Anti-microbial and anti-cancer activities of Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ (x $\leq$ 0.1) nanoparticles

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ABSTRACT

Combining two or more nanoparticles is a promising approach. Previously we have reported synthesis of nanoparticles Dysprosium (Dy) substituted with manganese (Mn) zinc (Zn) by using ultrasonication method. The five different nanoparticles (NPs) Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ (x $\leq$ 0.1) have been structurally and morphologically characterized but there is no report on the biological application of these NPs. In the present study, we have examined the anti-cancer, anti-bacterial, and anti-fungal activities of Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ (x $\leq$ 0.1) NPs. Human colorectal carcinoma cells (HCT-116) were tested with different concentrations of NPs by using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. In addition, the impact of NPs was also examined on normal cells such as human embryonic kidney cells, HEK-293. After 48 h of treatment, Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ NPs (x = 0.02, 0.04 and 0.06) showed no inhibitory action on cancer cell's growth and proliferation, whereas Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ NPs (x = 0.08 and 0.1) showed profound inhibitory action on cancer cell's growth and proliferation. However, the treatment of Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ NPs on the normal cells (HEK-293) did not show cytotoxic or inhibitory action on HEK-293 cells. The treatment of Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ NPs (x $\leq$ 0.1) also inhibited both the bacteria (Escherichia coli ATCC35218 and Staphylococcus aureus) with lowest MIC and MBC values of 4 and 8 mg/mL and fungus (Candida albicans) with MIC and MFC values of 4 and 8 mg/mL on treatment with x = 0.08 and 0.1.

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Introduction

The nanoparticles (NPs) possess potential applications in biomedical fields, especially in diagnosis, screening, and treating cancer. One of the distinctive properties of NPs is their high surface area, high cell penetration capabilities, and better biocompatibility and bioavailability [1]. Moreover, the magnetic nanoparticles (MNPs) exhibit distinct magnetic properties [2–4]. These MNPs have been used for many biological applications such as bio-imaging, cellular labelling, hyperthermia, and drug delivery [5–8]. Over the past few years, these MNPs have been especially used in cancer treatments [9–13] and, also in gene therapy, magnetic, photothermal, and photodynamic therapy and cancer detection [14]. MNPs have also been used in cancer treatments [15–20]. There are also reports of the use of different types of nanoparticles in the colon or colorectal cancer treatments [21–24], and anti-bacterial activities [25, 26]. There are reports of applications of NPs as anti-cancer and anti-oxidant agents [27–29].

In our previous studies, we have shown that different kinds of MNPs showed potent anti-cancer and anti-bacterial activities [30–32]. Recently it has been found that a combination of two or more nanoparticles is effective for improved NPs delivery and treatments [33,34]. NPs can be synthesized by chemically and green technology [35, 36]. Previously we have reported that synthesis of Dysprosium (Dy) substituted with Manganese (Mn), Zinc (Zn) NPs by ultrasonication method. The Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ NPs (x $\leq$ 0.1) have been structurally and morphologically characterized [33], but there is no report on the biological application of Mn$_{0.5}$Zn$_{0.5}$DyxFe$_{2-x}$O$_4$ NPs (x $\leq$ 0.1). Interestingly, MNPs have useful applications in...
cancer detection and treatment [28,33,37–39]. We have examined the impacts of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) on HCT-116, HEK-293 cells, bacteria (Escherichia coli ATCC35218, and Staphylococcus aureus), and fungus (Candida albicans).

Materials and methods

Nanoparticle preparation and characterizations

The Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) were prepared as per previously described method [33] by ultrasonic irradiation method. All products were structurally and morphologically analysed by an X-ray powder diffractometer (XRD), transmission electron microscopy (TEM), and scanning electron microscopy (SEM) methods.

Anti-bacterial activity

Minimal inhibitory/bactericidal concentration (MIC/MBC)

Anti-bacterial activity of synthesized Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) was examined by obtaining the MIC and MBC using Escherichia coli ATCC35218 as gram negative and Staphylococcus aureus ATCC29213, as gram positive bacteria. The nanomaterial ranging in the concentration of 0.5–16 mg/mL, was suspended and later sonicated in LB (Luria Bertani) to achieve the suspended broth-drug solution. The test bacteria were grown overnight and brought to cell concentration of 2.5 × 10^5 CFU/mL. The Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) and culture broth media suspension were incubated at temperature of 37 °C for 24 h. Both bacteria without the addition of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) were taken as negative control. The value of MIC is recorded as the effective amount of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) that arrests 99% of microbial growth [40].

