Journal of Applied Life Sciences International

15(4): 1-8, 2017; Article no.JALSI.38444
ISSN: 2394-1103

Copper Nanomaterials as Drug Delivery System against Infectious Agents and Cancerous Cells

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JALSI/2017/38444
Editor(s):
(1) Palanisamy Arulselvan, Institute of Bioscience, Universiti Putra Malaysia, Malaysia.
Reviewers:
(1) Hasan Hüseyin Doğan, Selcuk University, Turkey.
(2) Imran Ali, Jamia Millia Islamia (Central University), India.
(3) B. G. Viswanath, Gandhi Medical College & Hospital, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/22496

Mini-review Article

Received 27th November 2017
Accepted 22nd December 2017
Published 28th December 2017

ABSTRACT

Pathogenic infections have raised a serious threat on public health world-wide owing to the resistance to broad spectrum antimicrobials. The emergence of multi drug resistant biofilms and non functional conventional antibiotics has directed nanotechnological advances to overcome biofilm infections as drug delivery system. Copper nanomaterials, among other metallic nanomaterials based therapies and treatments, have demonstrated their significant maximum efficacies in damaging pathogenic cells due to their higher toxic property. This review is focussed on different forms of copper nanomaterials such as copper nanoparticles, copper oxide nanoparticles and copper sulfide nanoparticles, featuring their synthesis, size, surface characteristics, dissolution, mechanism of action and toxicity, which provide valuable insights into the possible mechanism of damaging against various infectious agents and cancerous cells, as possible drug delivery system.

Keywords: Infectious agents; cancerous cells; copper nanomaterials; mechanism of action; toxicity; drug delivery system.

ABBREVIATIONS

MDR: Multi-drug resistant; Cu NMs: Copper nanomaterials; ROS: Reactive oxygen species; Cu NPs: Copper nanoparticles; CuO NPs: Copper oxide nanoparticles; CuS NPs: Copper sulfide nanoparticles; $[Cu(CH_3COO)_2.H_2O]$: Copper (II) acetate; NaOH: Sodium hydroxide; NLTA: N-lauryltyramine.

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1. INTRODUCTION

Infectious diseases, caused by bacteria, virus, fungi and parasites, are responsible for the demise of over 17 million global people annually. The emerging and re-emerging infectious diseases suffer from discovery of new drugs and drug-resistance, respectively, to control or treat the dreadful diseases [1-3]. Although the human immune system has the capability to defend the body from infectious agents through innate immune response, followed by adaptive immune response [4], some contagious and virulent microorganisms overpower body immunity, and become transmitted to host cells. In this concern, pathogens may enter the host body via natural orifices resulting in growing, and multiplication in host cells and extracellular spaces, followed by tissue damage [5].

Many multi-drug resistant (MDR) bacteria [6] have the potency to colonize and adhere to surfaces through hydrophobic interactions [7,8] by producing a matrix of extracellular polysaccharide substances, called the biofilm [9], which is used as barrier to diffusion of antibiotics when treated [10]. Bacteria in biofilm-layer may be a persisting source of contamination for damaging food grains, carrying products with potential pathogens [11]. Furthermore, it has been reported that certain diseases such as cystic fibrosis, colitis, periodontitis, native valve endocarditis, otitis media and chronic prostatitis seem to be associated with biofilm-related microorganisms [12].

To overcome drug-resistance, new infections and biofilm development, it has given emphasized on nanotechnology-based therapeutics to treat the associated diseases. Metal-based nanoparticles are featured by their small sizes (~2-100 nm) and high surface to volume ratio for the good interactions with biomolecules within the cells and on the cell surfaces, accompanying cell permeability [13-18]. Moreover, use of metallic nanoparticles cannot develop resistance to microorganisms or pathogenic cells, as metals having multifaceted complex microbicidal and anticarcinogenic activities [19-21].

As an alternative to conventional anti-pathogenic therapy, copper nanomaterials (Cu NMs) have been explored preliminary as anti-microbial and anti-carcinogenic agents [22-25]. The nanosized materials exhibit anti-pathogenic activity through liberating positive copper ions and generating reactive oxygen species (ROS) to damage site specific cellular structure. Although Cu NMs are highly toxic [26], these particles act as efflux pump inhibitor, prevent biofilm formation, and disrupt cancerous cells at lower concentrations [27-29,25]. The beneficial anti-pathogenic activity of copper nanoparticles (Cu NPs) may be exploited by maximizing their therapeutic efficacies and minimizing their toxicity through proper surface modifications e.g. sulfidation of Cu NPs [27] and ligand coatings [21]. Another aspect of applications for Cu NMs, has been emerged as a promising platform in photothermal cancer therapy, due to their photodynamic properties [30-32].

