

RESEARCH ARTICLE

Optimized Gold-Coated CoFe₂O₄ Magnetic Nanoparticles: Advancing Theranostic Applications in MRI Enhancement and Magnetic Hyperthermia for Cancer Treatment

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ABSTRACT

Objective(s): Magnetic nanoparticles (MNPs), including cobalt ferrite (CoFe₂O₄), have been investigated as promising tools in improvement of medical imaging and treatment methodologies. While CoFe₂O₄ exhibits superior magnetic properties, its biomedical applications require surface modifications to address biocompatibility concerns. This study is another step to explore the dual functionality of optimized gold-coated CoFe₂O₄ nanoparticles, aiming to enhance magnetic resonance imaging (MRI) contrast and improve the efficacy of magnetic hyperthermia (MH) within a cellular environment.

Methods: Optimized CoFe₂O₄@Au (cobalt ferrite core, gold shell) nanoparticles were utilized in this study. MR imaging parameters (r1, r2, and r2/r1) were then calculated in cellular environments. Subsequently, the effects of magnetic hyperthermia induction on cell survival were evaluated at temperatures of 41°C, 44°C, 47°C, and 52.5°C immediately after treatment using the MTT assay.

Results: Among various incubation times, CoFe₂O₄@Au exhibited the highest r2 value of 165.5 mM⁻¹s⁻¹ at 4 hours incubation time in a cell medium. A phantom prepared with the MDA-MB 231 cell line incubated with CoFe₂O₄@Au@dextran showed a magnetic susceptibility artifact. Inducing cellular hyperthermia at temperatures below 47°C did not significantly affect cell survival, while higher temperatures (47-52.5°C) caused substantial cell damage and death through protein denaturation and thermoablation.

Conclusions: These findings highlight the potential of CoFe₂O₄@Au@dextran nanoparticles in theranostic applications, combining diagnostic imaging with targeted cancer therapy. Further research is essential to optimize these nanoparticles for clinical use, with a focus on achieving a balance between efficacy, safety, and biocompatibility.

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INTRODUCTION

Cancer theranostics has emerged as an advanced strategy that integrates diagnostic imaging and targeted therapy within a single platform, enabling simultaneous disease monitoring and treatment [1]. Nanotechnology has played a

pivotal role in advancing this field by facilitating the design of multifunctional nanostructures capable of improving imaging sensitivity while enhancing therapeutic efficacy [2]. In particular, magnetic nanoparticles (MNPs) have attracted significant attention due to their dual functionality as contrast agents in magnetic resonance imaging (MRI)

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and as heat mediators in magnetic hyperthermia (MH) under an alternating magnetic field (AMF) [3]. Superparamagnetic iron oxide nanoparticles (SPIONs) were the first magnetic nanomaterials approved for clinical use, primarily for MRI-related applications. Dextran-coated iron oxide nanoparticles demonstrated acceptable safety and biocompatibility, leading to their approval for specific diagnostic purposes by regulatory agencies such as the U.S. Food and Drug Administration (FDA) [4]. Currently, Ferumoxsil remains one of the clinically approved iron oxide-based agents for gastrointestinal imaging [4]. Over time, the application of SPIONs in clinical practice has expanded well beyond their initial use. These versatile nanoparticles are now widely utilized due to their unique properties, which allow for both T1 and T2 relaxation shortening effects in magnetic resonance imaging (MRI) [4, 5]. Despite their clinical relevance, SPIONs suffer from intrinsic limitations, including relatively low magnetic anisotropy and reduced heating efficiency, particularly at smaller particle sizes and under physiological conditions [6]. Moreover, interactions between iron ions and biological components such as hemoglobin may adversely affect their magnetic performance and biological stability [6, 7]. To address these limitations, cobalt-based ferrite nanoparticles have been proposed as promising alternatives to conventional iron oxide systems. Cobalt ferrite (CoFe_2O_4) exhibits higher magnetic anisotropy than iron oxide, resulting in enhanced heat generation efficiency during magnetic hyperthermia, especially at the nanoscale [8-10]. However, the application of ferromagnetic nanoparticles raises concerns related to aggregation, oxidation, and potential vascular complications following systemic administration [11, 12]. Consequently, appropriate surface modification is essential to ensure colloidal stability, biocompatibility, and reduced toxicity. Surface coating strategies using biocompatible materials, including polymers, organic compounds, and noble metals, have been widely employed to mitigate these challenges [13]. In particular, gold (Au) shells offer chemical stability, low surface reactivity, and improved biocompatibility, making them attractive for biomedical applications [14]. Polymer coatings such as dextran further enhance dispersion stability and biological compatibility, resulting in core-shell nanostructures suitable for theranostic use. In this study, we investigate

a dextran-coated gold-shelled cobalt ferrite nanostructure ($\text{CoFe}_2\text{O}_4@\text{Au@dextran}$) as a multifunctional theranostic agent. The synthesized nanoparticles were evaluated for their potential to enhance MRI contrast and to generate heat efficiently for magnetic hyperthermia at the cellular level. By focusing on imaging-guided hyperthermia and translational applicability, this work aims to contribute to the clinical advancement of magnetic nanoparticle-based cancer theranostics.