Minimum bactericidal concentration (MBC)

After the study of MIC, 25 μL of the incubated Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) and bacterial suspension with no turbidity seen, were inoculated on new sterile Mueller Hinton Agar (MHA) plates and kept for incubation at 37 °C for 24 h. MBC value is taken as the effective amount of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) that kills 100% of microbial cell growth.

Antifungal activity

Candida albicans ATCC 14053 (yeast) was used for the antifungal activity of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1). Candida was aerobically grown in Sabouraud’s broth (SDB) at 28 ± 2 °C for 24 h. Subsequently, the cells were harvested and washed using phosphate buffer saline (PBS), and cell density was adjusted to approximately 10^7 CFU/mL. The Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) were sonicated and prepared using SDB in the concentration, ranging from 0.5 to 16 mg/mL.

Minimal inhibitory concentration (MIC)

The standard broth dilution method was used for anti-fungal activity by evaluating the MIC of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1). The suspension of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) and SDB was added with freshly prepared inoculum and subjected to incubation with aeration at 28 ± 2 °C for 24 h. Subsequently, the MIC was recorded as the minimum concentration of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) were used, which had no growth visible (absence of turbidity) [40].

Minimal fungidical concentration (MFC)

MFC was obtained by selecting the MIC, having no visible growth. Briefly, 10 μL from MIC was inoculated onto the freshly prepared SDA plates and further incubated at 28 ± 2 °C for overnight. The plates were observed for MFC, which was recorded as the minimum concentration of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1), which completely killed the Candida cells or had CFUs less than three.

Morphological analysis of treated Candida

The morphological effect of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) on Candida cells was studied by SEM. As described in previous section, Candida was treated with synthesized NPs at the concentration recorded as its MIC value. The untreated Candida was also included in the experiment, as a control. On completion of incubation period, the treated cells were obtained by centrifugation. The cell pellet was washed multiple times with PBS and re-centrifuged. The cells were fixed with 2.5% glutaraldehyde for 4 h, at 4 °C and fixed again, with 1% osmium tetroxide for 30 min. The fixed cells were washed multiple times using PBS. Further, the Candida cells were dehydrated for 10 min by using varying concentration of ethanol, and later again washed with PBS. The fixed Candida was placed onto aluminium stub and dried using a desiccator. Dried cells were gold coated and examined at 20 kV by SEM [40].

One way ANOVA followed by Tukey’s test was used to compare mean concentration. p value less than .05 was considered to show significant difference.

Anticancer assay

In vitro cell culture and testing of NPs

Human colorectal or colon carcinoma cells (HCT-116) were taken to study the impact of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1). The normal cells, such as human embryonic kidney cells (HEK-293), were taken as control cells. The cell culture method and in vitro testing method of nanoparticles were followed as per previously published work [32, 41]. Briefly, the cells were treated with various concentrations of (2.5–45 μg/mL) Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1). In the control group, Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x \leq 0.1) was not added. After 48 h of NPs treatment, MTT (5 mg/mL) (Sigma Aldrich, St. Louis, MO, USA) was treated for 4 h and then treated with dimethyl sulfoxide and optical density (OD) was measured at a wavelength of 570 nm.
Effect of NPs on DNA of cancer cells
Colon cancer cells were treated with Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1) and in control group, Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1) was added. After 48 h of treatment, cells were immersed in ice-cold paraformaldehyde for 15 min. Cells were washed three times with Triton X100 in phosphate buffered saline and DAPI (1.0 µg/mL) was added to each well, and cells were stained for 5–10 min. The cancer cell morphology was examined (Confocal Scanning Microscope, Zeiss, Frankfurt, Germany).

Statistical analysis
The mean ± standard deviation (SD) from control and NPs group was calculated. All statistical analyses were completed with GraphPad Prism 6.0 (GraphPad Software). The difference between control and NPs groups by a one-way analysis of variance (ANOVA), p-values were calculated by Student’s t-test.

