



ORIGINAL ARTICLE

Pectin mediated green synthesis of Fe₃O₄/Pectin nanoparticles under ultrasound condition as an anti-human colorectal carcinoma bionanocomposite



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Abstract This work described the one-pot synthesis of apple pectin encapsulated Fe₃O₄ nanoparticles (Fe₃O₄/Pectin NPs) which is prepared by co-precipitation of Fe(II)/(III) ions in alkaline solution mediated by pectin under ultrasound condition. This process led to formation of magnetic nanoparticles within the network of pectin. Physicochemical characterization of the as-synthesized Fe₃O₄/Pectin NPs was carried out through electron microscopy (SEM and TEM), energy dispersive X-ray spectroscopy (EDX), vibrating sample magnetometer (VSM) and X-ray diffraction (XRD). The in vitro cytotoxic and anti-colorectal cancer effects of biologically

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synthesized Fe₃O₄/Pectin NPs against Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29 cancer cell lines were assessed. The anti-colorectal cancer properties of the Fe₃O₄/Pectin NPs could significantly remove Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29 cancer cell lines in a time and concentration-dependent manner by MTT assay. The IC₅₀ of the Fe₃O₄/Pectin NPs were 317, 337, 187, and 300 µg/mL against Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29 cancer cell lines. The antioxidant activity of Fe₃O₄/Pectin NPs was determined by DPPH method. The Fe₃O₄/Pectin NPs showed the high antioxidant activity according to the IC₅₀ value. It seems that the anti-human colorectal cancer effect of recent nanoparticles is due to their antioxidant effects.

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1. Introduction

The reasons for the clinical trials' failed to achieve the desired multilayer results are complex and intertwined. Unfortunately, therapeutic agents (chemotherapy, biology, and nanotechnology) are so selective and effective in targeting in vitro cancer cells, and even in proportionate animal specimens (Stewart B., Wild C.P. *World Cancer Report*, 2014; Rasmussen et al., 2010; Felice et al., 2014; Fernandes et al., 2015). However, failing in clinical trials is not a rule but a rule. This is because the biological distribution of therapeutic agents can be a fundamental factor in these fractures. Inadequate concentration at unwanted concentration and target sites elsewhere, leading to dose-limiting poisoning (Rasmussen et al., 2010; Felice et al., 2014). The biological distribution of drug agents is controlled largely by the drugs ability to penetrate biological barriers. Strategy for Adding Targeting Sections to Therapeutic Nanoparticles to Improve Location Specification to date, despite 30 years of effort in pharmaceutical companies and many laboratories, it has not yet been able to produce clinically approved drugs (Felice et al., 2014; Fernandes et al., 2015). This failure is because the addition of molecular agents increases the targeting of cognitive characteristics. However, it does so in the face of much greater difficulty in managing biological barriers (Caputo et al., 2014; Veisi et al., 2020; Doustkhah et al., 2018; Maier-Hauff et al., 2011; Kolosnjaj-Tabi et al., 2014).

Nanotechnology is defined in different ways in several countries, which affects the nanodrugs clinical validation. However, what these different definitions have in common is the use of nanoscale structures (Caputo et al., 2014; Veisi et al., 2020; Doustkhah et al., 2018). There are several distinct benefits to using nanotechnology in the diseases treatment. Nanoparticles, especially metal nanoparticles and metal oxides, have been widely used by medical consumers and manufacturers. The mechanism of nanoparticle-induced toxicity against cancer cells is the production of reactive oxygen species (ROS) (Maier-Hauff et al., 2011; Kolosnjaj-Tabi et al., 2014; Bhattacharyya et al., 2011; Hilger and Kaiser, 2012). Excessive production of reactive oxygen species can lead to oxidative stress, disruption of normal physiological maintenance, and oxidation regulation. These effects in turn lead to DNA damage, unregulated cell signaling pathways, changes in cell evolution, cytotoxicity, apoptotic death, and the onset of cell death (Orel et al., 2015; Van Landeghem et al., 2009; Silva et al., 2011; Johannsen et al., 2010). Critical-

