https://doi.org/10.48048/tis.2024.8519

Enhanced Cancer Biomarker Detection using Fe_3O_4 Magnetic Nanoparticles: Synthesis, Surface Modifications and Diagnostic Applications: A Review

Tulus Na Duma[1], Syahrul Humaidi[1,*], Muhammadin Hamid[1], Erwin Amiruddin[2], Martha Rianna[1] and Novita[1]

[1]Postgraduate Program (Physics), Fakultas Matematika Dan Ilmu Pengetahuan Alam, Jl. Bioteknologi No. 1, Universitas Sumatera Utara, Medan 20155, Indonesia
[2]Department of Physics, Fakultas Matematika Dan Ilmu Pengetahuan Alam, Universitas Riau, Pekanbaru, Riau 28293, Indonesia

([*]Corresponding author's e-mail: syahrul1@usu.ac.id)

Received: 1 June 2024, Revised: 25 June 2024, Accepted: 2 July 2024, Published: 5 October 2024

Abstract

Fe_3O_4 magnetic nanoparticles exhibit significant potential for cancer detection due to their unique magnetic properties and versatility. This review examines their role in enhancing cancer biomarker detection, focusing on synthesis methods, surface modifications and diagnostic accuracy. Fe_3O_4 nanoparticles serve as sensitive MRI contrast agents, facilitating early cancer diagnosis and improving patient prognosis. Synthesis techniques influence their properties, morphology and dimensions, which affect performance. Surface modifications enhance targeting and reduce immunological reactions, enabling precise biomarker detection and effective drug delivery to tumours, minimizing damage to healthy tissue. Despite these advantages, challenges remain in optimizing delivery efficiency and overcoming medication resistance. Further research is required to understand the pharmacokinetics and pharmacodynamics of these nanoparticles, including their distribution, metabolism and physiological impacts. This review provides insights into the potential of Fe_3O_4 magnetic nanoparticles as cancer detection agents, aiming to guide future research towards developing safer and more efficient applications in medical diagnostics and treatment.

Keywords: Biocompatibility, Biomarker identification, Cancer detection, Drug delivery, Early diagnosis, Fe_3O_4 magnetic nanoparticles, Nanoparticle synthesis, Surface modification

Introduction

As a pathological condition marked by the unregulated proliferation of cells, cancer can invade and impair adjacent tissue [1]. This process commences with a genetic mutation resulting of lack control over their proliferation and immune response. Normal cells reproduce, divide and being apoptosis by the physiological demands of the organism. Concurrently, cancer cells persistently proliferate and replicate uncontrolled until they coalesce into a solid mass as known as tumour. Cancer varies depending on the specific area or cellular type it affects. It encompasses conditions like breast cancer, lung cancer, colon cancer, carcinoma, sarcoma, leukaemia and lymphoma.

Cancer symptoms might vary from weight loss to exhaustionedema or nodules, and skin alterations. Cancer diagnosis entails a sequence of precise evaluations, such as blood tests, medical imaging and biopsies. Technological advancements and research have led the frequency of cancer treatment methods,

including surgical therapy, chemotherapy and radiotherapy according to the kind and stage of cancer. Early cancer detection and prevention through a healthy lifestyle and periodic evaluations play a critical role in improving prognosis and delivering a successful treatment.

In line with advancements in cancer detection technologies, there are notable obstacles in terms of accuracy, rapidity and specificity. Detecting cancer biomarkers in low quantities can be challenging, therefore more advanced detection methods needed to enhance accurate diagnosis. Magnetic nanoparticles (MNPs) are a substance that can detect molecules and highly sensitive in the development of biosensors and cancer biomarker detection technology [2].

MNPs are exerting a significant impact in many different kind of fields. MNPs, which have a size smaller than 100 nm [3], can enhance properties without causing atomic structure damage [4]. An optimal atomic structure will yield a functional system that exhibits greater sensitivity when compared to materials of larger size [5]. MNPs possess superparamagnetic properties [6], enabling them to be magnetized with the support of an external magnet [7,8]. In addition to superparamagnetic properties, MNPs also exhibit distinctive physical features, excellent biocompatibility, high stability, a large surface area, unique optical properties and convenient application [9,10]. In medicine, nanoparticles can be precisely guided or gathered at specific body to enable an enhanced approach to identification and management of diseases like cancer [11].

MNPs are used in targeted magnetic therapy to treat cancer by delivering nanoparticles to the cancerous area. This therapy allows direct targeting of diseased cells, thereby reducing the impact on surrounding tissue. Additionally, MNPs can be used as medical imaging agents in Magnetic Resonance Imaging (MRI) which can increase the accuracy and resolution of cancer images to differentiate between cancer cells and normal tissue MNPs also use as magnetic biosensors to detect cancer biomarkers in blood. This aims to increase the effectiveness of early detection and monitoring of disease. Although the potential of MNPs as a cancer detector is very promising, the safety and biocompatibility of MNPs materials are important aspects that must be considered. The selected material can influence the biocompatibility of the MNPs [12].

