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Synthesis and characterization of cobalt ferrites nanoparticles with cytotoxic and antimicrobial properties

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ABSTRACT

Recently, the application of nanotechnology in food sector and the agriculture attract the attention compared to its biomedical application. The aims of the current study was to synthesize and characterize cobalt ferrites nanoparticles [($CoFe_2O_4$) NPs] by combustion method employing glycine as fuels and to evaluate their antimicrobial against pathogenic bacteria and fungi and anti cancer properties against MCF-7 breast cancer cells line. The results indicated that the particles size of the synthesized ($CoFe_2O_4$) NPs was 40 nm. These ($CoFe_2O_4$) NPs showed potential antibacterial properties against Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*) and Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus cereus*) as well as the pathogenic fungi (*Aspergillus flavus* and *Aspergillus ochraceus*) in a dose dependent manner with maximum concentration of 1.8 mg/ml. ($CoFe_2O_4$) NPs also showed weak antiradical but have cytotoxic effects against MCF-7 breast cancer cells line and succeeded to decrease the cell viability at a concentration of 2 mg/ml. It could be concluded that ($CoFe_2O_4$) NPs is a promise candidate as antimicrobial and anticancer agent for food sector and medical application.

INTRODUCTION

Food safety is a major concern worldwide which has serious reflection on public health. Food contamination with pathogens can occur at different steps throughout the food production, processing, distribution, retail marketing, handling and preparation. Several epidemiological studies have implicated foods of animal origin as the major vehicles caused illnesses caused through food-borne pathogens (Petersen and James, 1998). Several attempts should be considered to limit the hazardous of these pathogens on human wellbeing. However, control constitutes the most significant component of overall management of food-borne pathogens. Recently, the unique properties of nanomaterials have given rise to enormous research activity towards nanoparticles fabrication and characterization as well as applications. Nanomaterials are rapidly expanding and used in various areas of research, such as food, feed, health management and environmental aspects (Bouwmeester *et al*. 2007; Kiruba Daniel *et al*. 2013). Metal-oxide nanoparticles draw attention due to their unique magnetic properties and other characteristics such as excellent chemical stability and mechanical hardness (Meng *et al*., 2009; Phua *et al*., 2009; Sanpo *et al*., 2013). Cobalt ferrite ($CoFe_2O_4$) nanoparticles offer potential applications in several fields such as food, medicine, cancer treatment (Jamon *et al*., 2009) and other applications (Amiri and Shokrollahi, 2013; Sanpo *et al*., 2013a). These applications depend on the properties of ferrite which in turn depend on the conditions of preparation, the size and shape of the nanoparticles.

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Yamamoto (2001) enumerated the influence of particle size on the antibacterial activity and reported that the activity was increased with decreasing particle size. The antimicrobial application of magnetic nanoparticles is gaining attention because they can be manipulated through an external magnetic field. Moreover, several nonmagnetic metals nanoparticles or metal oxides were found to be antimicrobials against pathogenic bacteria (Gajjar *et al*., 2009). The antimicrobial activities of magnetic nanoparticles are well established by Chifiriuc *et al.* (2011). Cobalt ferrites nanoparticles were synthesized using different techniques such as solid state reaction (Rafferty *et al.,* 2008) microemulsion (Choi, 2003), combustion (Yan, 1999) the redox process (Rajendran, 2001), chemical co-precipitation (Pannaparayil and Komarneni, 1989), the hydrothermal method (Daou, 2006), and microwave synthesis (Bensebaa, 2004). Generally, the evaluation of magnetic nanoparticles for drug delivery, and sensing applications are widely studied. However, the use of cobalt ferrite nanoparticles as cytotoxicity and antimicrobials against pathogenic and drug resistant microbes are not well investigated. Therefore, the aim of the current work was to study the characteristics and antimicrobial activity of prepared cobalt ferrite nanoparticle against several pathogenic microorganisms and evaluation their cytotoxic effect against MCF-7 breast cancer cells.