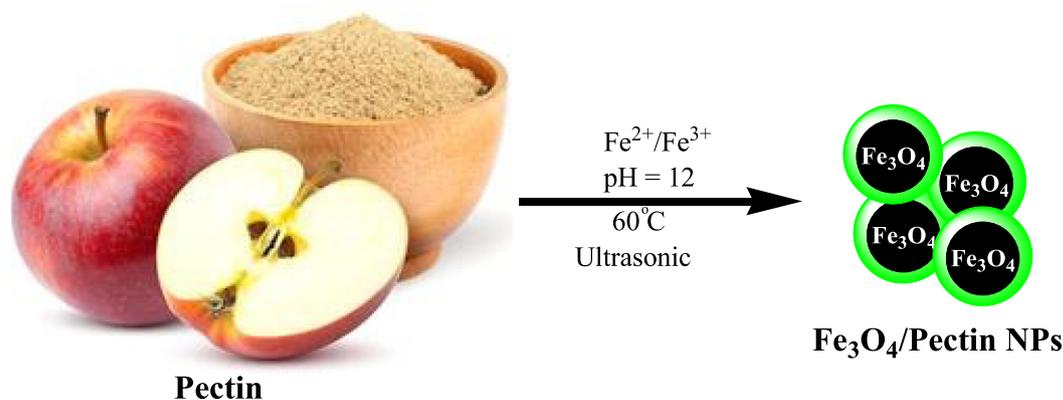
deterministic factors can affect the production of reactive oxygen species. These critical-deterministic factors include shape, size, nanoparticle surface area, particle surface baroelectricity, surface-forming groups, Particle solubility, metal ion emission from nanomaterials and nanoparticles, optical activation, model of cell reactions, inflammatory effects and ambient pH (Johannsen et al., 2010; Bañobre-López et al., 2013; Klein et al., 2014; Chatterjee et al., 2008; Zhang and Sun, 2004). Metal nanoparticles and oxides of metal nanoparticles due to their optical properties due to the large active area and high atomic number, amplify the photoelectric and Compton effects of both X-ray and gamma-ray interactions with the adsorbent in the diagnostic and therapeutic range (Thevenot et al., 2008; Colon et al., 2010; Wason et al., 2013; Tarnuzzer et al., 2005). Finally, they can lead to the development of methods for the destruction of tumor cells and reduce their survival with minimal side effects in radiation therapy. As a result, increasing industrial knowledge in the field of scalable nanoparticle synthesis, along with the design of multifunctional nanoparticles, will dramatically change the strategies of microenvironmental preparation and therapeutic-diagnostic nanoparticles for cancer treatment (Ali et al., 2014; Neri and Supuran, 2011; Seo et al., 2007; Hou et al., 2015; Cui et al., 2013; Lucky et al., 2015; Idris et al., 2014).

Pectin is a natural biopolymer, which is usually obtained from fruit. Therefore, this polymer, polygalacturonic acid, is a polysaccharide that contains carboxylate groups in each monomer. This fact can cause pectin to have some additional advantages rather to other analogues. Carboxylate groups can act as a covalently chelating agent to Fe₃O₄ nanoparticles and surrounds it as shell. A general and schematic pathway for one-pot preparation of Fe₃O₄/Pectin NPs that presented in Scheme 1. In the current research, the properties of Fe₃O₄/Pectin NPs against common colorectal cancer cell lines i.e. Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29 were evaluated.

2. Experimental

2.1. Preparation of orange pectin coated Fe₃O₄ nanoparticles (Fe₃O₄/Pectin NPs)

In a typical procedure, 0.2 g of apple pectin was dissolved in deionized water (50 ml) in a 100-mL three-necked flask equipped with a stirrer and dropping funnel. Then, FeCl₃·6H₂O



Scheme 1 Schematic one-pot preparation of Fe₃O₄/Pectin NPs under ultrasound condition.

O (0.84 g) and FeCl₂·4H₂O (0.34 g) were slowly added into the mixture. The mixture was sonicated for 15 min at 60 °C, and then 1 mol/L NaOH aqueous solution was added under ultrasonic condition by dropping into the mixture until the pH increased to 12. The products from this system were magnetized for 30 min by a magnet. The precipitates were cooled, washed and diluted to neutrality by deionized water. The powder of Fe₃O₄/Pectin NPs was obtained by air drying.

2.2. DPPH assay protocol

DPPH is a free radical that changes color in the presence of substances with antioxidant properties and captures electrons. Yellow to purple color change is the basis of antioxidant properties. Solutions with different concentrations (10 to 1000 µg/ml) were prepared from phenolic powder and BHT synthetic antioxidant in methanol solvent. 1 ml of DPPH methanol solution was added to 1 ml of concentrate to 3 ml of nanoparticles and the resulting mixture was stirred vigorously. The test tubes were placed in a dark place for 30 min. After this period, the absorbance at the wavelength of 517 nm was read. It should be noted that in the control sample, the nanoparticles was replaced with 3 ml of methanol. Finally, the DPPH radical's inhibition percentage was calculated with this formula (Chen et al., 2006; Das et al., 2007; Korsvik et al., 2007; Hong et al., 2006; Zangeneh et al., 2019):