There are various reports about the anti-pathogenic activity of Cu NMs [33-35], but most are primary evaluations, having rarely investigations on their efficacies in infected animal model, possibly due to their high toxic side effects, which are barriers for clinical applications [36-38]. Therefore, Cu NMs should be designed for biomedical applications through modifications on stability, biocompatibility, non-aggregation, selectivity to target cells / tissues, non-toxicity and affordability. This review is focussed mainly on Cu NPs, copper oxide nanoparticles (CuO NPs) and copper sulfide nanoparticles (CuS NPs) for consideration as potential therapeutics in efficiency, for the treatment of microorganisms and carcinoma cells.

2. SYNTHESIS OF COPPER NANO-MATERIAL COMPOSITES

Cu NPs are synthesized through several procedures such as chemical reduction, thermal reduction, sol-gel processing, laser ablation, and biological process, with the modified polyol method and the external stimulation of UV radiation [39-42]. Cu NPs (~8 nm diameter) may be synthesized from pure copper metal wire using an inert gas condensation [43]. After synthesis, particles are dispersed in pre-sterilized de-ionized water by ultra-sonication to prevent their agglomeration.

Cu NPs are also prepared by one pot synthesis modified thermal decomposition method. In brief, an aqueous 0.1-0.5 M copper sulphate solution is stirred at 50℃ for 10 min. Then 0.5 M sodium hydroxide is added drop wise to adjust the pH of the solution to 6.0. The formation of Cu NPs indicates its color change

from pale blue to brown. After filtration and drying, Cu NPs are washed with Milli-Q water and transferred to a glass plate for heating to 200℃ for 2 days following cooling at room temperature for further studies.

CuO NPs are synthesized by γ-radiolysis, laser irradiation, reverse micelles, thiol-induced reduction and green synthesis [44-47]. They may be synthesized by aqueous precipitation method while copper (II) acetate [$Cu(CH_3COO)_2.H_2O$] as a precursor and sodium hydroxide (NaOH) as a reducing agent are used. Briefly, 2 mL glacial acetic acid (CH_3COOH) and 600 mL 0.2 M copper (II) acetate solution are poured into round-bottomed flask and boiled under magnetic stirring. 30 mL 6M NaOH solution is then added into the flask and a black suspension is formed by changing its blue color. After carrying out the reaction under stirring and boiling for 2.5 h, the mixture is cooled to room temperature and spun to obtain a wet CuO precipitate. The deposits are filtered, washed with distilled water and absolute ethanol, and dried at 60℃ for 6 h to get dry powder of CuO NPs.

To prepare CuS NPs, at first, N-lauryltyramine (NLTA) capped Cu NPs are prepared [23]. Briefly, 1 mg dissolved NLTA in 100 µL ethanol is added to 50 mL 2.5 mM NaOH solution. Then 200 µL ammonium hydroxide and 1mM copper chloride are added to the solution and followed stirring at 600 rpm for 5 min. After that, 400 µL of hydrazine hydride is added to the solution and observed the change of blue color to reddish brown in 6 h. The as-obtained Cu NPs are directly allowed to react with 1mM sodium sulphide for 3 h until a green solution is developed, suggesting formation of CuS NPs which are dialyzed against water for 24 h before use.

3. SIZE AND SURFACE CHARACTERISTICS OF COPPER NANOMATERIALS

Copper and its compounds exhibit a wide range of potential physical properties such as high temperature super conductivity, spin dynamics and electron correlation effects [48,49] while Cu NPs and their hybrids show stronger antimicrobial activity for longer period owing to a better electron transfer in comparison to CuO NPs [50]. During the production of copper nanomaterials, thermal treatment, number, size, shape and surface to volume ratio of nanomaterials are considered as the main factors that can affect their antimicrobial property. Generally, Cu, CuO and CuS nanoparticles are synthesized in the size range of 8-60 nm by thermal decomposition using various precursors and following other methods while the spherical Cu NPs possess the average size of 55 nm. The decreasing size results in increasing the specific surface area of nanoparticles which enhances the interactions between nanoparticles and biomolecules by promoting their accumulation and increase in reactivity. Surface characteristics such as surface charge and surface modifications of nanoparticles are other key factors that can be interacted via the functionalization of nanoparticles with functional molecules [51,52].

It is reported that the excitation of Plasmon resonance / inter-band transition indicates the metallic characteristics of NPs while UV-visible spectral analysis exhibits their different surface Plasmon resonances depending on various particle sizes at 540 nm and 556-580 nm [53,39].

4. DISSOLUTION

Cu, CuO and CuS nanoparticles are more soluble than their bulk forms as nanosized particles possessing larger surface areas to interact with solvent molecules compared to bulk ones regarding the same weight, and exhibit faster dissolution forming copper ions [54]. In natural water, CuO NPs may exist as aggregates which are driven by the divalent ions and the low zeta potential resulting their fusion and reduction in total particle surface area [55]. The solubility of NPs is also related to the pH of the solution and its temperature [56]. It is demonstrated that Cu may be released from its nanoparticulated form while its soluble quantity differs in various media [57]. In this aspect, it is believed that both dissolved ions and nanoparticles may contribute to cytotoxicity as the combined effects of soluble and particles.

