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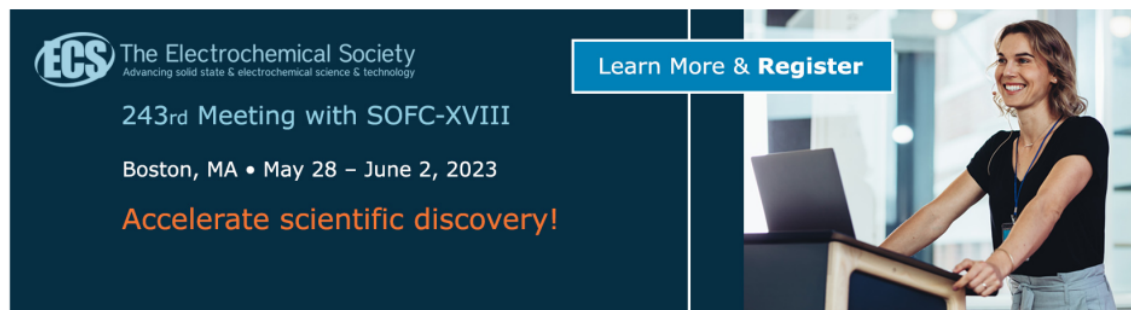
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Antioxidant activity and dose enhancement factor of CeO₂ nanoparticles synthesized by precipitation method

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Abstract. CeO₂ nanoparticles (CeO₂ NPs) have been considered as promising antioxidant and radioprotectant due to its mixed valence state that can prevent cell damage induced by ionizing radiation. The aim of this study is to investigate the antioxidant activity and dose enhancement factor (DEF) of CeO₂. The NPs were synthesized by using a precipitation method. The structure of CeO₂ NPs was characterized with an X-ray diffractometer (XRD). The antioxidant activity of CeO₂ NPs was analyzed by the reduction of 1,1-diphenyl-2-picrylhydrazil (DPPH) stable free radical using UV-vis spectroscopy. The dose enhancement factor (DEF) of CeO₂ NPs was examined using X-ray radiation with an energy of 6 MV. The radioprotective ability of CeO₂ NPs was evaluated by mixing CeO₂ NP suspension with *E. coli* and exposing it to X-ray radiation with a dose of 2 Gy. The XRD pattern analysis reveals that CeO₂ NPs possess a cubic fluorite structure. CeO₂ NPs show activity with IC₅₀ value of 4.4 mg/ml. CeO₂ NPs also show the ability to absorb X-ray radiation with DEF value < 1 and reduce the *E. coli* damage induced by X-ray radiation. The amount of irradiated *E. coli* in the presence of 0.2 mg/ml CeO₂ NPs was found to be 23 times larger than that irradiated *E. coli* in the absence of CeO₂ NPs.

1. Introduction ²⁰

The application of nanoparticles in radiotherapy has been a subject of considerable interest. Radiotherapy is the reliable way for cancer treatment by exposing cancer cells to ionizing radiation. During radiotherapy of cancer, the ionizing radiation resulted in an increased rate of not only cancer cell death but also normal cell death. The main challenge in the cancer therapy is to increase the radiation ability to kill cancer cells by increasing the dose effectiveness and minimizing damage to the surrounding normal cells. The dose effectiveness to kill cancer cells could be increased by using radiosensitizer, while radioprotector is used to protect normal cell [1-3]. Many free-radical scavengers or antioxidants have been investigated and used to overcome the effects of radiation on normal cell. Amifostine is the only compound as radioprotector recommended by US FDA (Food and Drug Administration) [4, 5]. However, this compound has limitations due to short life and poor penetration to the location where the free radicals produced.

The current nanotechnology makes it possible to develop a variety of nanoparticles to be used for biomedical application with superior properties. Nanoantioxidants, including inorganic nanoparticles have shown promise as high-performance therapeutic nanomedicine in attenuating oxidative stresses. However, the small size and large surface area of nanoparticles resulted in particles aggregation and led



to difficulty in the handling of nanoparticles in liquid [6]. A few metal oxides nanoparticles were reported as antioxidants, including TiO₂ [7], ZnO [9-11], and CeO₂ [12-17]. Among metal oxide nanoparticles, applications of CeO₂ nanoparticles (CeO₂ NPs) in biomedical have experienced growing attention due to lower toxicity than the other oxide nanoparticles that commonly investigated such as TiO₂ and ZnO. Furthermore, CeO₂ nanoparticles are known as catalysts that have pharmacological potential and promising therapeutic agent. The redox reaction that occurs between Ce³⁺ and Ce⁴⁺ with superoxide and oxidizing hydrogen peroxide are similar to the behavior of antioxidant enzymes [18, 19]. The antioxidant properties of CeO₂ NPs are determined by the presence Ce³⁺ which depend on shape, size, valence states and synthesis method [13-15].