$$\text{Inhibition(\%)} = \frac{\text{SampleA.}}{\text{ControlA.}} \times 100$$

2.3. MTT assay protocol

Cell culture is the process of culturing eukaryotes in a culture medium where the culture conditions are different for each cell type and these conditions must be provided for its better growth; But in general, artificial environments should contain nutrients such as vitamins, minerals, sugars, amino acids, hormones and gases. In this environment, physical and chemical conditions must also be adjusted for the cells to grow better. Due to the differences in cell types, some of these cells need a surface to attach to grow, and others can grow floating in the culture medium. In the laboratory, there is a specific cell culture medium for specific cells. The culture medium suitable for hepatocytes is different from the culture medium for neu-

rons. For the better proliferation of cells in the culture medium, the cell density in the culture medium should not be high. The cells should be transferred to a new medium (passage) every few days. If the density and volume of the cells increase, the proliferation decreases due to lack of contact and the cells differentiate. Evaluation of cells in terms of growth, nutritional requirements and growth arrest, changes in cell morphology under a microscope are the goals of cell culture. To study the cell growth cycle, control the growth of cancer cells and study the expression of genes, cell culture must be performed outside the body to better study the type of growth and growth rate of cells. The study of animal evolution is one of the applications of cell culture. How can a fertilized cell become a percellular organism, and how does each cell differ in morphology under a microscope? To answer this question, it is better to culture the fertilized a cell in the laboratory and evaluate the stages of cell culture based on evolution. In cell culture medium, cells are prepared that are in the process of differentiation and differentiate into new cells with hormones and growth factors. By cell culture, identical cells are produced and intracellular functions such as DNA replication, DNA transcription, RNA and protein synthesis, and cell metabolism are examined. After the molecule binds to its membrane receptor, intracellular reactions such as complexes, intracellular messages, and message transmission are evaluated. The cultured cells can be stored at a very low temperature. The low temperature maintained the growth rate or genetic composition of the cells. Cells can be used when needed, for example, a month later. This method prevents cell aging. In studies with animals such as rats and rabbits, animal homeostasis and experimental stress should be considered. However, this is not the case in cell culture. Standardizing laboratory tests is easier than studying animals; in the laboratory, it is easier to control physicochemical factors, cell environments such as acidity, heat, osmotic pressure, and oxygen and carbon dioxide pressures (Jalalvand et al., 2019).

In this study, the anticancer effects of Fe₃O₄/Pectin NPs samples against the colorectal cancer cells (Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29) were investigated.

These cells in DMEM culture medium (Gibco, USA) with 10% FBS (Gibco, USA) and penicillin/streptomycin (100 µl/100 µg/ml) in an incubator containing 5 % Carbon dioxide with 90% humidity was stored at 37 °C. Then, when about 80% of the flask was filled, cell passage was performed

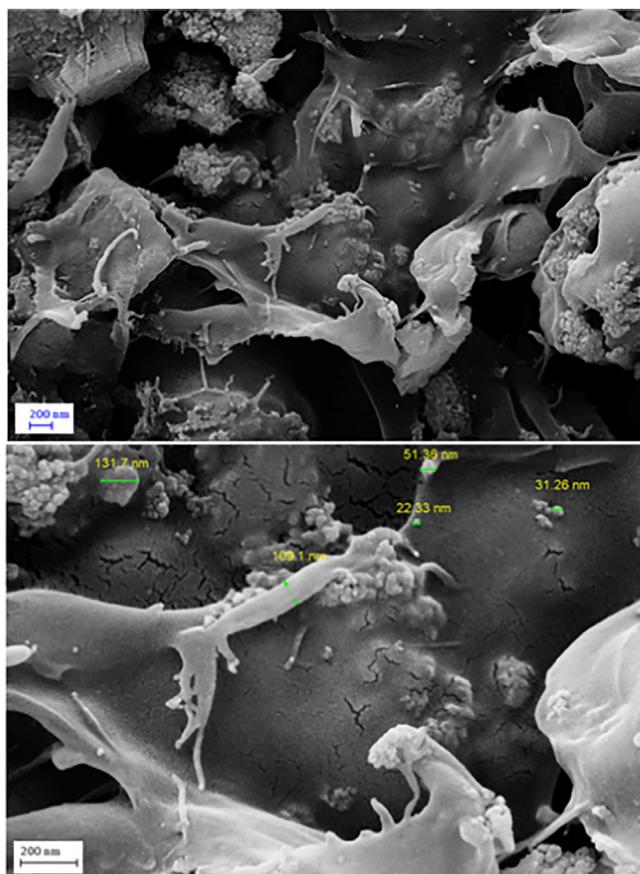


Fig. 1 FE-SEM images of $\text{Fe}_3\text{O}_4/\text{Pectin}$ NPs.

