7th International Conference on
Science and Development of Nanotechnology

The effects of biogenic bismuth oxide nanoparticles on radiosensitivity of gastric cancer cells

Fatemeh B. Masoudi, *Department of Biology, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran*

Mansour Mashreghi[1], *Department of Biology, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, , Iran, . Industrial Biotechnology Research Group, Institute of Biotechnology, Ferdowsi University of Mashhad, Mashhad, , Iran, Nano Research Center, Ferdowsi University of Mashhad, Mashhad, , Iran*

Fatemeh B. Rassouli, *Novel Diagnostic and Therapeutics Research Group, Institute of Biotechnology, Ferdowsi University of Mashhad, Mashhad, Iran*

Hamid Gholamhosseinian, *Medical Physics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

Ali Nakhaie Pour, *Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, , Iran*

Abstract

Gastric cancer is the 5th most common neoplasm and the 3rd most deadly cancer worldwide. In this study, we produced bismuth oxide (Bi_2O_3) and bismuth oxide-zeolite nanocomposites (Bi_2O_3-Z NCs) using *Vibrio* sp. *VLC* bacteria and investigated their effects on radiosensitivity of human gastric cancer cells.

After synthesis of Bi_2O_3 NPs and Bi_2O_3-Z NCs by *Vibrio* sp. *VLC* bacteria, the characterization of NPs were evaluated using UV-visible, FTIR, XRD, DLS, Zeta potential, TEM and FESEM. Then, MKN-45 cells, a human gastric adenocarcinoma cell line, were pretreated with 25 µg/ml Bi_2O_3 NPs (in two forms of heated and non-heated) and Bi_2O_3-Z NCs, while bismuth salt and zeolite were considered as controls. After 24 h, cells were exposed to 200, 400 and 600 centigray (cGy) of X-radiation and recovered for 72 h. At the end, viability of cells was determined by resazurin assay.

Findings of present research indicated that Bi_2O_3 NPs (non-heated) as well as bismuth salt and zeolite pretreatments increased the effects of 200 cGy radiation. Moreover, Bi_2O_3 NPs (heated) significantly (p <0.05) improved the sensitivity of MKN-45 cells to 400 cGy X-ray. More interesting results were observed when 600 cGy radiation was applied, as Bi_2O_3 NPs (heated) and Bi_2O_3-Z NCs significantly (p <0.0001 and p <0.05, respectively) enhanced radiosensitivity of cells.

In conclusion, obtained results revealed that Bi_2O_3 NPs and Bi_2O_3-Z NCs could act as potent radio sensitizers, although more investigation on other gastric cell lines is required to confirm our findings.

1-Corresponding Author

Keywords: Bismuth oxide nanoparticles, zeolite nanocomposite, gastric cancer, radiosensitivit