MATERIAL AND METHODS

Cell line and Chemicals

In this study, the MDA-MB-231 human breast cancer cell line was obtained from the Pasteur Institute of Iran. All chemicals were purchased from commercial suppliers: sodium hydroxide (NaOH), gold chloride (HAuCl_4), glycine, sodium tetrahydroborate, trisodium citrate, ascorbic acid, and dextran (10,000 Da) were obtained from Merck, while cobalt chloride (CoCl_2) and ferric sulfate ($\text{Fe}_2(\text{SO}_4)_3$) were acquired from Aldrich.

The Synthesis of $\text{CoFe}_2\text{O}_4@\text{Au@dextran}$

The cobalt ferrite (CoFe_2O_4) core was synthesized using a three-necked flask containing oxygenated water and a mixture of cobalt and iron precursors in the presence of glycine. The reagents were added sequentially at 15-min intervals under continuous stirring to ensure homogeneity. The reaction temperature was gradually increased from room temperature to 80 °C, followed by dropwise addition of sodium hydroxide until the pH reached 12.5 [10]. The synthesis of $\text{CoFe}_2\text{O}_4@\text{Au}$ nanoparticles was performed in multiple steps. First, CoFe_2O_4 nanoparticles (0.1 g) were dispersed in 50 mL of methanol to obtain Product A. Gold nanoparticles (Product B) were synthesized by reducing a gold salt with citrate and sodium borohydride. Product A was then slowly added to Product B, followed by dilution with distilled water. After three washing steps, the resulting product (Product C) was characterized by UV-Vis spectroscopy. Gold coating of the CoFe_2O_4 nanoparticles (Product D) was achieved by sonicating Product C with a gold salt solution and subsequently adding ascorbic acid as a reducing agent. After washing, the resulting $\text{CoFe}_2\text{O}_4@\text{Au}$ nanoparticles were dispersed in distilled water. Dextran functionalization was then carried out by adding a dextran solution containing sodium carbonate and cyanogen bromide. The pH was

adjusted, sodium dihydrogen phosphate was added, and the mixture was stirred and dialyzed to obtain the final dextran-coated nanostructures [10].

Characterization of the nanostructures

The nanostructures were characterized using a range of analytical techniques, including transmission electron microscopy (TEM), X-ray diffraction (XRD), scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDS), and atomic absorption spectroscopy (AAS) [10].

Relaxometric experiments

The MDA-MB-231 cell line was employed to evaluate the MR imaging properties of the nanostructures at the cellular level. Cells were incubated with CoFe₂O₄ and CoFe₂O₄@Au nanoparticles at concentrations of 0.01, 0.02, 0.04, 0.08, 0.15, and 0.3 mM CoFe₂O₄ for 0.5, 2, 4, or 24 hours. Following incubation, the cellular samples were placed in a water phantom and subjected to relaxometry using a 1.5 Tesla MRI system (Siemens). In subsequent experiments, optimized nanoparticles (CoFe₂O₄@dextran and CoFe₂O₄@Au@dextran) were assessed using relaxometry at both 1.5 and 3 Tesla. Nanoparticles at concentrations of 0.04, 0.08, 0.15, 0.3, and 0.6 mM were imaged to determine their relaxation properties under magnetic field strengths of 1.5 and 3 Tesla.

Magnetic hyperthermia in the cellular environment

A total of 4×10^4 MDA-MB-231 cells were seeded in 35-mm Petri dishes for the different experimental groups. After drug incubation, magnetic hyperthermia was applied using an MSI magnetic induction heating system (USA) at a resonance frequency of 425 MHz, a magnetic field intensity of 33.5 mT, and a power output of 4.3 kW. The temperature was raised to 41°C, 44°C, 47°C, and 52.5°C, as monitored by fiber-optic thermometry and thermographic imaging. Immediately after exposure to the alternating magnetic field, cell viability was assessed using an MTT assay. To further investigate the effects of supra-therapeutic hyperthermia, an additional set of 4×10^4 cells was incubated with CoFe₂O₄@dextran and CoFe₂O₄@Au@dextran nanostructures (0.1 mg/mL) for 24 hours, followed by hyperthermia treatment for 1.5 minutes, during which the temperature reached 52.5°C.