This paper describes the antioxidant activity and dose enhancement factor of CeO₂ NPs synthesized by precipitation method. The antioxidant activity of nanoparticles CeO₂ was examined using DPPH method. The dose enhancement factor of CeO₂ NPs was determined using the absorbed dose of X-ray radiation measurement. The capability of CeO₂ NPs as radioprotector was evaluated by loading those CeO₂ NPs into *E. coli* culture under X-ray irradiation.

2. Experiment

The CeO₂ NPs were synthesized by precipitation method from cerium nitrate solution as described in previous report [20]. The solution of 0.08 M cerium nitrate (Sigma-Aldrich) was prepared in demineralized water/isopropanol mixed solvent with a volume ratio of 1:6. NH₄OH was then added drop by drop under stirring into the solution until a pH value of 10 was reached. Precipitates were repeatedly washed by isopropanol. The precipitates were then dried at 60 °C for 2 hours and calcined at 500 °C for 2 hours.

The crystallinity and phase of CeO₂ NPs was characterized by X-ray powder diffractometry (XRD) with Cu K_α radiation (λ = 1.54060 Å). UV-Vis transmittance of the CeO₂ NPs was examined using UV-Vis spectrophotometer. Antioxidant activity of CeO₂ NPs was evaluated using DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging method. The suspension of CeO₂ NPs with different concentration (1.5, 3.0, 4.5, 6.0, 7.5, and 9.0 mg/mL) were sonicated using sonicator bath at room temperature for 10 minutes to avoid agglomeration. The absorbance of samples (the mixture of CeO₂ NPs and DPPH solution) and control (DPPH solution without CeO₂ NPs) were measured by UV-Vis spectrophotometer. The ability of CeO₂ NPs to scavenge DPPH radical was calculated using equation (1). Furthermore, the required concentration to inhibit 50% of DPPH (IC₅₀) was determined by linear regression.

$$\% \text{ inhibition} = \frac{A_c - A_s}{A_c} \times 100\% \quad (1)$$

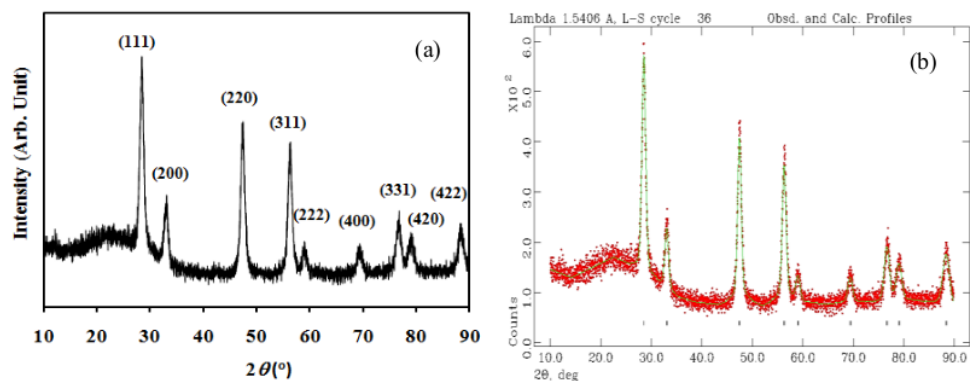
To investigate dose enhancement factor (DEF), the absorbed dose of CeO₂ NPs with various mass of 0,5 g, 1 g, 2 g, and 2,5 g was measured using detector. Measurements were made for photon energy of 6 MV and dose rate of 200 cGy/min, SSD of 100 cm, the field size of (2x2) cm², and detector position at 1 cm below phantom surface. The absorbed dose was measured in the absence and in the presence of CeO₂ NPs. The dose enhancement factor (DEF) was defined as ratio of radiation dose in the presence of CeO₂ NPs to radiation dose in the absence of CeO₂ NPs.