MATERIALS AND METHODS

Preparation of cobalt ferrite nanoparticles [($CoFe_2O_4$) NPs]

Cobalt ferrite nanoparticles [($CoFe_2O_4$) NPs] were prepared using the method described by Deraz (2010, 2012). In brief, the calculated proportions of iron and cobalt nitrates with a known amount of glycine, with molar ratio of 2:1:6, respectively, were mixed. The mixed precursors were concentrated in a porcelain crucible on a hot plate at 300 ^{o}C for 5 min. The crystal water was gradually vaporized during heating and when a crucible temperature was reached, a great deal of foams produced and spark appeared at one spot which spread through the mass, yielding a brown voluminous and fluffy product in the container. The product was washed several times with water and then dried in oven at 70 ^{o}C for 2h.

Characterization of nanoparticle

X-ray diffraction data collection of mixed oxide solids was carried out using a BRUKER D8 advance diffractometer (Germany). Data were collected with Cu Kα radiation at 40 KV and 40 mA with scanning speed in 2θ of 2^{o} /min. Scanning electron micrographs (SEM) were recorded on JEOL JAX-840A and JEOL JEM- 1230 electron micro-analyzers, respectively. The samples were dispersed in ethanol and then treated ultrasonically in order disperse individual particles over a gold grids.

Antifungal activity

The antifungal activity of ($CoFe_2O_4$) NPs was tested against fungal cultures (*Aspergillus flavus* and *Aspergillus ochraceus*). The fungal cultures were obtained from the Plant Pathology Department, National Research Centre, Cairo, Egypt. The qualitative assessment of the antifungal effect was done using well agar diffusion test. The sterilized Potato Dextrose Agar (PDA, BD Difco™, MD 21152, USA) medium was poured into petri plates and allowed to dry. Test cultures were inoculated over the dried surface of PDA plate. The appropriate number of wells was bored into the plates using sterile cork borer of 9-mm in diameter. Different concentrations of ($CoFe_2O_4$) NPs were added to these wells and incubated for 7 days at 25 ± 2°C. The contact biocidal property was determined by measuring the diameter of the zone of inhibition around the well.

Antibacterial activity

The antibacterial activity of ($CoFe_2O_4$) NPs was tested against bacterial cultures of Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*) and Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus cereus*). The pathogenic bacteria were obtained from the Department of Microbial Chemistry, National Research Centre, Cairo, Egypt. The bacteria were pre-grown on Nutrient agar (NA, Sigma-Aldrich, St. Louis, MO63103, USA) for 16 h at 37.0 ± 0.1°C. The qualitative assessment of the antibacterial effect was done using two approaches (Disk Diffusion test and Bacterial Linear growth). Disc diffusion assay was determined using the protocol of Jorgensen and Turnidge (2007). Overnight grown bacterial cultures in nutrient broth were individually lawn cultured on nutrient agar plates. Three ($CoFe_2O_4$) NPs concentrations (0.6, 0.8 and 1.8 mg/mL) were prepared in sterile water and dispensed by sonication. Sterile filter paper discs (5.0-mm) were saturated by the ($CoFe_2O_4$) NPs solution and placed above the culture and incubated at 37 ± 0.1°C for 24 h after which the zone of inhibition were recorded. Sterile filter paper was saturated with sterile water and used as control. The same concentrations for bacterial linear growth were examined whereas each concentration was individually set in three petri dishes. The NA medium was poured in the plates and rotated to ensure an even distribution of the nanoparticle. Control Petri dishes were prepared containing no ($CoFe_2O_4$) NPs. Petri dishes were individually inoculated at the center with equal disks (5.0-mm) of tested bacterial cultures. The average linear growth of each bacterium was measured after 24 h of incubation at 37.0 ± 0.1°C.

DPPH and ABTS free radical scavenging assay of ($CoFe_2O_4$) NPs

($CoFe_2O_4$) NPs at different concentrations was mixed with 2 ml of methanol solution containing $DPPH^{\bullet}$ radicals resulting in a final concentration of 6.10^{-5} M $DPPH^{\bullet}$. The mixture was shaken vigorously for 15 s and then left to stand in the dark at room temperature for 30 min. The absorbance (Abs) of the resulting solution was measured at 517 nm using a UV-visible spectrophotometer (Shimadzu UV-1605) against methanol as a blank according to the method described by Shimada *et al.* (1992). The scavenging ability was calculated by the following equation:

$DPPH^{\bullet}$ Scavenging ability (%) = $(1 - Abs_{sample}/Abs_{control}) \times 100$

DPPH$^{\bullet}$ radical scavenging activity was expressed as the half-maximal inhibition concentrations (IC_{50}). IC_{50} value, which expressed as the antioxidant concentration to reduce the radicals by 50%, was calculated for each compound by linear regression analysis (Gulcin, 2010).

