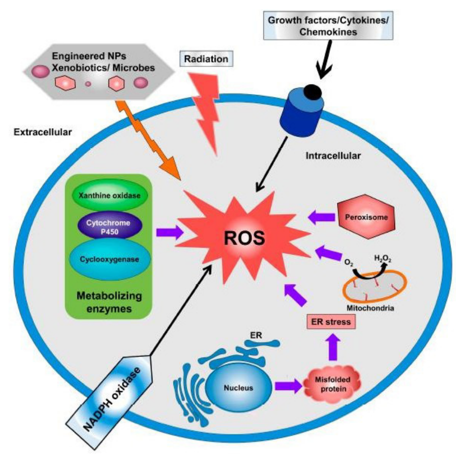

Fig. 1 Reactive oxygen species (ROS) generation [36]

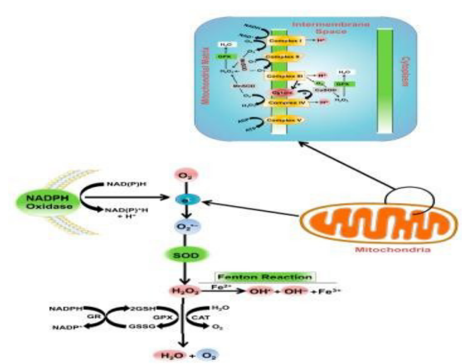

Fig.2 ROS generation by Mitochondria and NADPH oxidase [13]

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Biomedical applications of CuO

Antibacterial activity

CuO Antibacterial activity is investigated on different bacterial strains such as staphylococcus aureus, bacillus circulens BP2, Escherichia coli and P. aeruginosa. The growth curve of bacterial culture was measured in an antibacterial activity test in the presence of CuO nanoparticles. A spectrophotometer (600 nm) was used to measure the optical density (OD) of bacterial culture. The result showed prominent bacterial growth inhibition in culture with the respect to control.

It is supposed that bacterial growth is inhibited/killed by the use of CuO nanoparticles. Although a high concentration of copper oxide nanoparticles show more bactericidal effect [37].

Copper shows antibacterial activity because it damages protein, nucleic acid and cell membrane respectively [38, 39]. Copper attach to guanine of DNA molecule activation of oxidative stress occur which lead to dislodging of DNA strands and resulting of 8-hydroxy-2-deoxyguanosine [40]. Recently it is observed that copper has biocidal activity, it not only effective against bacteria like Staphylococcus aureus strain but also against virus-like influenza viruses and bronchitis, human immunodeficiency virus, and bacteriophage [41, 42]. Reactive oxygen species produced by CuO nanoparticles penetrate into the cell by interacting with cells membrane which leads to disruption of cell enzymes [43].

Sensors for biomolecules detection

Ultrafine mono-dispersed CuO nanoparticles deposited on Indium tin oxide glass substrate electrophoretically, used as a sensor for detection of cholesterol [44]. CuO-graphene nanospheres used as a cholesterol sensors [45]. CuO nanoparticles consisting of copper oxide-CeO_2 used as a lactate biosensor [46]. Glassy carbon electrode having CuO nanoparticle with single-walled carbon nanotube, used in DNA sequence detection of bacteria and virus for identification of disease [47]. CuO nanoparticles used for the assay of Anti-HIV drug [48].

Sensor for glucose detection

CuO nanoparticles are used in glassy carbon electrodes for the detection of glucose in a basic medium [49]. CuO/graphene nanocomposite modified glassy carbon electrode highly selective and sensitive for the detection of glucose [50].

Sensor for hydrogen peroxide detection

Hydrogen peroxide is an intermediate in a biological system. So, its detection is important in hypoxic conditions and oxidative stress in all tissue and cell [51]. CuO nanoparticles have the ability to oxidize many chemical compounds. Hydrogen peroxide determined by the nanostructure of CuO [52]. CuO graphene nanocomposite can be used to monitor hydrogen peroxide in vivo method.

Immunosensor for immune complex

Copper nanostructure such as CeO_2-CuO [53], Ag-CuO [54], platinum-CuO [55], Palladium-CuO [52], ferrocene-CuO [56] used as tumor biomarker like alpha-fetoprotein [57, 58]. It has been noted that CuO nanoparticles give a synergetic effect and accelerate signal transduction.

Sensors for dopamine detection

Dopamine is a neurotransmitter that is an integral part of the central nervous system. It causes low-level neurological disorders like senile dementia, epilepsy, Parkinson's Huntington's schizophrenia and Alzheimer's disease [59-62].

CuO nanoparticles with modified glassy carbon electrode and combination with other nonmaterial used for dopamine sensor [63]. CuO/CNTs/Nafion

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composite used to enhance dopamine oxidation along with better peak current signals [64].