The protection effect of CeO₂ NPs was investigated by mixing CeO₂ NPs suspension with *E. coli* culture at various concentrations in the range 0.02 to 0.1 mg/mL. The *E. coli* cultures were irradiated by using a photon energy clinical linear accelerator (LINAC) of 6 MV X-ray with a dose rate of 200 cGy/min, a depth of 10 cm and source-to-surface distance (SSD) of 90 cm. The number of live *E. coli* was determined by using total plate count method.

3. Results and discussion

The X-ray diffraction (XRD) pattern of CeO₂ NPs synthesized using precipitation method is shown in Figure 1. The XRD pattern reveals that the prepared nanoparticles are polycrystalline of cubic fluorite

CeO₂ structure. Four preferred diffraction peaks at the 2θ values of about 28.46°, 32.97°, 47.44° and 56.18° are observed corresponding to (111), (200), (220), and (311) planes, respectively. Those diffraction peaks are in good agreement with the Joint Committee on Powder Diffraction Standard (JCPDS) No. 34-0394. No other peaks related to impurities or other phases are detected in the XRD pattern which confirmed the prepared CeO₂ NPs are single phase crystalline of CeO₂. This result was confirmed by Rietveld refinement as shown in Figure 1(b). The Rietveld refinement shows good agreement between experimental and simulated XRD pattern with the refinement factors being $R_{wp} = 9.6\%$ and $R_p = 7.55\%$ with the goodness-of-fit (χ^2) = 1.146. The refined cell parameter of CeO₂ NPs is 5.419 Å which is slightly larger than that of bulk CeO₂ (5.411 Å) indicating the prepared CeO₂ NPs consist of nanocrystallite. The crystallite size was calculated using Scherer formula to be about 9 nm.



10 **Figure 1.** XRD pattern (a) and Rietveld refinement (b) of CeO₂ NPs synthesized by precipitation method.

6 The UV-Vis absorbance spectrum of the CeO₂ NPs is shown in Figure 2. The peak of absorbance was observed at wavelength of 207 nm and 303 nm corresponding to characteristic absorption peak of Ce³⁺ and Ce⁴⁺ of CeO₂ NPs. The spectrum reveals that CeO₂ NPs consist of Ce³⁺ and Ce⁴⁺ ions. The present of Ce³⁺ ion has an important role on the antioxidant activity of CeO₂ NPs [14].

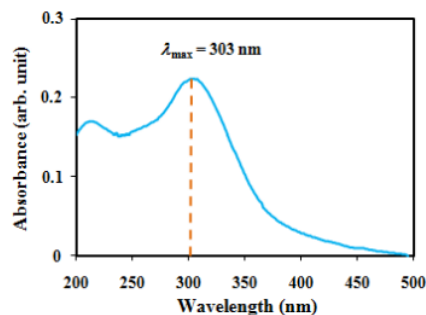


Figure 2. Absorbance spectrum of CeO₂ NPs.

3 In this study we use DPPH as a stable free radical to determine the radical scavenging activity of CeO₂ NPs. The absorbance of DPPH decreased due to the scavenging of DPPH by donation of electron

or hydrogen from antioxidant substance to form the stable DPPH molecule. The radical scavenging activity values were expressed as percentage of inhibition as ratio of percentage of sample absorbance decrease and the absorbance of DPPH solution in the absence of antioxidant substance at absorption peak of DPPH ($\lambda = 520$ nm). Figure 3 shows radical scavenging activity of CeO₂ NPs. The inhibition of DPPH increased up to 67% at concentration of CeO₂ NPs of 9 mg/mL. In another study, CeO₂ NPs prepared by co-precipitation method and coated by polysaccharide showed DPPH scavenging activity with % inhibition of 85% [13] whereas, CeO₂ NPs prepared by hydrothermal and solvothermal methods showed DPPH scavenging activity up to 55% and 30% respectively [15]. The DPPH scavenging activity of our CeO₂ NPs is smaller than levan-coated CeO₂ NPs, but higher than that CeO₂ NPs prepared by hydrothermal and solvothermal methods. The CeO₂ NPs possess antioxidant activity with IC₅₀ value of 4,38 mg/ml. The CeO₂ NPs exhibited the higher antioxidant activity than ZnO nanoparticles (IC₅₀ ~ 8 – 10 mg/mL) that reported in the literature [9-11]. The antioxidant properties of CeO₂ NPs would be explained as due to transfer of electron from CeO₂ NPs to odd electron located at nitrogen atom in DPPH.