The ABTS radical scavenging activity of ($CoFe_2O_4$) NPs was determined according to the method described by Re *et al.* (1999). The reaction between 7 mM ABTS and 2.45 mM potassium persulfate in H_2O made the $ABTS^{\cdot+}$ radical cation. The last solution was left to stand in the dark, at room temperature, for 12–16h before use. Before analysis, the $ABTS^{\cdot+}$ solution was diluted with ethanol at 30°C, in order to obtain an absorbance of 0.700 ± 0.025 at 734 nm. Then, different concentrations of ($CoFe_2O_4$) NPs in solid form were mixed with 1 ml of diluted $ABTS^{\cdot+}$ solution. The mixture was shaken vigorously for 15 s and then left to stand in the dark at room temperature for 20 min. The absorbance of $ABTS^{\cdot+}$ was measured at 734 nm against ethanol as a blanck. The extent of decolorization is calculated as the percentage reduction of ABTS absorbance by following equation:

$ABTS^{\cdot+}$ radical scavenging activity (%) = $(1 - Abs_{sample}/Abs_{control}) \times 100$

$ABTS^{\cdot+}$ radical scavenging activity was expressed as the half-maximal inhibition concentrations (IC_{50}). All analyses were carried out in triplicate and results represented the mean values with standard deviation.

Anti-proliferative activity

Cell culture

MCF-7 (ECACC, United Kingdom) breast cancer cells line were cultured in monolayers at in Dulbecco's modified eagle medium (DMEM) medium (Sigma, Germany), with 10% fetal bovine serum (FBS) (EuroBio, France) and 1% of antibiotic penicillin-streptomycin (GIBCO, USA). The cells were usually split when reaching confluence (2-3 days). They were first rinsed with Dulbecco's phosphate-buffered saline without calcium (D-PBS) (Sigma, Germany) and then trypsinised with a solution containing 0.25% trypsin and 1 mM EDTA (GIBCO, USA). MCF-7 breast cancer cells lines were seeded into 96-well microplates at 5×10^4 cells/well in 200µl of appropriate culture medium. After 24 h, the cells were exposed to 0.2 mg (final concentration 1 mg/ml) of ($CoFe_2O_4$) NPs and then incubated for 48 h at 37 °C, under 5% CO_2 atmosphere. A control was used without ($CoFe_2O_4$) NPs with the same conditions.

Cell viability

The number of living cells was determined using methyl thiazolyldiphenyl-tetrazolium bromide (MTT) assay (Sigma, Germany) based on the reduction of the tetrazolium salt, methyl thiazolyldiphenyl-tetrazolium bromide into a crystalline blue formazan product by the cellular oxidoreductases of viable cells (Maher and McClean, 2006). The resultant formazan crystal formation is proportional to the number of living cells. After the incubation for 2 days, 250 µl of MTT (2 mg/ml in PBS, pH 7.4) were added to all wells and the plate was then incubated at 37 °C under 5% CO_2 atmosphere for 4 h. Medium with MTT was then gently removed and 1 ml of isopropanol (60 %) was added to all wells for dissolving of the formazan crystals. The plates were then shaken at room temperature for 10 min and the absorbance was read at 540 nm in a microplate reader. The relative cell viability was calculated according to the following equation:

$$\text{Relative cell viability (\%)} = [(1 - (Abs_{\text{treated cell}}/Abs_{\text{control}})] \times 100$$

Where $Abs_{\text{treated cells}}$ and Abs_{control} are the absorbance values at 540 nm of sample with treated cells and control, respectively. Each test was carried out in six copies, and each experiment was repeated triplicate. For analysis of cell morphology and spreading, images of MCF-7 breast cancer cells were taken after 2 days incubation. The cell images were taken at 10x magnification using an inverted optical microscope (Olympus, Tokyo, Japan) equipped with a digital camera (DXM1200F, Nikon).

Statistical analysis

All data were statistically analyzed using the General Linear Models Procedure of the Statistical Analysis System SAS (1982). The significance of the differences among treatment groups was determined by Waller-Duncan k-ratio. All statements of significance were based on probability of $P \leq 0.05$.