Statistical Analysis

All experiments were performed in triplicate and repeated at least three times independently. Statistical analysis was conducted using IBM SPSS Statistics 26 software. Differences among multiple groups were analyzed using one-way analysis of variance (ANOVA) for normally distributed data. Post hoc pairwise comparisons were performed using Tukey's test to identify significant differences between treated and control groups. For non-normally distributed data, the Kruskal-Wallis test followed by Dunn's post hoc test was applied. A p-value < 0.05 was considered statistically significant.

RESULTS

Characterization of the nanostructures

In our previous work, we thoroughly analyzed and optimized a cobalt ferrite-based nanostructure. HRTEM showed the core had an amorphous structure with ~10.5 nm particle size. XRD confirmed the expected crystalline phases for both bare cobalt ferrite (CoFe₂O₄) and gold-coated CoFe₂O₄@Au nanoparticles. EDX verified the presence of Co, Fe, O, and Au elements. IR spectroscopy revealed distinct peaks for each component, especially after dextran coating. Magnetic measurements showed unsaturated magnetization for CoFe₂O₄ and a ~40 emu/g saturation for CoFe₂O₄@Au. UV-Vis spectroscopy confirmed gold shell deposition, with absorption peaks at 520 nm (AuNPs) and 552 nm (CoFe₂O₄@Au). the saturation magnetization was estimated by extrapolation and determined to be 7.5 emu/g, Figure 1 [10].

Relaxometric experiments

A water-containing phantom was positioned and imaged using a 1.5 Tesla MRI relaxometer system. Relaxometry analysis revealed that CoFe₂O₄ acts as a contrast agent in the cellular environment of the MDA-MB-231 cell line. The resulting relaxivity (r_2) values were 202.5 mM⁻¹S⁻¹, 137. mM⁻¹S⁻¹, and 142 mM⁻¹S⁻¹ with incubation times of 0.5, 2, and 4h, respectively (figure 1). Figure 2 illustrates the changes in r_2 as a function of incubation time for CoFe₂O₄@Au nanostructures too. For the CoFe₂O₄ nanostructure, r_2 initially decreases with increasing incubation time, then decreases further. Therefore, the maximum r_2 was observed at a 0.5h incubation time. This trend of changes is repeated for the CoFe₂O₄@Au nanostructure, with the r_2

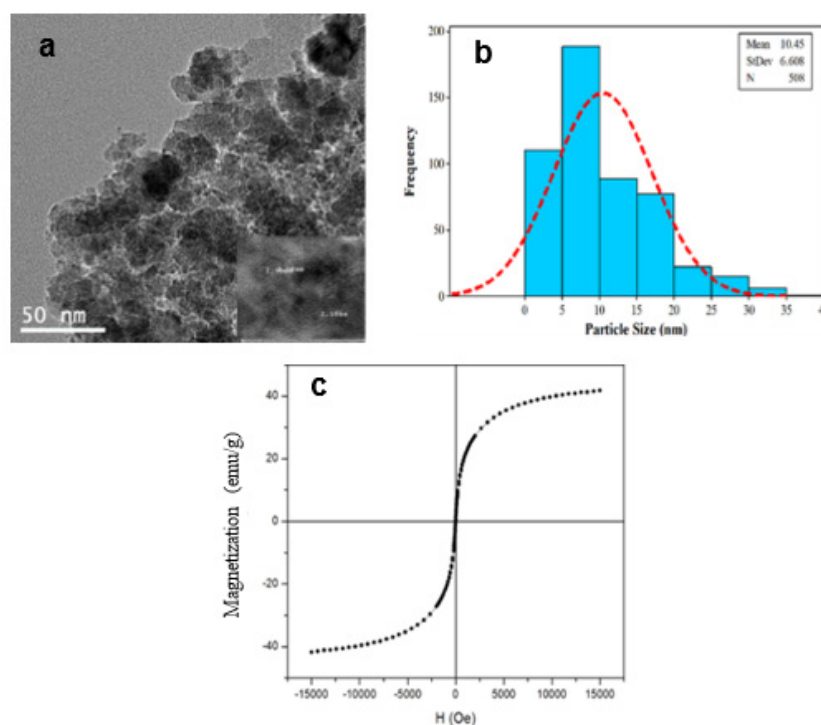


Fig. 1. a) HRTEM image of CoFe_2O_4 MNPs, b) particle size distribution histogram fitted with a Gaussian function, and c) magnetic hysteresis loop recorded at room temperature under an applied magnetic field of $-15,000$ to $15,000$ Oe.