Results and discussion
Characterization
The structural and morphological characterizations of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1) were analysed by an XRD, TEM and SEM methods which has been previously published study by Almessiere et al. [33]. As per XRD, the average size of the MNPs was in the range from 11 to 18 nm. Direct optical energy band gaps were in a small band range of 1.61–1.67 eV. All products displayed super-paramagnetic properties at room temperature [33]. The SEM analysis showed that NPs revealed a regular size and uniform distribution of cubic particles with aggregation and the average particles size was less than 20 nm and was found to increase in size with increasing the Dy content. Similarly, the TEM analysis showed that NPs were agglomeration of cubic nanoparticles because of the magnetic interaction among nanoparticles [33].

Antibacterial activity
Antibacterial activity of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs FeO_{4} (x ≤ 0.1) was obtained by studying the MIC/MBC values. The concentration of test nanomaterial was used in the amount ranging from of 0.5 mg to 16 mL^{-1}. The values for MIC/MBC were obtained as follows: 8/16, 8/16, 8/16, 8/4, 4/8 for x = 0.02, 0.04, 0.06, 0.08 and 0.10, respectively, for E. coli (Figure 1(b)). However, S. aureus has shown the MIC/MBC as follows: 8/16, 8/16, 8/16, 8/16, 4/8 for x = 0.02, 0.04, 0.06, 0.08 and 0.10, respectively, (Figure 1(b)). It could be seen that the antibacterial action is getting slightly enhanced with the addition of ‘x’ content, hence the significant MIC/MBC was achieved by x = 0.08 and 0.10. The significant variation was obtained with the increasing concentration of x content. Moreover, gram negative bacterium was seen to be affected slightly better than the gram-positive bacterium. This slightly selective action towards the gram positive and gram-negative bacteria is probably due to the structural variation in the chemistry of cell wall between the two [28]. In several studies many amalgamations of metal nanomaterial like zinc, copper, manganese are recorded to have antibacterial impact, however, the antibacterial impact of the current combination of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1) is rare in the reported literature, to the best of author’s knowledge [42].

Antifungal activity
MIC And MFC
In the present study, C. albicans was used for the antifungal activity of synthesized Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1). The MIC and MFC values of Dy (x = 0.02, 0.04, 0.06, 0.08, 0.1) were obtained as 8/16, 8/16, 8/16, 4/8, 4/8 mg/mL, respectively (Figure 2). The lowest MIC and MFC values of 4 and 8 mg/mL were recorded with x = 0.08 and 0.1. The antifungal activity of treated Candida culture was achieved as the manipulation of the element Dy(x = n) in the nanomaterial. The significant variation was obtained with the increasing concentration of x content. The obtained results proved, that the antifungal activity was relatively increased with the elevated concentration of ‘x’ content and goes in agreement with some previous studies, which stated the same effect, on combination of several metallic NPs [40,30,43,44].

Morphological analysis by scanning electron microscope (SEM)
It is evident from SEM micrographs (Supplementary Figure S1), that Candida treated with Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1) were appearing as deformed and distorted as compared to the untreated cells, which appeared normal and smooth in shape (Figure 3(a)). The cell wall and cell membrane of treated Candida indicated the loss of the integrity of membrane which resulted in distortion and ultimately to cell death [45]. The best possible reason of this action could be the size and easy attachment of NPs to the cellular surfaces and targeting the ergosterol, which is a main sterol responsible for the integrity of fungal cell wall [46,47]. Among all the ratios of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1) (x ≥ 0.02), x = 0.08 and 0.1 has been the most effective in causing the morphogenesis as well as the reduction in the number of cells (Supplementary Figure S1). Different studies have also suggested that the NPs induces the production of hydrogen peroxide, creates oxidative stress and lipid peroxidation, and deactivation of cellular enzymes, which leads to inhibition of microbial growth and morphogenesis [48].