RESULTS AND DISCUSSION

RD investigation of the synthesized sample showed that all the characteristic peaks of spinel $CoFe_2O_4$ phase with crystallite size of their particles 40 nm (Deraz, 2010, 2012). The microstructure of ($CoFe_2O_4$) NPs was analyzed using SEM technique and the micrograph showed the formation of spongy and fragile network structure (Fig. 1).

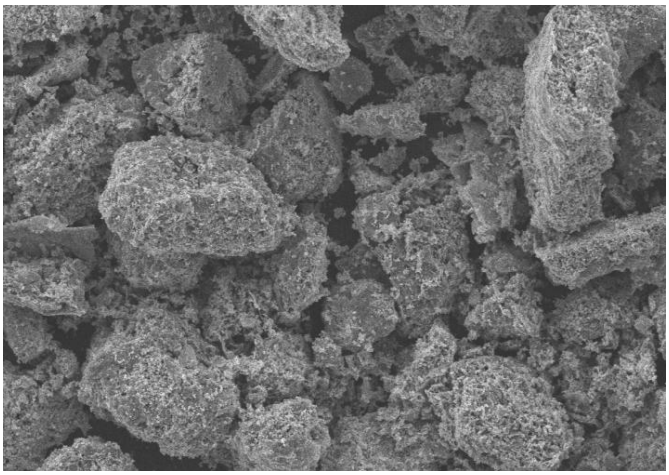


Fig. 1: SEM image for ($CoFe_2O_4$) NPs.

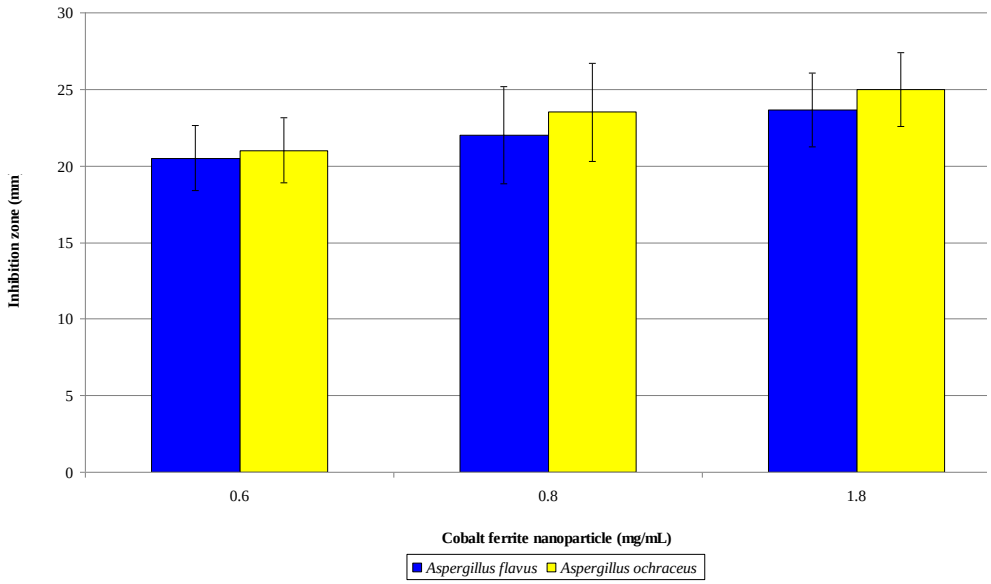


Fig. 2: Antifungal activity of ($CoFe_2O_4$) NPs using well agar diffusion test. Bars represent SD of three replicates.