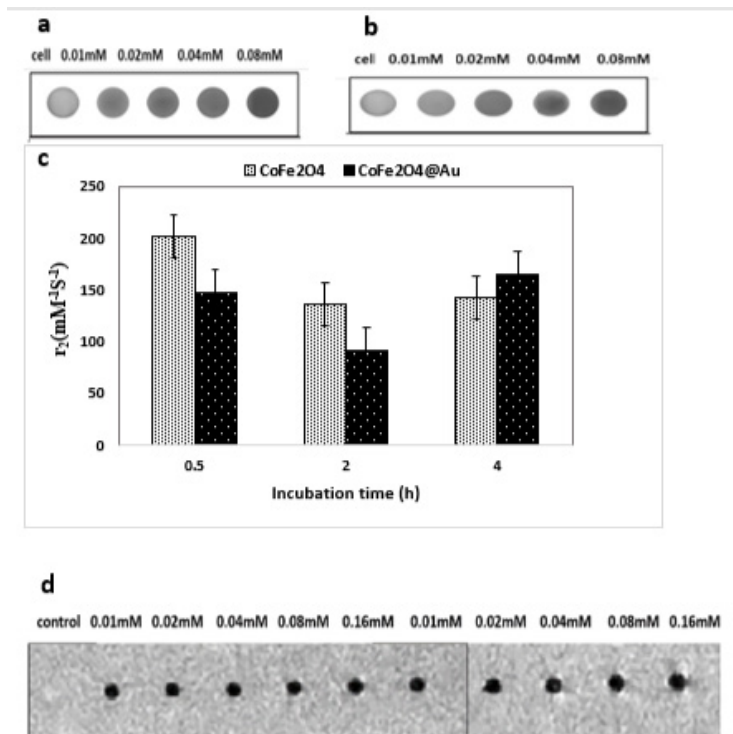


Fig. 2. a, b) Cellular phantom images of CoFe_2O_4 at concentrations of 0.01–0.16 mM after 0.5 and 2 h incubation, respectively. c) r_2 relaxivity as a function of incubation time for CoFe_2O_4 and $\text{CoFe}_2\text{O}_4\text{@Au}$ in MDA-MB-231 cells acquired at 1.5 T. d) Multi-echo T_2 -weighted images of cellular phantoms containing $\text{CoFe}_2\text{O}_4\text{@dextran}$ and $\text{CoFe}_2\text{O}_4\text{@Au@dextran}$ at various concentrations after 24 h incubation (1.5 T, 1-mm slice thickness).

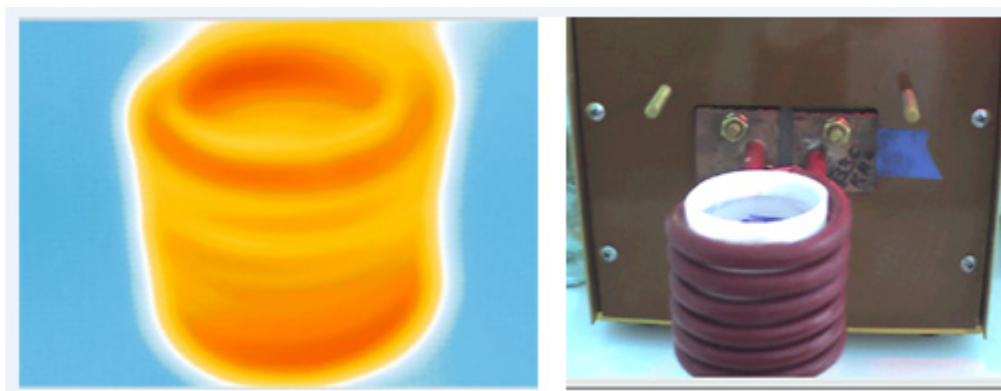


Fig. 3. Thermography images of coil of magnetic hyperthermia systems for evaluating the uniformity of field intensity along the coil.

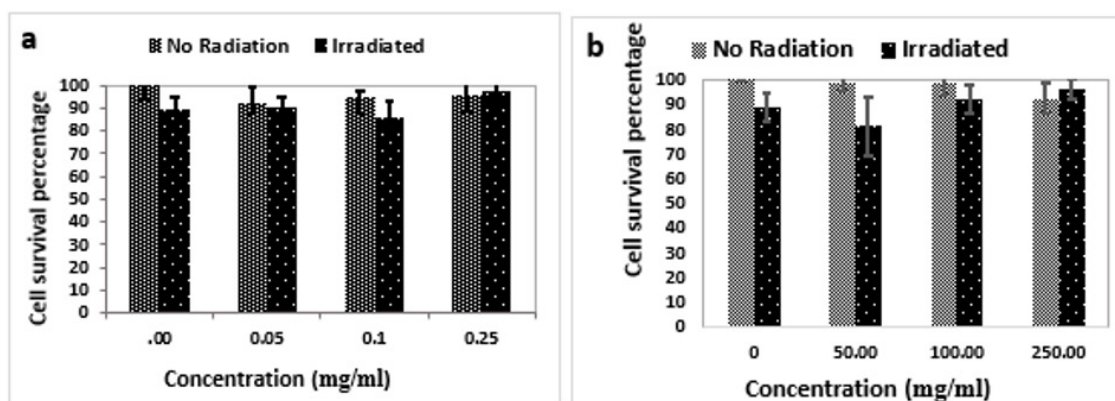


Fig. 4. Comparison of cell viability at different concentrations of (a) CoFe₂O₄@dextran and (b) CoFe₂O₄@Au@dextran before and after magnetic hyperthermia (41 °C; 425 MHz; 33.5 mT; 4.3 kW).