and about 5×10^4 cells (per square centimeter) were placed in 24 house bacterial petri dishes in the usual environment. The cells were treated with different concentrations of nanoparticles 24 h later and kept in this condition for 3 days. The survival rate of cultured cells was prepared with different concentrations. In this experiment, cells were cultured at 3×10^4 cells/well in 24-well plates and kept in an incubator at 37°C for 24 h. Then the old culture medium was taken

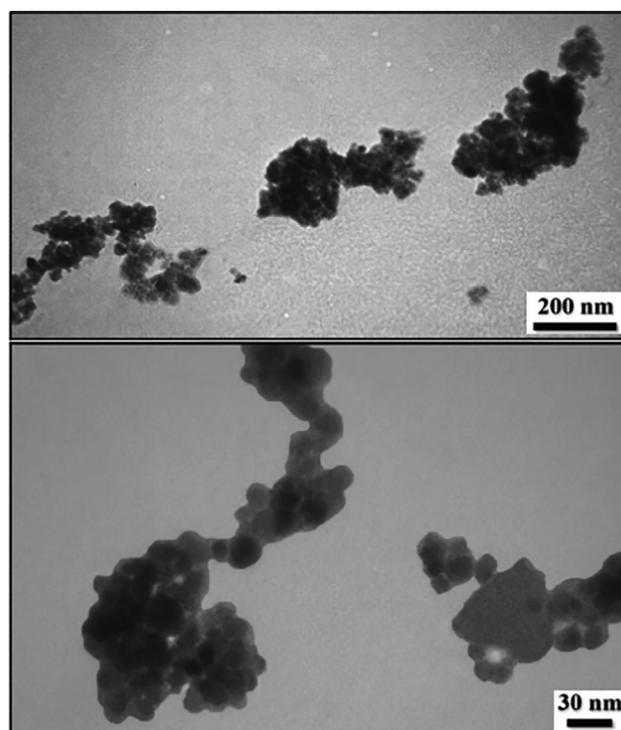


Fig. 2 TEM images of $\text{Fe}_3\text{O}_4/\text{Pectin}$ NPs.

out of the wells and the cells were treated with different concentrations of nanoxidro. This test was performed on the first, second and third days after exposing the cells to the compounds; thus, at the appropriate time after culturing the cells in plates of 24 cells, the culture medium was removed and about $300 \mu\text{l}$ of fresh medium containing $30 \mu\text{l}$ of MTT solution was added to each cell. After 3–4 h of incubation at 37°C , MTT solution is removed and $200 \mu\text{l}$ (Dimethyl Sulfoxide, Merck, USA, 100%) DMSO is added to each house. Then the sample absorption was read at 570 wavelengths using ELISA rider (Expert 96, Asys Hitch, Ec Austria). This experiment was repeated 3 times and each time, four wells were considered for each nano oxide concentration. Cell survival

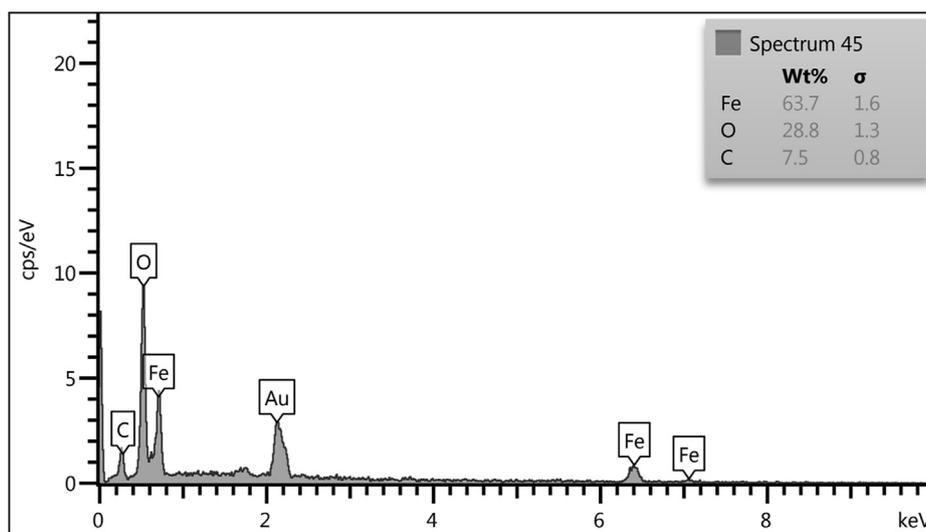


Fig. 3 EDX spectrum of $\text{Fe}_3\text{O}_4/\text{Pectin}$ NPs.