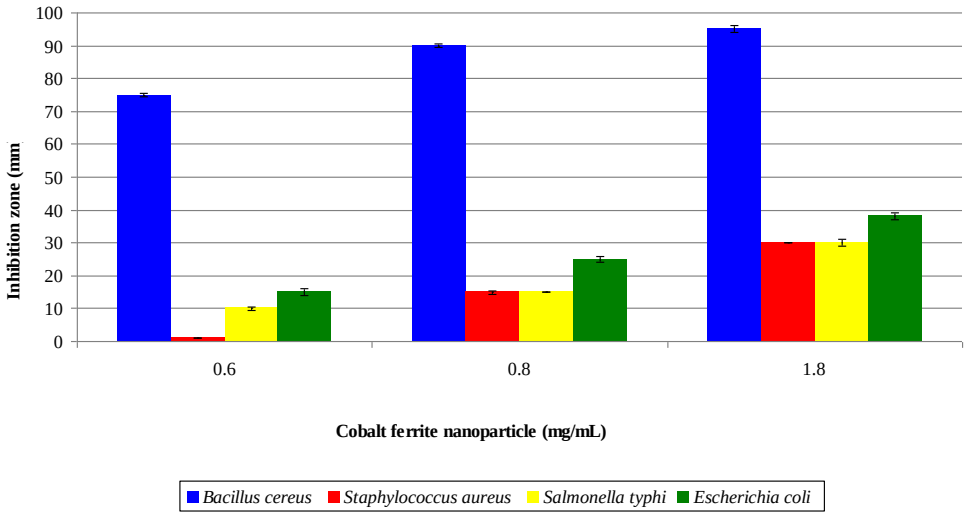


Fig. 3: Antimicrobial activity of cobalt ferrite nanoparticles using disk diffusion test. Bars represent SD of two replicates.

Antimicrobial activity

The antifungal activity of ($CoFe_2O_4$) NPs was tested against fungal cultures (*Aspergillus flavus* and *Aspergillus ochraceus*). The qualitative assessment of the antifungal effect was done using well agar diffusion test and the current results showed that the highest antifungal activity of ($CoFe_2O_4$) NPs was recorded at concentration 1.8 mg/mL against *Aspergillus flavus* and *Aspergillus ochraceus* although no significant difference was observed between the three tested concentrations of ($CoFe_2O_4$) NPs. The zone inhibition of *A. ochraceus* was absent at concentration of 0.8 mg/mL ($CoFe_2O_4$) NPs (Fig. 2).

Although there is limited data about the use of ($CoFe_2O_4$) NPs against pathogenic fungi, Chifiriuca *et al.* (2011) reported that ($CoFe_2O_4$) NPs produce a strong inhibitory effect on the adherence to the cellular substrate of *C. albicans* strains. On the other hand, the use of other metals nanoparticles such as ZnO showed antifungal activity against *Aspergillus*, *Fusarium*, *Penicillium* etc. (He *et al.*, 2011; Lipovsky *et al*., 2011; Chitra and Annadurai 2013; Dimkpa *et al*., 2013). The antifungal activity of metals nanoparticle may be due to suppression of extracellular enzymes and metabolites that helps its survival when exposed to stress as reported by Bhainsa and D' Souza (2006) and Vahabi *et al.* (2011).

The antibacterial activity of ($CoFe_2O_4$) NPs was qualitatively measured by performing disk diffusion test against pathogenic microorganisms (*Bacillus cereus*, *Staphylococcus aureus*, *Salmonella typhi* and *Escherichia coli*). The absence of growth around the nanoparticle is an indirect measure of the ability of the material to inhibit the bacteria growth. The zone inhibition produced by the nanoparticle against the gram negative and the gram positive bacteria is shown in Fig. (3). These results revealed that ($CoFe_2O_4$) NPs efficiently inhibited the growth of the microbes, whereas *B. cereus* was the most sensitive microorganism to the nanoparticles. It was also noticed that the

zone inhibition was increased by increasing the concentration from 0.6 to 1.8 mg/mL of ($CoFe_2O_4$) NPs. The effect of ($CoFe_2O_4$) NPs on bacterial linear growth (Fig. 4) revealed that the bacterial growth was decreased by increasing the concentrations of the nanoparticles. Similar results were reported by Sanpo *et al.* (2013a) who reported an antibacterial activity of ($CoFe_2O_4$) NPs against *E. coli* and *S. aureus*. In the same trend the rate of inhibition of *E.coli* was higher than that of *S. aureus*. The current results are in good harmony with several authors who reported that the nanocomposites of $CoFe_2O_4$ (Sanpo *et al*., 2013), polyaniline and nanosilver (Kooti *et al.*, 2014), and $CoFe_2O_4$/SiO2/Ag composite (Kooti *et al.*, 2015) showed high antibacterial activity. Moreover, Antoniea *et al.* (2012) found that the magnetite and ($CoFe_2O_4$) NPs induced the most significant effects in *S. aureus* and *B. subtilis*. Grumezescu *et al.* (2010) studied the effect of ($CoFe_2O_4$)/oleic acid nanoparticles and found that they induced inhibitory effects on clinical isolates of bacterial and fungal strains at concentrations between 1000 and 1.9 µg/mL. Another study conducted by Sanpo *et al*. (2013b), the authors focused on the influence of chelating agents, namely polyvinyl alcohol and citric acid, on the microstructure and antibacterial property of cobalt ferrite nanopowders, and demonstrated that both types of cobalt ferrite nanopowders showed an effective antibacterial activity against *E. coli* and *S. aureus* Several mechanisms have been suggested for the antibacterial action of nanoparticles. However, the actual inhibitory mechanism of the nanoparticles may require further studies (Moritz and Moritz, 2013). The antimicrobial activity of the nanoparticles is known to be the function of surface area which is adhesion to the microorganisms. The small size and the high surface to volume ratio i.e., large surface area enhances the interaction between the nanoparticles and the microbes to carry out a broad range of probable antimicrobial activities (Ravishankar and Jamuna, 2011).