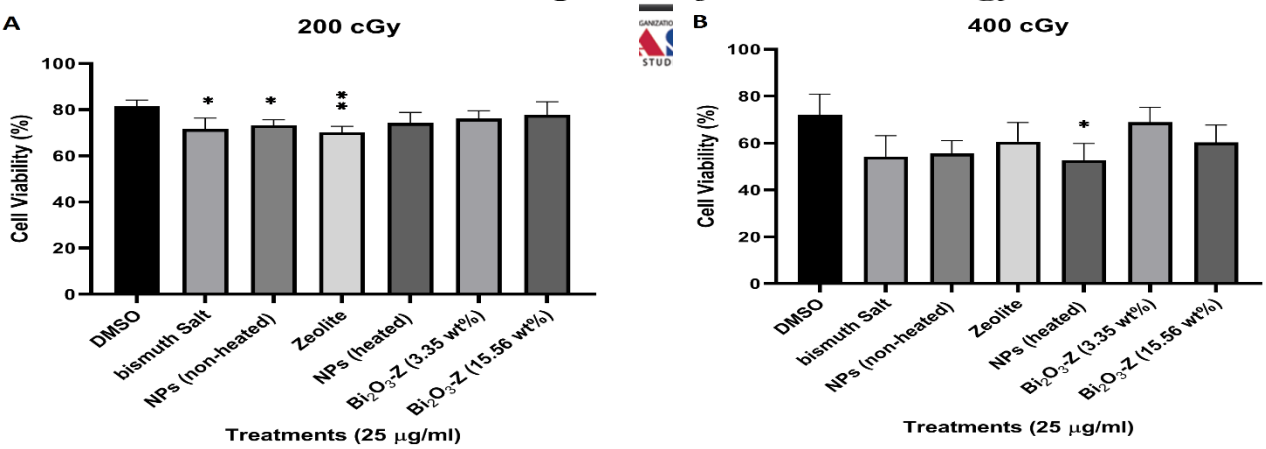
Introduction

Gastric cancer is a life threatening malignancy, which is known as the 5th most common neoplasm and the 3rd most deadly cancer worldwide The incidence and mortality rates of gastric cancer are highly variable due to diet and *Helicobacter pylori* infection [1]. Beside surgery, radiotherapy is a common approach for patients with gastric cancer, although resistance of cells reduce clinical outcomes and leads to disease relapse [2]. Therefore, more advanced and effective methods are needed to enhance radiosensitivity of gastric cancer cells. Nanoparticles (NPs) have the ability to perform diagnosis and treatment functions together (theranostics) [3]. Bismuth oxide (Bi_2O_3) NPs possess more penetration ability and less unfavorable effects than conventional radiosensitizers [4]. It has been shown that encapsulated copper bismuth sulfide NPs induce tumor inhibitory effects in synergy with radio-chemotherapy at moderate doses [5]. Hence, the aim of present study was to investigate whether Bi_2O_3 and biologically synthesized Bi_2O_3-zeolite (Bi_2O_3-Z) NCs using by *Vibrio* sp. *VLC* bacteria could improve radiosensitivity of human gastric cancer cells *in vitro*.

Methods

For biosynthesis of Bi_2O_3 NPs by cell lysate supernatant (CLS), at first bacteria were grown in Sea Water Complete (SWC) medium. After 48 h, the cultures were centrifuged at 5000 rpm for 20 min, and pellets were resuspended in sterile distilled water. Upon 24 h incubation, samples were sonicated for 22 min and centrifuged at 10000 rpm for 10 min. Then, the supernatant, which is called CLS, was incubated with $Bi(NO)_3.5H_2O$ (10 mM) for 24 h at 37 °C. For biosynthesis of Bi_2O_3-zeolite nanocomposites (Bi_2O_3-Z NCs), zeolite was treated with NaOH for 24 h, combined with $Bi(NO)_3.5H_2O$ (10 mM) during 72 h, and finally mixed with CLS. At the end, Bi_2O_3 and Bi_2O_3-Z NCs were centrifuged at 10000 rpm for 20 min at 4°C, followed by washing with deionized water and ethanol (70%) and dried in oven at 34 °C for 24 h. the characterization of Bi_2O_3 and Bi_2O_3-Z NCs were evaluated using UV-visible, FTIR, XRD, DLS, Zeta potential, TEM and FESEM analysis.

Human gastric cancer cells, MKN-45 cell line, were grown in DMEM medium containing 10% fetal bovine serum and incubated at 37 °C and 5% CO_2 in humidified atmosphere. Before treatments, cells were seeded with a density of 2000/well in 96-well plates and after 24 h, they were treated with 25 µg/ml Bi_2O_3 NPs (in two forms of heated and non-heated) and Bi_2O_3-Z NCs (with 3.35 wt% and 15.56 wt%), while bismuth salt and zeolite were considered as controls. After 24 h, cells were exposed to 200, 400 and 600 centigray (cGy) of X-radiation and recovered for 72 h. At the end, viability of cells was determined by resazurin assay, which is based on the reduction of the blue resazurin to the pink-colored resorufin. Briefly, 18 µl resazurin (0.1 mg/ml) was added to each well, and after 2.5 h of incubation at 37°C, the absorbance of cells was measured at 600 nm. To calculate the cell viability (%), the following formula was used; 100-((AT-AU)/(AB-AU)×100), in which AT and AU were absorbance of treated and untreated cells, respectively, and AB was absorbance of blank control.



Results and Discussion

Findings of present research indicated that radiosensitivity of MKN-45 was improved by Bi_2O_3 and Bi_2O_3-Z nanocomposites (NCs). As demonstrated in Figure 1-A, Bi_2O_3 NPs (non-heated) as well as bismuth salt and zeolite pretreatments increased the effects of 200 cGy radiation. To note, the lowest cell viability were observed upon pretreatments with zeolite (70.16%), bismuth salt (71.64%) and non-heated Bi_2O_3 NPs (73.25%). Moreover, heated Bi_2O_3 NPs significantly (p <0.05) improved the sensitivity of MKN-45 cells at 400 cGy X-ray, as cell viability was decreased to down 52.68% (Figure 1-B). More interesting results were observed when 600 cGy radiation was applied; heated Bi_2O_3 NPs, Bi_2O_3-Z NCs (3.35 wt%) and bismuth salt significantly (p <0.0001 and p <0.05, respectively) enhanced radiosensitivity of cells. The lowest cell viability were observed upon pretreatments with heated Bi_2O_3 NPs (59%), bismuth salt (66.3%) and Bi_2O_3-Z NCs (67.25%) (Figuer 1-C).

Figure (1) Viability of MKN-45 cells after pretreatments with 25 µg/ml of bismuth salt, non-heated Bi_2O_3 NPs, zeolite, heated Bi_2O_3 NPs, Bi_2O_3-Z NCs (3.35 wt%) and Bi_2O_3-Z NCs (15.56 wt %) followed by 200 (A), 400 (B) and 600 (C) cGy radiation. All experiments were repeated at least three times and results are presented as mean ± SD.

Conclusion

Obtained findings revealed that Bi_2O_3 NPs and Bi_2O_3-Z NCs could act as potent radio sensitizers on human gastric cancer cells. Nevertheless, more investigation on other cancer cell lines is required to confirm current results, and also reveal the mechanism of observed effects.

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