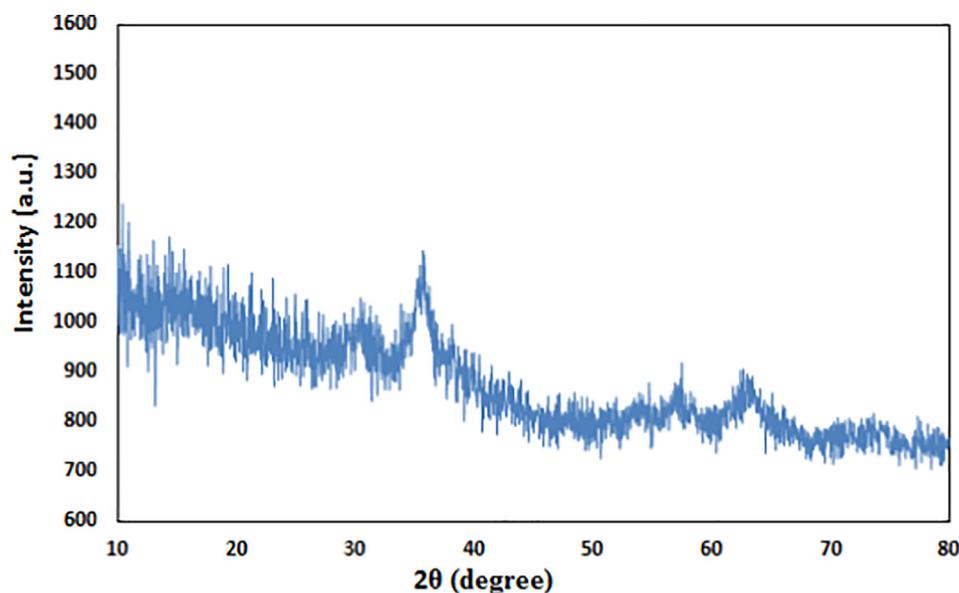


Fig. 4 XRD pattern of Fe₃O₄/Pectin NPs.

percentage was evaluated by the following formula (Jalalvand et al., 2019):

$$\text{Cellviability}(\%) = \frac{\text{SampleA.}}{\text{ControlA.}} \times 100$$

The results were evaluated as Mean \pm SE using SPSS software version 12 and statistical tests of variance of completely randomized block design. Drawing graphs in Excel software was performed and the significance level of the differences was considered $p < 0.01$.

3. Results and discussion

3.1. Catalyst characterization data analysis

We have used co-precipitation of Fe(II) and Fe(III) in the presence of orange pectin leading to formation of Fe₃O₄/Pectin NPs in one-pot (Scheme 1). The structural, morphological and physicochemical properties of the Fe₃O₄/Pectin NPs were determined by various analytical techniques including FE-SEM, EDX, TEM, VSM and XRD study.

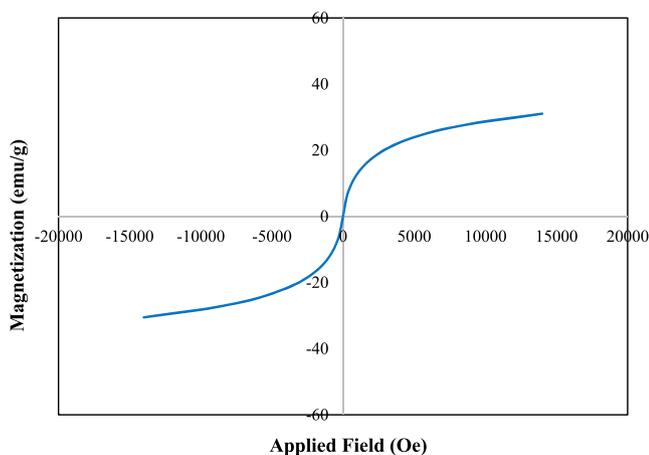


Fig. 5 VSM analysis of Fe₃O₄/Pectin NPs.

In order to have an idea of structural morphology, shape and size of Fe₃O₄/Pectin NPs nanocomposite, the electronic microscopic analysis (TEM and SEM) were performed (Figs. 1 and 2). The particles are of globular shape. The grey and black particles represent the Fe₃O₄ NPs that encapsulated in the pectin matrix. The homogeneous growth in the form of a thin layer of pectin polymer can be detected by close observation (Fig. 1 and Fig. 2). The pectin also stabilizes the corresponding NPs not to agglomerate together.

Chemical composition of the nanocomposite was assessed from EDX analysis and the profile is shown in Fig. 3. It represents Fe, O, and C as elemental components. The occurrence of carbon confirmed the presence of pectin and successful fabrication of Fe₃O₄/Pectin NPs.