MNPs consist of magnetic elements such as iron, cobalt, nickel and their alloys [13]. Materials that have been successfully developed and show potential for further research are iron oxide nanoparticles, such as magnetite (Fe_3O_4) or the oxidized form of maghemite (g-Fe_2O_3) [14]. This is due to the natural magnetic properties and crystal structure of magnetite. Strong magnetic materials such as cobalt and nickel are less desirable due to their susceptibility to oxidation and toxicity [15].

Fe_3O_4 can be found in various types of rocks, such as metamorphic and sedimentary rocks. Fe_3O_4 magnetic nanoparticles can be produced by synthesizing iron sand [16,17] and iron ore [18-20]. Fe_3O_4 nanoparticles are synthesized using several methods such as chemical processes [21], physical processes [22,23] and biological processes [24]. Each selecting methods will affect the properties of the Fe_3O_4 magnetic nanoparticles. Fe_3O_4 magnetic nanoparticles must have unique qualities to be used as an efficient cancer detection agent [25]. Fe_3O_4 magnetic nanoparticles must have a very small or nanometer size. The nanoscale size helps the process of penetration into biological tissue and increases the surface area for interacting with cancer cells [26]. In addition, Fe_3O_4 magnetic nanoparticles must demonstrate biocompatibility, stability and resistance to agglomeration or structural changes that could affect detection performance.

Fe_3O_4 magnetic nanoparticles have been widely applied in various fields. This field can include heat transfer applications [27], catalysts [28], water remediation [29], lithium-ion batteries [30], magnetic storage media [31] and various biomedical applications [32,33]. In the biomedical field, Fe_3O_4 magnetic nanoparticles are used as drug delivery agents by binding to antibodies [34] and chemotherapy drugs [35].

Cell motility and the development of metastases can arise due to the effects of using Fe_3O_4 magnetic nanoparticles, so it is important to test the initial mechanism before using them directly [36,37]. Tests that have been carried out show further potential in the application of Fe_3O_4 magnetic nanoparticles [38].

This article will explore the characteristic capabilities of Fe_3O_4 magnetic nanoparticles. The discussion regarding methods that are considered effective in the synthesis of Fe_3O_4 magnetic nanoparticles will be analyzed to determine the most effective approach. In addition, this article will briefly examine the potential of Fe_3O_4 magnetic nanoparticles as a cancer biomarker detector and the challenges that will arise in their future use.

Characteristics of Fe_3O_4 magnetic nanoparticles

Magnetite, also known as Fe_3O_4, belongs to the group of iron oxide materials. It has the chemical formula (Fe^{2+}) $(Fe^{3+})_2O_4$ and has a cube-like crystal structure [39]. Fe_3O_4 shows a dark hue and is non-toxic [40]. Magnetite can be found in sedimentary rocks in the form of fine grains. It has a density of 5.2 g/cm^3 and a hardness ranging from 5.5 to 6.5 on the Mohs scale [41]. The performance of Fe_3O_4 can be determined based on its physical, mechanical and chemical characteristics.

Physically, the characteristics of Fe_3O_4 magnetic nanoparticles can be influenced by magnetic field strength, temperature and reaction time during the synthesis process. Fe_3O_4 magnetic nanoparticles directed by an external magnetic field can access hard-to-reach areas during the process of penetration into biological tissue [42]. The reaction rate is affected by the increase in temperature. Synthesis at higher temperatures will produce Fe_3O_4 magnetic nanoparticles with stronger magnetic properties compared to those synthesized at low temperatures. The reaction rate is affected by the increase in temperature. Synthesis at higher temperatures will produce Fe_3O_4 magnetic nanoparticles with stronger magnetic properties compared to those synthesized at low temperatures. Meanwhile, particle size can be influenced by increasing reaction time. Synthesis over a longer time will produce Fe_3O_4 magnetic nanoparticles with a smaller particle size compared to those synthesized in a shorter time [43]. Apart from that, temperature and synthesis time also influence the surface morphology of Fe_3O_4 nanoparticles, which under certain conditions can cause agglomeration [44].

Mechanically, Fe_3O_4 exhibits a very high level of hardness. The mechanical characteristics of Fe_3O_4 magnetic nanoparticles can be influenced by other materials when interacting. Hardness regulation is very important, especially in drug delivery applications or in detection systems that require mechanical stability. Chemically, the characteristics of Fe_3O_4 magnetic nanoparticles are influenced by reactivity, chemical bonding and toxicity. The Fe_3O_4 surface can be chemically modified to improve biocompatibility, colloidal stability and specific reactivity toward specific targets. **Table 1** shows the physical and mechanical characteristics of Fe_3O_4.

Table 1 Physics and mechanics properties of Fe_3O_4 [41].