parameter decreasing from 148.5 mM⁻¹S⁻¹ at a 0.5h incubation time to 92.5 mM⁻¹S⁻¹ at 2h, and then increasing to 165.5 mM⁻¹S⁻¹ at the 4h incubation time. Therefore, the maximum r_2 was achieved at a 4h incubation time for this nanostructure. Since nanostructure phantom images are influenced by both concentration and field intensity, we evaluated two nanostructures, CoFe₂O₄@dextran and CoFe₂O₄@Au@dextran, under two different field intensities and at low concentrations, using slice thicknesses of 1 mm and 3 mm. Figure 3 presents the 1-mm slices, in which no artifacts were observed, whereas the 3-mm slice images exhibited magnetic susceptibility artifacts.

Magnetic hyperthermia in the cellular environment

Figure 2 displays thermographic images of the magnetic hyperthermia system's coil, illustrating the uniformity of field intensity along the coil. The

results obtained at the minimum hyperthermia temperature (41°C) indicated that, across all concentrations of the CoFe₂O₄@dextran and CoFe₂O₄@Au@dextran nanostructures, there was no significant reduction in cell viability between the treatment and control groups (Figure 4). Statistical analysis further confirmed no significant difference between the drug control and treatment groups at all three tested concentrations. At the hyperthermia temperature of 44 °C, the results demonstrated no significant difference in cell viability between the treatment and control groups across all tested concentrations of CoFe₂O₄@dextran and CoFe₂O₄@Au@dextran nanostructures (Figure 5). However, Figure 6 and indicate that groups incubated with concentrations of 0.05 mg/mL and 0.1 mg/mL of CoFe₂O₄@dextran and CoFe₂O₄@Au@dextran exhibited a significant difference in comparison to their respective treatment groups

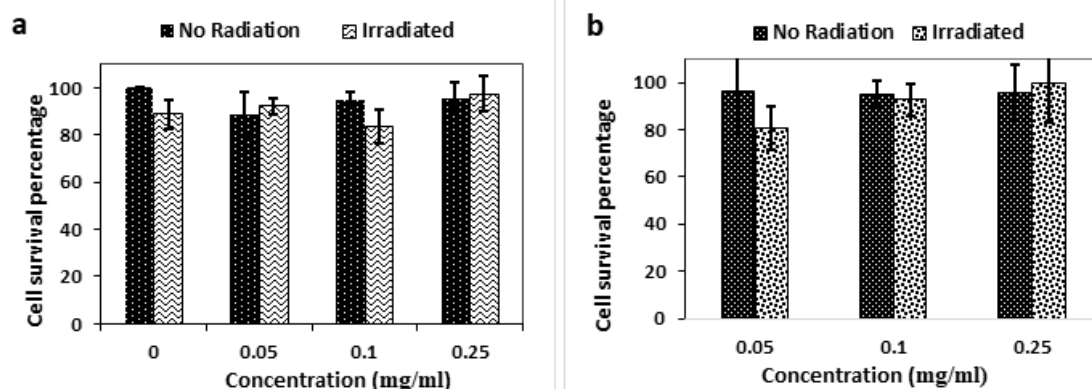


Fig. 5. Comparison of cell viability at different concentrations of a) CoFe₂O₄@dextran and b) CoFe₂O₄@Au@dextran before and after magnetic hyperthermia (44 °C; 425 MHz; 33.5 mT; 4.3 kW).

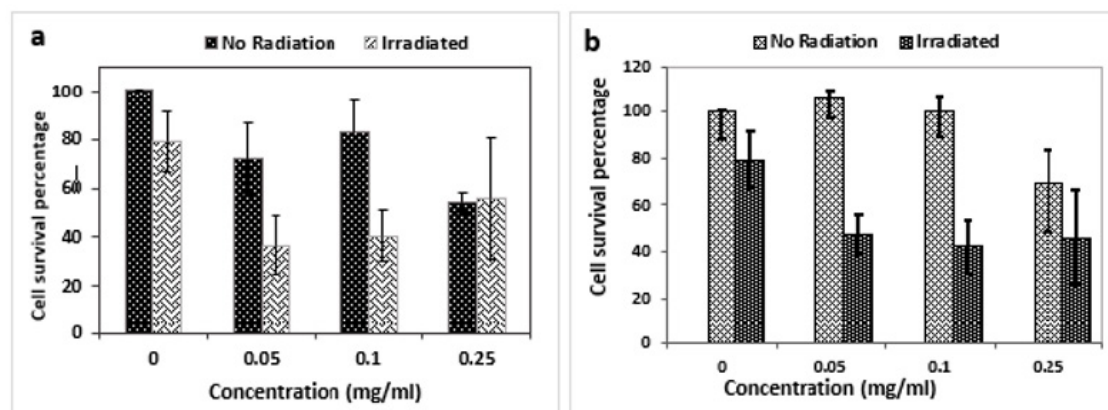


Fig. 6. Comparison of cell viability at different concentrations of a) CoFe₂O₄@dextran and b) CoFe₂O₄@Au@dextran before and after magnetic hyperthermia (47 °C; 425 MHz; 33.5 mT; 4.3 kW).