Crystalline phases and the diffraction planes of the Fe₃O₄/Pectin NPs was ascertained by XRD study, that shown in Fig. 4. It represents a single phase profile indicating a united entity of the assembled counterparts. The typical diffraction peaks due to Fe₃O₄ are observed at $2\theta = 30.1, 35.4, 43.3, 53.6, 57.1, 62.7^\circ$ corresponding to (220), (311), (400), (422), (511) and (440) Bragg reflection planes respectively (JCPDS file, PDF No. 65-3107). Three additional broad diffraction peaks observed at $2\theta = 10-20^\circ$ are contributed from pectin polymers.

VSM study was carried out to determine the magnetic properties of the Fe₃O₄/Pectin NPs. On passing an external magnetic field of -20kOe to $+20\text{kOe}$, a magnetic hysteresis curve is obtained and the corresponding saturation magnetiza-

Table 1 The IC₅₀ of Fe₃O₄/Pectin NPs in the anti-colorectal carcinoma test.

	Fe ₃ O ₄ /Pectin NPs ($\mu\text{g/mL}$)
IC ₅₀ against Ramos.2G6.4C10	317 ± 0^b
IC ₅₀ against HCT-8 [HRT-18]	337 ± 0^b
IC ₅₀ against HCT 116	187 ± 0^a
IC ₅₀ against HT-29	300 ± 0^b
IC ₅₀ against HUVEC	–

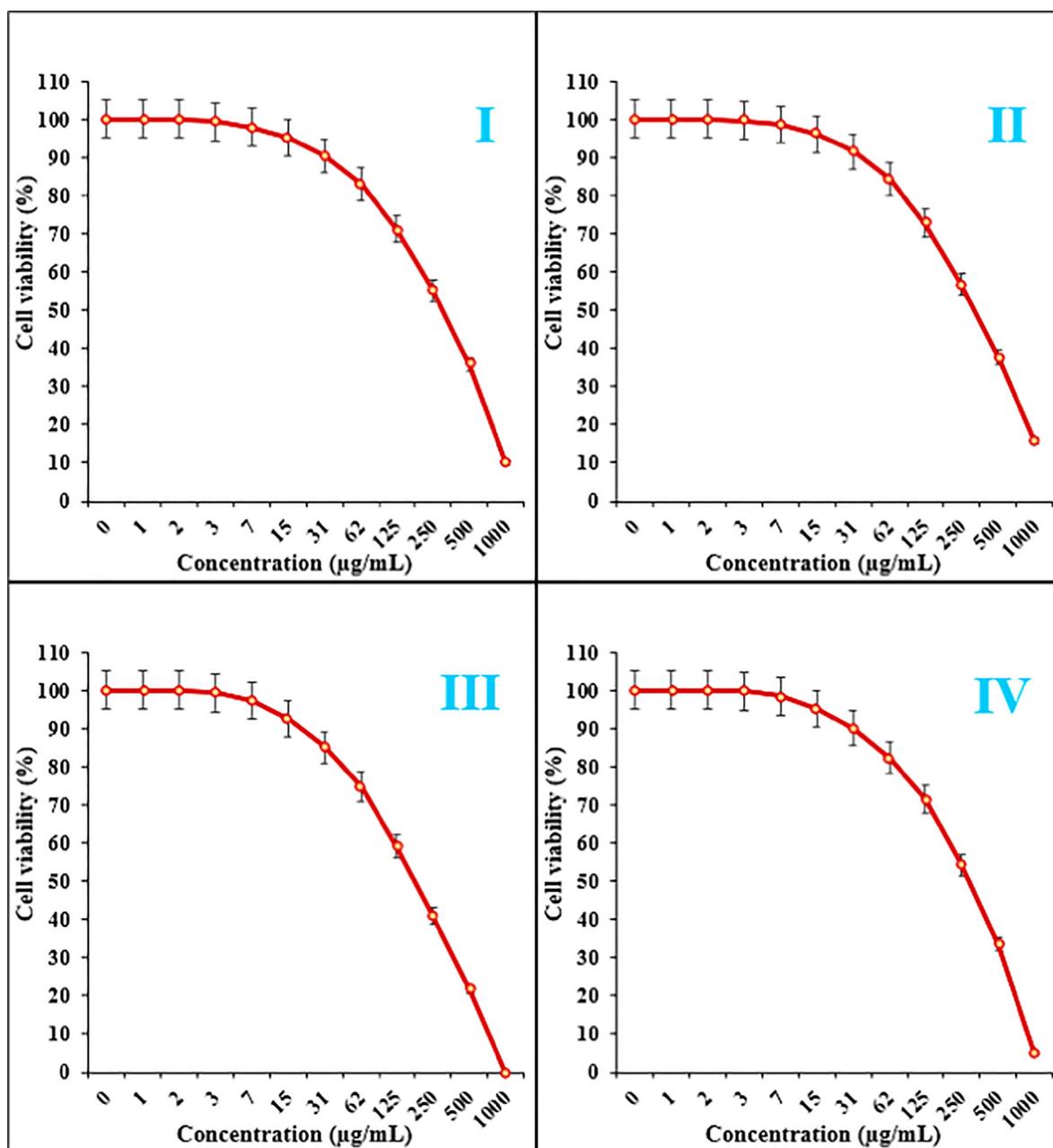


Fig. 6 The anti-colorectal carcinoma properties of Fe₃O₄/Pectin NPs against Ramos.2G6.4C10 (I), HCT-8 [HRT-18] (II), HCT 116 (III), and HT-29 (IV) cell lines.