Moreover, Vidya and Venkatesan (2015) suggested that nanoparticle bind to the membranes of microorganisms which can prolong the lag phase of the growth cycle and increase the generation time of the organisms. Other mechanisms contributing to the occurrence of antibacterial activity of nanoparticles is the release of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) and super-oxide (O^{2-}) generated from the surface of nanoparticles (Sawai, 2003; Hashim *et al.*, 2013). Furthermore, the penetration rate of an active oxide through the bacteria cell wall may play a part in the bacterial killing rate by nanoparticles (Xavier *et al*., 2014).

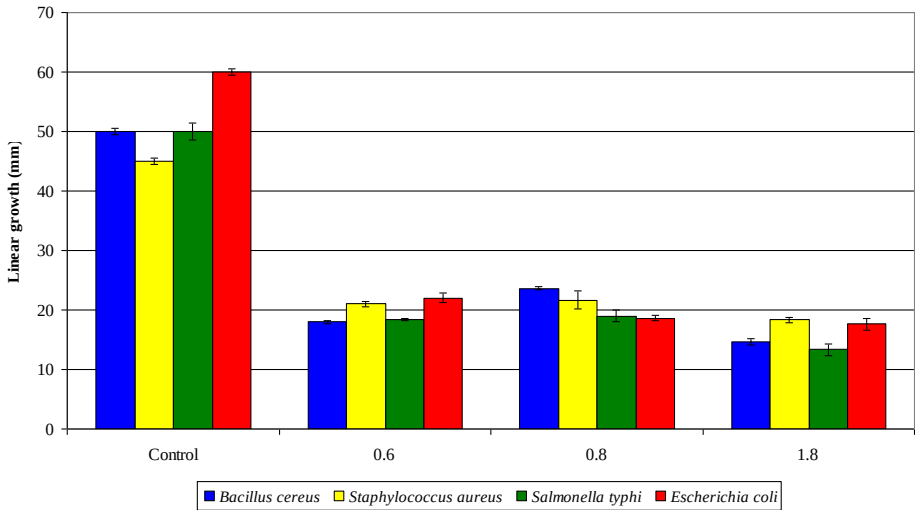
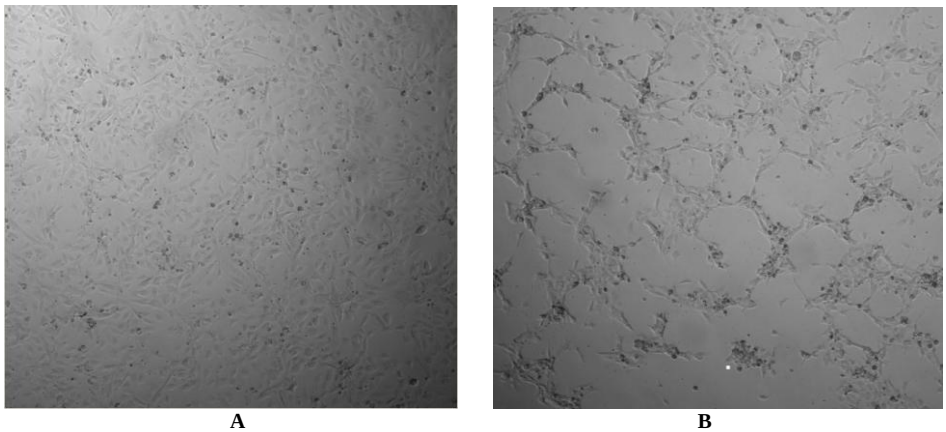


Fig. 4: Linear growth of pathogenic bacteria after treatment with different concentrations of cobalt ferrite nanoparticle. Bars represent SD of three replicates.