at 47 °C. In contrast, the control groups and the 0.25 mg/mL concentration group did not show a statistically significant difference. Furthermore, based on Figure 7, it can be inferred that exposure to the alternating magnetic field resulted in thermocoagulation, cellular deformation, and cell death at 52.5 °C. According to the MTT assay, at a concentration of 0.1 mg/mL, both nanostructures exhibited a reduction in cell viability of more than 50%.

Figure 8 presents thermal imaging and morphological analysis of MDA-MB-231 cells incubated with CoFe₂O₄@dextran and CoFe₂O₄@Au@dextran nanostructures at a concentration of 0.1 mg/mL for 24 hours. As shown in Figure 8a, the thermal map of untreated cells incubated with CoFe₂O₄@dextran displays an average temperature of 32 °C. Following treatment and thermal exposure, the temperature of the cell culture increased to a maximum of 41 °C (Figure 8b).

Notably, no significant morphological alterations were observed at 41 °C or 44 °C when compared to the pre-radiation condition, indicating minimal thermal damage at these temperatures. In contrast, Figure 8c shows that exposure to a higher temperature of 47 °C resulted in noticeable morphological changes, suggesting the onset of thermal damage at this threshold. Furthermore, Figures 8e and Figures 8f depict the morphology of cells treated with the CoFe₂O₄@Au@dextran nanostructure under identical incubation conditions. Following an increase in temperature to 52.5 °C, significant morphological disruptions were evident, including cell ablation, deformation, and extensive cell death, indicating effective thermal ablation at this elevated temperature. Figure 9 shows thermographic temperature maps of Petri dishes subjected to hyperthermia radiation are shown before and after treatment. Figure 9a, the Petri dish contains MDA-MB-231 cells

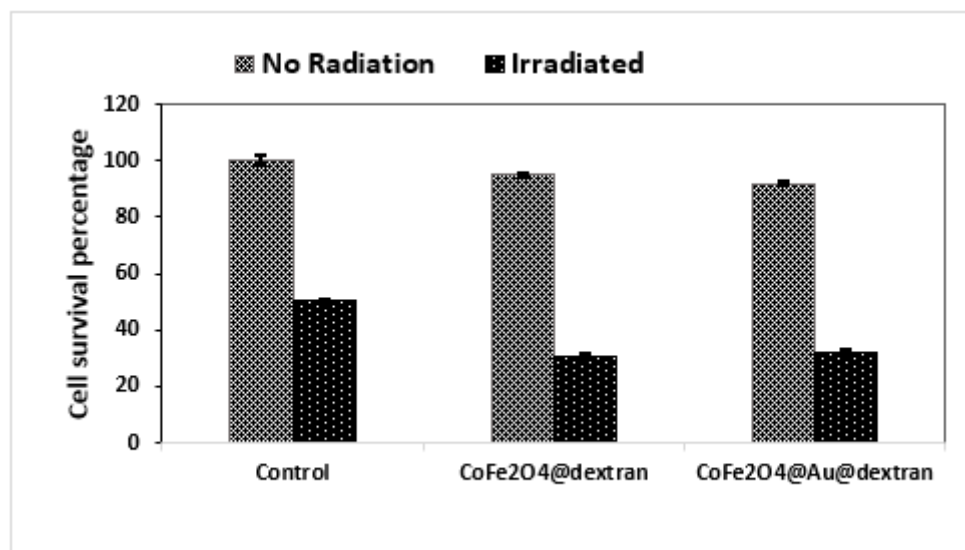


Fig. 7. Comparison of cell viability at 1.0 mg/mL of $\text{CoFe}_2\text{O}_4@\text{dextran}$ and $\text{CoFe}_2\text{O}_4@\text{Au}@\text{dextran}$ before and after magnetic hyperthermia (52.5 °C; 425 MHz; 33.5 mT; 3.4 kW). * indicates statistical significance compared to the non-treated group.