tion (M_s) value of Fe₃O₄/Pectin NPs was 52.5 emu/g (Fig. 5). It clearly reveals the material to be superparamagnetic in nature.

3.2. The bio application of Fe₃O₄/Pectin NPs

Regarding cancer, efforts have been made to use smart nano-materials (nanoparticles, nanostructures), which have a greater ability to target cancer cells, to treat such patients. That is, they kill malignant cells by irradiating them, providing a microscopic therapeutic effect within electrons (Hilger and Kaiser, 2012; Orel et al., 2015; Van Landeghem et al., 2009; Silva et al., 2011; Johannsen et al., 2010). Nanoparticles are

programmed to achieve optimal therapeutic efficacy, delivering therapeutic loads to target cells. Studies have also been performed on several nanocarriers based on lipids, polymers, and peptides for delivery to the respiratory system (Bañobre-López et al., 2013; Klein et al., 2014; Chatterjee et al., 2008; Zhang and Sun, 2004). Properties of nanoparticles for targeted delivery of nanoparticles to tumors is the motivation for targeted drug delivery in cancer treatment to kill cancer cells. In a way, that has the least damage to healthy cells (Thevenot et al., 2008; Colon et al., 2010; Wason et al., 2013; Tarnuzzer et al., 2005; Ali et al., 2014). One of the nanotechnology goals is to mount drugs on carriers, send them and release them into the target cell, which is called targeted drug

delivery. Using nanoparticles, the drug can be intelligently delivered to the desired tissue, and improve the tissue without damaging other tissues (Neri and Supuran, 2011; Seo et al., 2007; Hou et al., 2015; Cui et al., 2013; Lucky et al., 2015; Idris et al., 2014).

In this study, the treated cells with different concentrations of the present Fe₃O₄/Pectin NPs were assessed by MTT assay for 48 h about the cytotoxicity properties on normal (HUVEC) and colorectal malignancy cell lines i.e. Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29. The absorbance rate was evaluated at 570 nm, which represented viability on normal cell line (HUVEC) even up to 1000 µg/mL for Fe₃O₄/Pectin NPs (Table 1 and Fig. 6,7). The viability of malignant colorectal cell line reduced dose-dependently in the presence of Fe₃O₄/Pectin NPs. The IC₅₀ of Fe₃O₄/Pectin NPs were 317, 337, 187, and 300 µg/mL against Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29 cell lines, respectively (Table 1 and Figs. 6 and 7).

Nanoparticles have several compounds, each with a different structure. The extraction of these compounds depends on several factors, the most important of which are the type of solvent and the extraction method. It will be very difficult to choose a solvent for any group of nanoparticles compounds, because with these compounds, there are other substances that affect the degree of solubility of these substances (Thevenot et al., 2008; Colon et al., 2010; Wason et al., 2013; Tarnuzzer et al., 2005; Ali et al., 2014). When extracting nanoparticles, it should be noted that always use a method that has the best performance in the survival of antioxidant compounds. Usually nanoparticles have unique antioxidant effects (Seo et al., 2007). Recent studies have shown that when the plant extracts are placed in metal nanoparticles as stabilizing and reducing compounds, they form nanocomposites with extraordinary antioxidant effects. Antioxidants are generally referred to as substances that can delay, slow down, and even stop oxidation processes (Zangeneh et al., 2019; Jalalvand

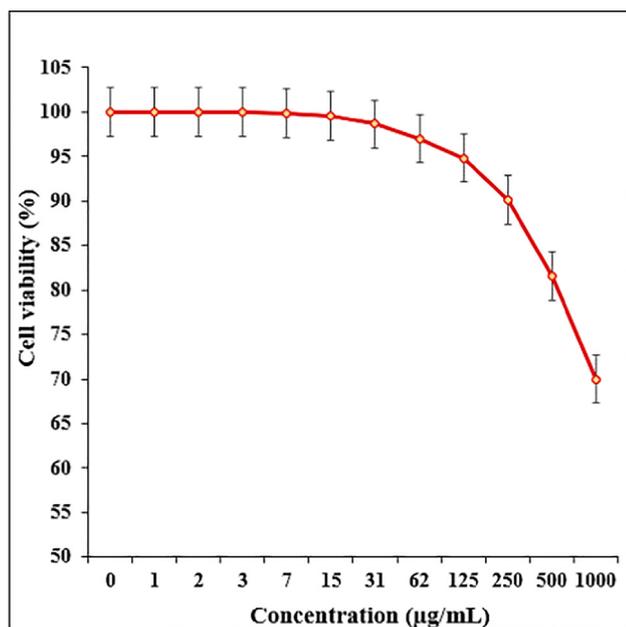


Fig. 7 The cytotoxicity effects of Fe₃O₄/Pectin NPs against normal (HUVEC) cell line.