Cancer nanomedicines

CuO nanoparticles selectively induce apoptosis in tumor cells and inhibit growth which leads to metastasis of melanoma [65, 66]. CuO nanoparticle used against tumor of prostate, eye [67], breast [68], liver [69], brain [70], kidney [71] and lungs [72]. Upon entering of nanoparticles into cell or nucleus, cause mitochondrial localization, DNA damage, mutation and alteration of gene expression. CuO nanoparticles target mitochondria and start apoptosis due to oxidative stress in cells [71].

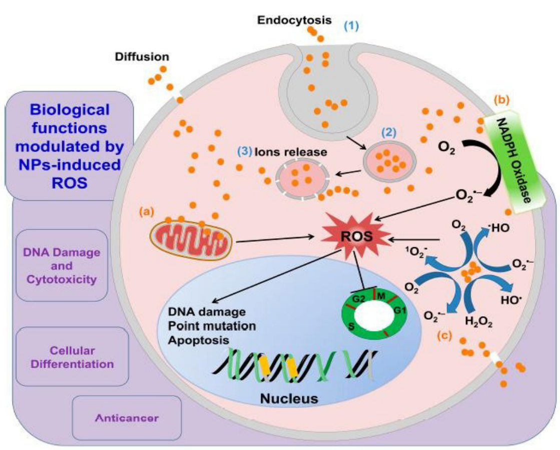

Fig.3 ROS generation and its consequences on human cell [24]

4.0 Toxic effects

CuO nanoparticles have many applications in-vitro and in-vivo experiments. CuO nanoparticles pose toxicity due to their small size and positive surface charge which facilitate interactions between nanoparticles and cells. CuO nanoparticles pose a more toxic effect on algae and protozoan *Tetrahymena Thermophila*as compared to bulk form [4]. A study revealed that CuO nanoparticles enhance oxidative DNA damage, mitochondrial and DNA damage [73]. CuO nanoparticles showed a more toxic effect on human skin organ culture and lungs culture cells [74].

A study reports that hemolysis increase when the cell membrane is damaged by CuO nanoparticles [10]. It has been reported that CuO nanoparticles affect human hepatoblastoma (HEPG2) cells which stops melanoma cell growth [75]. CuO nanoparticles pose neuronal toxicity by the loss of neurons membrane. CuO nanoparticles toxicity to eukaryotic cell mechanism is simplified in Fig.4. CuO nanoparticles induce cell death in lymphocyte and hence weaken the human immune system [76].

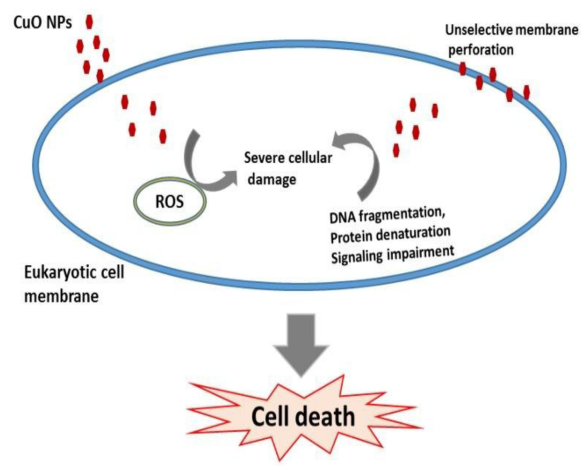

Fig. 4 CuO nanoparticles toxicity mechanism [77]

Conclusion

CuO nanoparticles possess fascinating physiological properties that can be used to get desirable properties. CuO is an emerging horizon for in-vitro and in-vivo therapy and application in the biomedical field. CuO nanoparticles are excellent antibacterial, antifungal and antioxidant material which control microbe effectively because CuO penetrates into membrane due to its high surface area. CuO nanoparticles are used in food packaging because it inhibits bacterial

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growth. Due to excellent chemical and thermal stability as well as electrical conductivity, Cu nanocomposites have many applications in biomedical detection. CuO acts as a drug carrier in nanomedicine. Nanomaterial-based drugs have been developed that selectively kill the cancerous cells in target cancer therapy in the field of nanomedicine. Modified CuO nanocrystals with specific ligands interact with specific receptors on the tumor cells. CuO nanoparticles can be used for the detection of many diseases like cardiac syndrome, neurological disorder, tumor, stress and diabetes. CuO acts as a biosensor for pollutants and metabolites. CuO nanoparticles can be used to sense different compounds such as detection of Cholesterol, lactate biosensor, DNA sequencing of microbe and analysis of the Anti-HIV drugs. It is found that the excess quantity of CuO nanoparticles promotes toxicity to humans, others living beings and as well as the environment.

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