Anti-cancer activities
The cytotoxic effect of Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.1) was examined on cancerous colon cells using MTT assay. After 48 h of treatment, we have found that Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x = 0.02, 0.04 and 0.06) showed no inhibitory action on colon cancer cells. Whereas Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x = 0.08 and 0.1) caused profound inhibitory action on colon cancer growth and proliferation (Table 1). The inhibitory concentration (IC50) of all Mn_{0.5}Zn_{0.5}Dy_{x}Fe_{2-x}O_{4} NPs (x ≤ 0.10) was calculated, as shown in Table 1. While we do not know the
reason for such varied action of Mn0.5Zn0.5DyxFe2-xO4 NPs on cancer cells, the catalytic role of Dysprosium (Dy) cannot be ruled out [49–51]. We have added different concentrations of Dy in the composites, the lower concentration of Dy (x = 0.02, 0.04 and 0.06) not able to induce inhibitory action on the cancer cells, whereas higher concentrations of x = 0.08, and 0.1 showed profound inhibitory action on the cancer cells. The catalytic effect of Dy in NPs may be
We have also examined the DNA of cancer cell post-treatment of MnzDyFe2-xO4 NPs ($x \leq 0.1$) by DAPI staining. The MnzDyFe2-xO4 NPs ($x = 0.08$ and $0.1$) treated DAPI-stained cells showed that NPs treatment caused an inhibitory action on colon cancer cells (Figure 3(B, C)) compared to control cells (Figure 1(A)). Colon cancer cells treated with MnzDyFe2-xO4 NPs ($x = 0.08$ and $0.1$) with concentration $(0.71 \mu g/mL)$ and $(1.48 \mu g/mL)$ showed a decrease in DNA stained cells due to cytotoxicity (Figure 3(B and C)).

Our results showed that the treatment of MnzDyFe2-xO4 NPs ($x = 0.08$ and $0.1$) possess potential application in colon cancer treatments. Previously reports supported that nanoparticles can significantly improve cancer treatment by selectively inhibiting growth and proliferation of the colon cancer cells [32,41,52]. The treatment of MnzDyFe2-xO4 NPs ($x = 0.08$ and $x = 0.1$) on colon cancer cells also induced cancer death due to DNA fragmentation as revealed by the loss of DAPI staining in the MnzDyFe2-xO4 NPs ($x = 0.08$ and $0.1$)-treated cells. Similar observations reported nanoparticles induced nuclear fragmentation and nuclear disintegration in the cancerous cells [32,56–60]. We suggest MnzDyFe2-xO4 NPs ($x = 0.08$ and $0.1$) have a robust anti-cancer capability.

Table 1. Impact of MnzDyFe2-xO4 NPs ($x \leq 0.10$) NPs on cancerous (HCT-116) and normal (HEK-293) cells.

| MnzDyFe2-xO4 NPs | IC50 (HCT-116) cells | IC50 (HEK-293) cells |
|-----------------|----------------------|----------------------|
| 0.02            | No inhibition        | No inhibition        |
| 0.04            | No inhibition        | No inhibition        |
| 0.06            | No inhibition        | No inhibition        |
| 0.08            | 0.95 $\mu g/mL$      | No inhibition        |
| 0.10            | 1.48 $\mu g/mL$      | No inhibition        |

Inhibitory concentration (IC).

**Conclusion**

There is no report on the biological application of MnzDyFe2-xO4 NPs ($x = 0.1$), and in the present study, we have examined both anti-cancer and anti-bacterial activities. The five different MnzDyFe2-xO4 NPs ($x \leq 0.1$) have been structurally and morphologically characterized but there is no report on the biological application of these NPs. In the present study, we have examined anti-cancer, antimicrobial activities of MnzDyFe2-xO4 NPs ($x \leq 0.1$). Human colorectal carcinoma cells (HCT-116) were tested with different concentrations of NPs by using MTT assay. In addition, the impact of NPs was also examined on normal cells such as human embryonic kidney cells, HEK-293. After $48\, \text{h}$ of treatment, MnzDyFe2-xO4 NPs ($x = 0.02$, $x = 0.04$, $x = 0.06$) showed no inhibitory action on cancer cells’ growth and proliferation, whereas MnzDyFe2-xO4 NPs ($x = 0.08$ and $x = 0.1$) showed profound inhibitory action on cancer cell growth and proliferation. When we tested these MnzDyFe2-xO4 NPs on the normal cells (HEK-293), which did not show cytotoxic or inhibitory action can HEK-293 cells. The treatment of MnzDyFe2-xO4 NPs ($x \leq 0.1$) also inhibited the bacteria (*Escherichia coli* ATCC35218 and *Staphylococcus aureus*) and fungus (*Candida albicans*).

**Authors consent**

All authors have approved the final version of the manuscript.

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**Disclosure statement**

There is no potential conflict of interest was reported by the author(s).

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