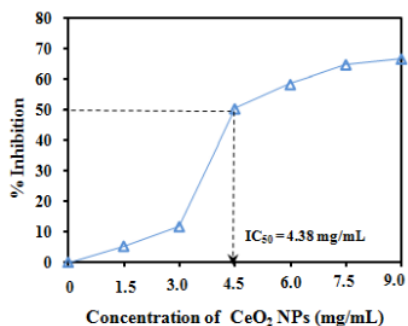


Figure 3. Radical scavenging activity of CeO₂ NPs.

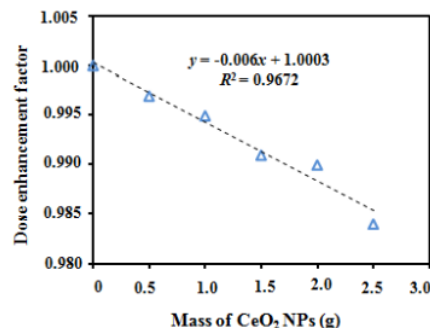


Figure 4. Dose enhancement factor for various mass of CeO₂ NPs.

Figure 4 depicts the dose enhancement factor (DEF) for various mass of CeO₂ NPs. The DEF values of CeO₂ NPs were 0.984 to 0.997 (DEF < 1). The DEF value decreased linearly as increase in mass of CeO₂ NPs. It shows the addition of CeO₂ NPs can decrease absorbed dose of about 1.2 cGy/g. The CeO₂ NPs are potent as radioprotector for preventing normal cell damage induced by X-ray radiation.

The protective effect of CeO₂ NPs was evaluated to protect *E. coli* from damages induced by X-ray radiation. Figure 5 demonstrates the protective effect of CeO₂ NPs. It can be seen that protective effect depends on concentration of CeO₂ NPs. X-ray radiation with dose of 2 Gy killed 98.92% *E. coli*. The increase in the amount of *E. coli* was found in *E. coli* treated with the presence of CeO₂ NPs. At the condition with addition of 0.02 mg/mL CeO₂ NPs, the amount of *E. coli* increased by 23 times larger than that irradiated *E. coli* without addition of CeO₂ NPs. These results suggested that CeO₂ NPs reduced the amount of *E. coli* death and protected *E. coli* damage induced by X-ray radiation. The amount of *E. coli* death increased with the increase in concentration of CeO₂ NPs. The CeO₂ NPs can reduce *E. coli* damage with concentration up to 0.06 mg/mL. However, the addition of CeO₂ NPs with concentration larger than 0.06 mg/ml did not act as radioprotector but as radiosensitizer. The protective effect mechanism of CeO₂ NPs is physical protection due to its ability to absorb radiation as described by DEF value < 1 and chemical protection through neutralization of reactive oxygen species (ROS) produced by radiolysis of water during irradiation [16]. The main protection mechanism that plays a role in our CeO₂ NPs is chemical protection. It is generally attributed to oxygen vacancy corresponding to surface Ce³⁺ fraction and/or Ce³⁺/Ce⁴⁺ redox switch.

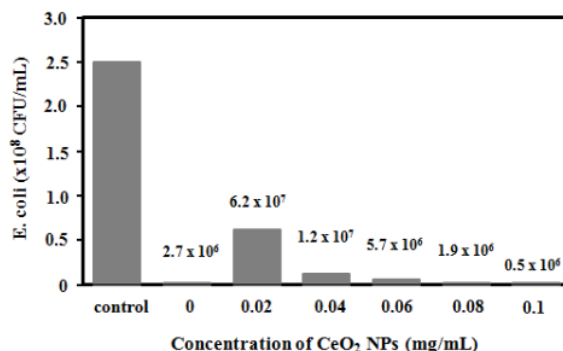


Figure 5. The number of X-ray irradiated *E. coli* with the presence of CeO₂ NPs at various concentration.

4. Conclusion

We have investigated the antioxidant activity and dose enhancement factor of CeO₂ NPs synthesized by precipitation method. The CeO₂ NPs possess good antioxidant activity and can reduce absorbed dose of X-ray radiation. The CeO₂ NPs with concentration of no more than 0.06 mg/ml show a protective effect on *E. coli* damage induced by X-ray radiation. These results indicated that CeO₂ NPs synthesized by precipitation method are a potent radioprotector. However, its effectiveness should be further investigated.

Acknowledgment

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