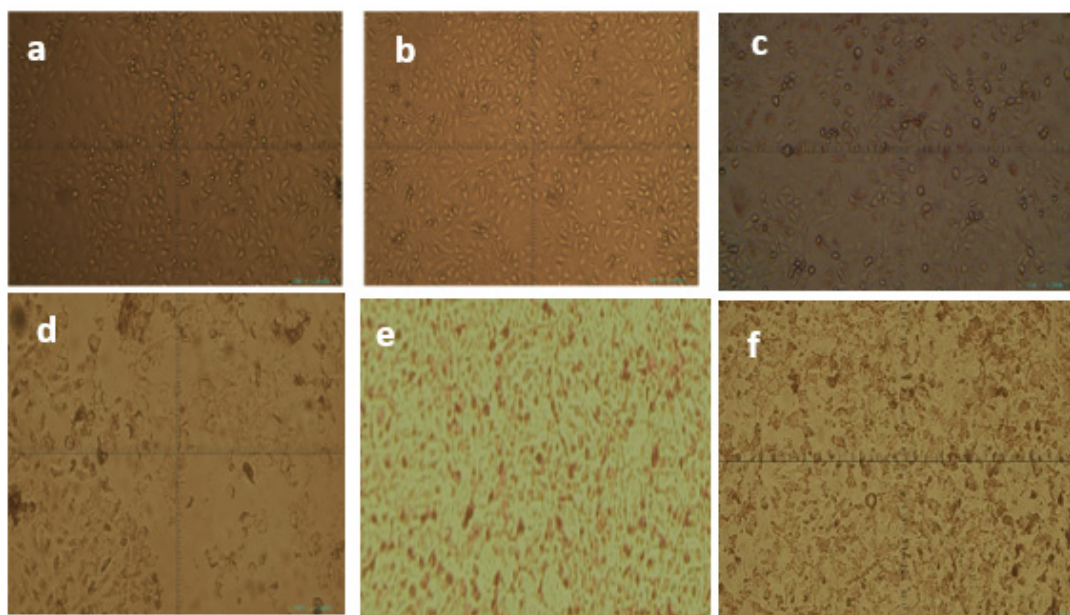


Fig. 8. Inverted bright-field microscopy images of MDA-MB-231 cells in petri dishes incubated with 0.1 mg/mL $\text{CoFe}_2\text{O}_4@\text{dextran}$. a) Before hyperthermia treatment, and after treatment at b) 41 °C, c) 44 °C, and d) 52.5 °C.

incubated with 10.1 mg/mL of $\text{CoFe}_2\text{O}_4@\text{dextran}$ nanoparticles for 24 hours, displaying a baseline average temperature of 32 °C prior to treatment. Following exposure to hyperthermia, the average recorded temperatures increased to 41 °C (Figure 9b), 44 °C (Figure 9c), 47 °C (Figure 9d), and 52.5 °C (Figure 9e), respectively.

DISCUSSION

The primary objective of this study was to evaluate the suitability of the synthesized nanostructures as MRI contrast agents and to assess their compatibility within a cellular environment. The MDA-MB-231 breast cancer cell line was selected due to its relevance for