5. MECHANISM OF ACTION

Copper is a structural component of many enzymes in living microorganism. It takes part in the transportation of oxygen in iron homeostasis and electron transport chain. At high concentration in free ionic form, it can generate ROS with the reduction of O_2 and the production of superoxide anion $O_2^{\cdot -}$ which come in contact with the cell membrane producing free radicals that enter the cell and cause disruptions of the

cellular internal contents and the biochemical processes, and blockage of the synthesis of DNA and amino acid by their binding with – SH groups disturbing the helical structure via cross linkage within and between the nucleic acid strands [58-61]. Furthermore, nanoparticles having a greater affinity for the amines and carboxyl groups owing to high surface to volume ratio for higher catalytic reactivity, adhere to cell walls due to their opposite electric charges, and transfer their electrons to cell membrane leading to its penetration, high permeability and rupture including cancer cells photothermolysis [62-64].

Several reports indicate that three different mechanisms of action for copper nanoparticles are involved on the basis of oxidative stress, coordination and non-homeostasis –effects that exert toxicity on the cells [65]. In this aspect, nanosized particles can diffuse into the cell through the membrane pores, ion channels and membrane transporter proteins. Some nanoparticles coated with ligands or vesicles may be endocytosed and interacted with oxidative mitochondria while redox active proteins activate ROS production in cells, and Cu^{2+} ions, produced by nanomaterials, can induce ROS by many chemical reactions such as DNA strand breaks affecting gene expressions. Moreover, Cu^{2+} ions, released by CuO NPs, disrupt homeostatic cellular metal cationic balance by increasing their local concentration to exert cellular toxicity.

Copper nanoparticles also have specific drug loading and efficient photoluminescence capability for targeted delivery of anti-cancer drugs where DNA may be degraded potentially by the action of Cu NMs via production of singlet oxygen, and cytotoxicity may be exerted by nanoparticles towards cancerous cells through apoptotic induction suggesting to design chemical modifications of Cu NMs to generate active molecules for interacting with more macromolecules [66].

6. TOXICITY

The smaller Cu NPs and CuO NPs show greater toxicities mediated through oxidative stress in comparison to their larger counterparts due to release of more copper ions and larger surface area-to-volume ratio and increased reactivity [67] while NPs-toxicity is higher than that of soluble ionic Cu owing to their larger release-uptake [68]. Toxicity assessment of the nanoparticles depends on the different exposure routes such as the oral gastrointestinal and respiratory tracts. Histopathological assessment on lung carcinogenic bioassays displays severe acute and chronic inflammatory changes in the rat lung at high and low doses respectively or with frequent intra tracheal instillations [69]. These nanoparticles when exposed to different cultured cells, such as, human lung epithelial A549 and liver HepG2 in normal medium, exhibited their cytotoxicity not only by generating ROS but also by blocking cellular antioxidant defences and causing cellular DNA damage, apoptosis and necrosis [70,71,25,72].

Furthermore, the evaluation of toxicological parameters by the administration of NLTA-CuS NPs (100 µM) into zebrafish assaying carboxylesterase and brain acetylcholinesterase activities, the markers for hepato and neuro toxicity respectively, indicates their insignificant changes in enzymatic activities. In addition, the hemocompatibility assay does not induce any adverse change in RBC morphology along with intact membrane having no haemoglobin release, which demonstrates intrinsic biocompatibility of NPs with no toxic side effect for using as antimicrobial and anticarcinogenic agent [73].

7. CONCLUSIONS

Based on the size, shape, surface to volume ratio and dimension of the nanomaterial, copper on a nanoscale may be utilized as promising antimicrobial and anticarcinogenic agent. To eradicate biofilm-associated MDR pathogens, application of Cu and CuO NPs may be considered as novel drug delivery system to overcome such infections for their high toxic nature. The synergistic administration of nanoparticles with other antibiotics may be another effective approach to control chronic and persistent infections of MDR microorganisms. However, the toxicity of NPs should be decreased to the insignificant level to avoid their side effect in in-vivo system. Therefore, proper exposure route selection and NPs-surface modifications using ligands, sugars, proteins, peptides and genes with or without vesicular drug [21,74] are required to enhance their efficacies against infection and cancer and to reduce toxicity in the biological system as further investigations.

In another aspect, the treatment of CuS NPs in zebrafish depleted the infectious microbes completely from the fish body through microbial

membrane damage triggered by ROS-mediated oxidative damage over glutathione-defense without hepato, neuro and hemo toxicity [73], supporting a better mode of therapeutic application against infection, though needed further studies with rodent model before clinical trial.

Cu, CuO, CuS NPs (~ 8 nm diameter), when administered, may be very effective against diseases for long term application while their reduced sizes (< 5 nm) due to oxidation and dissolution in the physiological system can be eliminated from the body through renal excretion [21], and the other Cu NMs can be exported by copper-transporting adenosine triphosphatases through the intestine as feces, the mammary gland as milk, the liver as bile product, and through the metabolism as micronutrient [75,76]. Cu^{2+} ions have also the capability for forming chelates with biomolecules or their dislodging in specific metalloproteins to inactivate functional proteins [65].

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
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