Table 2 The IC₅₀ of Fe₃O₄/Pectin NPs and BHT in antioxidant test.

	Fe ₃ O ₄ /Pectin NPs (µg/mL)	BHT (µg/mL)
IC ₅₀ against DPPH	180 ± 0 ^b	86 ± 0 ^a

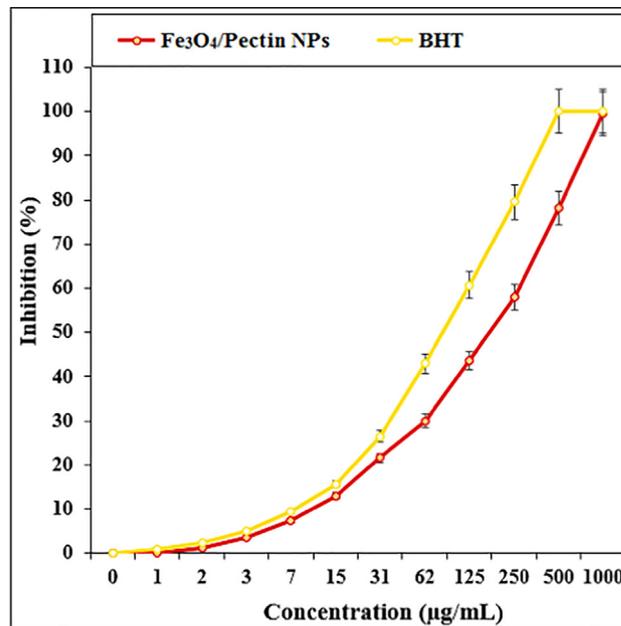


Fig. 8 The antioxidant properties of Fe₃O₄/Pectin NPs and BHT against DPPH.

et al., 2019; Barclay et al., 1990; Hamelian et al., 2018; Esumi et al., 2003). These compounds can optimally prevent changes in the color and taste of food because of oxidation reactions. The antidote to the mechanism of oxidants is that they prevent the spread of oxidation chain reactions by giving hydrogen atoms to free radicals. In recent years, the synthetic antioxidants use such as BHT, BHA, TBHQ as well as other chemical additives has been limited due to their potential toxicity and carcinogenicity. Today, most research in this area focuses on the use of new and safe antioxidants from plant, animal, microbial and food sources (Chen et al., 2006; Das et al., 2007; Korsvik et al., 2007; Hong et al., 2006).

The scavenging capacity of Fe₃O₄/Pectin NPs and BHT at different concentrations expressed as percentage inhibition has been indicated in Table 2 and Fig. 8. In the antioxidant test, the IC₅₀ of Fe₃O₄/Pectin NPs and BHT against DPPH free radicals were 180 and 86 µg/mL, respectively (Table 2 and Fig. 8).

4. Conclusion

In summary, we demonstrate herein a unique biocompatible, natural polymer-apple pectin modified and magnetically isolable Fe₃O₄/Pectin NPs being successfully prepared by green method in one-pot. The prepared Fe₃O₄/Pectin NPs was characterized by a wide range of analytical techniques. The viability of malignant colorectal cell lines reduced dose-dependently in the presence of Fe₃O₄/Pectin NPs. The IC₅₀ of Fe₃O₄/Pectin

NPs were 317, 337, 187, and 300 $\mu\text{g/mL}$ against Ramos.2G6.4C10, HCT-8 [HRT-18], HCT 116, and HT-29 cell lines, respectively. The Fe_3O_4 /Pectin NPs showed the best antioxidant activities against DPPH. So, the findings of the recent research show that biologically synthesized Fe_3O_4 /Pectin NPs might be used to cure colorectal cancer. In addition, the current study offer that Fe_3O_4 /Pectin NPs could be a new potential adjuvant chemopreventive and chemotherapeutic agent against cytotoxic cells. However, it necessitates clinical trial researches to ascertain their effect as anticancer agents.

Ethics explanation

This research was approved by The People's Hospital of Jianhu animal ethical committee, Approved No. JHQR210412.

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