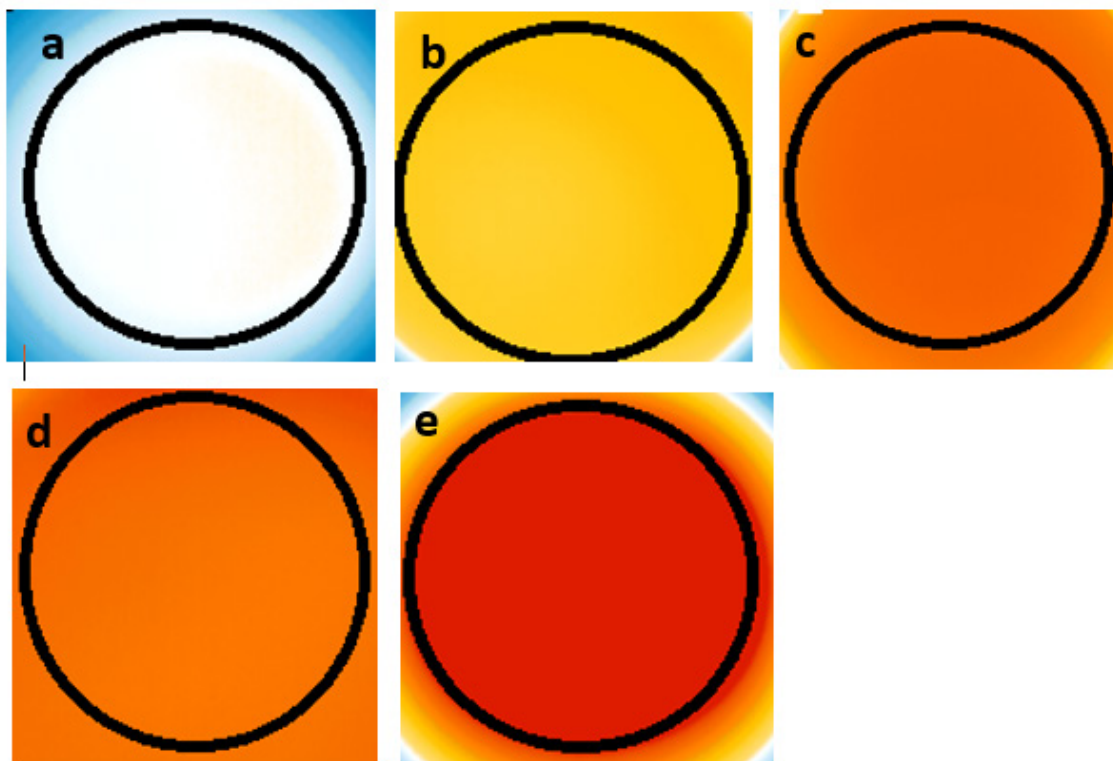


Fig. 9. Thermographic temperature maps of MDA-MB-231 cells in petri dishes incubated with 10.1 mg/mL $\text{CoFe}_2\text{O}_4@\text{dextran}$ for 24 h. a) Before hyperthermia (32 °C), and after treatment at b) 41 °C, c) 44 °C, d) 47 °C, and e) 52.5 °C.

potential local injection strategies in breast tissue, enabling both diagnostic imaging and therapeutic application. internalization. The decrease in r_1 can be explained by a two-compartment exchange model, consisting of a small intracellular proton pool with high contrast agent concentration and a larger extracellular pool with lower r_1 values, where restricted proton exchange leads to reduced intracellular relaxation compared to aqueous dispersions [15-17]. Similarly, the observed reduction in r_2 is attributed to intracellular nanoparticle aggregation, resulting in the formation of larger pseudo-particles and deviation from the motional averaging regime [18]. Among the evaluated formulations, CoFe_2O_4 nanoparticles exhibited the highest r_2 values after 0.5 h incubation, whereas $\text{CoFe}_2\text{O}_4@\text{Au}$ nanostructures reached their maximum r_2 after 4 h, indicating time-dependent cellular uptake. After 24 h incubation, dextran-coated nanostructures showed enhanced intracellular accumulation, as evidenced by concentration-dependent susceptibility artifacts in T_2 -weighted images at both 1.5 and 3 T. These

artifacts, originating from magnetic susceptibility effects, were effectively reduced by optimizing imaging parameters, including slice thickness, nanostructure concentration, incubation time, and phase and frequency encoding settings [19, 20]. Beyond their imaging performance, the therapeutic potential of the nanostructures was evaluated using magnetic hyperthermia. Hyperthermia enhances tumor cell sensitivity by elevating tissue temperature, particularly in hypoxic and acidic tumor microenvironments where conventional therapies are less effective [21, 22]. In magnetic hyperthermia, magnetic nanoparticles exposed to an alternating magnetic field generate localized heat through magnetic hysteresis losses and Néel and Brownian relaxation mechanisms, while additional cellular effects may arise from mechanically induced forces and reactive oxygen species generation [4, 23, 24]. Although magnetic hyperthermia has been proposed for several decades, it has only recently received clinical approval for selected cancers such as glioblastoma and prostate cancer [25]. The selected temperatures were chosen to represent

both clinically relevant mild hyperthermia (41–44 °C) and higher-temperature regimes associated with thermal damage and thermoablation (≥ 47 °C). This approach allows differentiation between sensitizing and cytotoxic thermal effects and provides a comprehensive evaluation of the hyperthermia performance of the nanostructures [26]. In this study, at moderate temperatures (41–44 °C), no significant reduction in cell viability or morphological alterations were observed. This outcome is attributed to the high viscosity of the intracellular environment, which limits nanoparticle mobility and reduces the specific loss power compared to aqueous conditions. These findings are consistent with previous reports indicating that substantial cytotoxic effects generally occur only at temperatures above 46 °C. In contrast, exposure to higher temperatures (47 °C and 52.5 °C) resulted in pronounced cytotoxicity. At 47 °C, significant cell death was observed depending on the nanostructure formulation, in agreement with the established mechanism of hyperthermia-induced protein denaturation and membrane disruption above 43 °C. Early stages of hyperthermia-induced cell death are characterized by loss of membrane integrity and increased permeability due to the formation of large membrane channels. Exposure to 52.5 °C induced thermoablation, resulting in more than 50% cell death, as confirmed by morphological analysis. Overall, these results highlight the dual theranostic capability of the synthesized nanostructures. While moderate magnetic hyperthermia temperatures primarily act as a sensitizing strategy, higher temperatures induce direct cytotoxic and thermoablative effects, emphasizing the critical role of temperature control in magnetic hyperthermia-based cancer therapy [27–32].

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest related to the research, authorship, or

publication of this manuscript. All authors have disclosed any financial or personal relationships that could potentially influence or bias the work presented.

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