A **B**

Fig. 5: Photos of MCF-7 breast cancer cells cultivated for 2 days (A) and after incubation with 0.1 mg/mL ($CoFe_2O_4$) NPs (B) by optical microscope (10x magnifications).

Antiradical properties by DPPH free radical scavenging and ABTS radical cation decolorization assays

The results of DPPH and ABTS radical scavenging activities of ($CoFe_2O_4$) NPs were expressed as the half-maximal inhibition concentrations (IC_{50}). These results showed that IC_{50} values in DPPH and ABTS scavenging of ($CoFe_2O_4$) NPs were determined as 6.8 ± 0.20 mg/ml and 0.25 ± 0.02 mg/ml, respectively. However, natural standard antioxidant Trolox as vitamin E analogue and ascorbic acid as vitamin C have IC_{50} values at 2.19 ± 0.02 µg/ml and 5.3 ± 0.3 µg/ml, respectively in ABTS scavenging (Aljawish *et al.*, 2014). By comparing with this standard antioxidant, ($CoFe_2O_4$) NPs are considered as weak antioxidant because the release of reactive oxygen species (ROS) generated from the surface of nanoparticles (Hashim *et al.*, 2013).

Anti-proliferative activity

The effect of ($CoFe_2O_4$) NPs on MCF-7 breast cancer cells lines (Figs. 5A, B) indicated that exposure of the breast cell lines to 1 mg/mL of $CoFe_2O_4$ NPs resulted in a significant decrease in the cell viability and the relative cell viability reached 63 ± 3.6 %. It is well documented that the effect of a compound on tumor cells is mainly due to their oxidative stress effects. Tumor cells may, however, be dependent on a certain amount of hydrogen peroxide and the deficiency of hydrogen peroxide may resulted in cell cycle arrest or apoptosis of these cells (Loo, 2003). Similar to the current results, Horev-Azaria *et al.* (2013) reported that the viability of cell-lines towards the ($CoFe_2O_4$) NPs may be mainly attributed to their ability to interact with NPs in case of either the adsorption of NPs to the cell surface and/or the uptake of NPs by the cells. Moreover, Nel *et al*. (2006) reported that oxidative stress which defined as the imbalance between the antioxidant defenses and the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) is considered to be the most important mechanism of NPs-induced hazards effects. In this concern, Horev-Azaria *et al.* (2013) found a high linear correlation between the toxicity of ($CoFe_2O_4$) NPs and the amount of generated ROS following the exposure to ($CoFe_2O_4$) NPs. Previous study showed that NPs could generate ROS, exhaust endogenous antioxidants, affect the function of mitochondria and induce oxidative damage to DNA and lipids (Moller *et al.*, 2010). Consequently, NPs-induced ROS activation encourages the elements of defense antioxidant response and if damage proceeds, the protective systems activate protein kinase and NF-κB-activated intracellular signaling which resulted in the release of pro-inflammatory cytokine, matrix metalloproteinase and chemokine leading to apoptosis (Shubayev and Pisanic, 2009).

CONCLUSION

The current results indicated that ($CoFe_2O_4$) NPs can be synthesized by combustion method using glycine as fuel and the average particles size was 40 nm. The synthesized ($CoFe_2O_4$) NPs showed a potential antimicrobial activity against gram positive and gram negative bacteria as well as the pathogenic fungi *Aspergillus flavus* and *Aspergillus ochraceus* in a dose dependent manner. The concentration of 1.8 g/ml of ($CoFe_2O_4$) NPs showed maximum growth inhibition for all bacteria and fungi tested. Moreover the tested ($CoFe_2O_4$) NPs at a concentration of 2 mg/ml showed weak antiradical activity but have high cytotoxic effects against MCF-7 breast cancer cells lines and succeeded to decrease the cell viability by about 63%. These findings suggested that the toxicity of ($CoFe_2O_4$) NPs is partially due to oxidative stress. The antimicrobial and anticancer properties of ($CoFe_2O_4$) NPs reported herein give these NPs great advantages to be used in food and biomedical applications.

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Conflict of Interests: There are no conflicts of interest.

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