Property	Iron Oxide		
	Hematite	**Magnetite**	**Maghemite**
Molecular formula	α-Fe_2O_3	Fe_3O_4	γ-Fe_2O_3
Density (g/cm^3)	5.26	5.18	4.87
Melting point (°C)	1350	1583 - 1597	-
Hardness	6.5	5.5	5

Property	Iron Oxide		
	Hematite	**Magnetite**	**Maghemite**
Type of magnetism	Weakly ferromagnetic or antiferromagnetic	Ferromagnetic	Ferromagnetic
Curie temperature (K)	956	850	820 - 986
M_s at 300 K (A-m^2/kg)	0.3	92 - 100	60 - 80
Standard free energy of formation ΔG_f^o (kJ/mol)	–742.7	–1012.6	–711.1
Crystallographic system	Rhombohedral, hexagonal	Cubic	Cubic or tetrahedral
Structure type	Corundum	Inverse spinel	Defect spinel
Space group	R3c (hexagonal)	Fd3m	$P4_332$ (cubic); $P4_12_12$ (tetragonal)
Lattice parameter (nm)	a = 0.5034, c = 1.375 (hexagonal) a_{Rh} = 0.5427, α = 55.3 ° (rhombohedral)	a = 0,8396	a = 0.83474 (cubic) a = 0.8347, c = 2.501 (tetragonal)

Method of synthesis of Fe_3O_4 magnetic nanoparticles

The physical and chemical characteristics of Fe_3O_4 magnetic nanoparticles such as particle size, shape, morphology, crystallinity and particle polydispersity were depending on method used [45]. The synthesis of Fe_3O_4 magnetic nanoparticles also involves physical, chemical and biological processes.

Synthesis of Fe_3O_4 magnetic nanoparticles using physical methods

Changing the size of Fe_3O_4 particles to nano-size can involve physical synthesis methods. Physical synthesis can be carried out using ball milling techniques. The ball milling process operates by employing metal or ceramic balls to crush or grind the basic material. The crushing process is conducted for a specific duration at a specific velocity till the particle size of the raw material transforms into nanoparticles. Ball milling techniques can be classified into 2 categories, namely conventional ball milling methods [46] and high-energy ball milling methods [47]. The ball milling technique has a simple principle, but the resulting product is easily contaminated [48]. **Table 2** shows the characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the ball milling technique.

The research conducted in **Table 2** indicates that the high-energy ball milling approach demonstrates more efficient results. High-energy ball milling method takes less time than conventional ball milling method, but results in smaller crystal and particle sizes. Long-term use of the high energy ball milling process might decrease crystal size by promoting agglomeration. Additional research is required to identify components that can enhance other properties of Fe_3O_4 magnetic nanoparticles by using this method. In addition, physical synthesis can also be carried out using laser evaporation and wire explosion methods.

Table 2 Characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the ball milling technique.

Synthesis Process	Characteristics					Ref.
	Milling Time (h)	Coercivity (Oe)	Crystalline Size (nm)	Particle Size (nm)	Ms (emu/g)	
Conventional ball milling	90	173	NE	0.5 - 16	37.80	[49]
	40	NE	49.9	NE	NE	[50]
	192	NE	12	NE	NE	[51]
	48	NE	33.2	NE	63.68	[52]
High-energy ball milling	12	NE	11 - 14	9	65.2	[53]
	6	322.09	NE	0.1 - 1.4	46.61	[54]
	24	153	35	15	65.6	[55]
	3	455.17	NE	4 - 6	30.52	[56]

Note: NE = Not explained.

The laser evaporation technique involves the condensation of a liquid or gas phase [57]. Laser evaporation, also known as laser ablation, works by vaporizing particles in a material. Evaporation is carried out with high radiation intensity through a laser beam centre. The particles will cause condensation which then forms nanoparticles [58]. This method is cost-effective and does not use chemicals, so the waste produced is not as dangerous as other physical methods [59]. Various research conducted utilising this method are included in **Table 3**. This method is currently under development to produce features suitable for biological applications.

Table 3 Research using laser ablation methods.

Synthesis Process	Specification of laser beam	Characteristics	Application	Ref.
Laser ablation	- Central wavelength: 1030 nm - Pulse duration: 230 fs - The repetition rate varies up to 100 kHz - Energy pulse: 80 μJ	- Ms: 24.3 emu/g - Magnetic field: ± 20 kOe - Surface are: 179 m^2/g - Pore volume: 0.341 cm^3/g - New bands between 800 and 1500 cm^{-1}	Catalytic degradation	[60]
Laser ablation	- Central wavelength: 1064 nm - Beat span: 9 ns - Redundancy recurrrence 1 Hz - Various energies: 80 and 200 mJ - Various removal times: 10 and 20 min	- The moment size conveyance between 60 and 135 nm - The moment size dispersion between 50 and 150 nm - Molecule size: 91.24 nm - Spherical nanocrystal	Anti-microbial	[61]
Laser ablation	- Wavelength: 1064 nm - Energy pulse: 180 mJ - Pulse length: 12 ns - Repetition rate: 10 Hz for 10 min	- Particles size: 30 nm (aceton), 27 nm (iron oxide) - Spherical - Cubic crystal	Biological applications	[62]

As another method, the wire explosion is a recently developed physicochemical technique. The wire explosion method works by melting or vaporizing metal wire in a controlled vacuum or inert gas condition. This is intended to prevent contamination. Fe_3O_4 magnetic nanoparticles are synthesized using a high-temperature heating process utilizing an electric current. Applying an electric current to the wire will cause it to melt, resulting in the formation of minute iron particles. After cooling, the particles perform a condensation process to create the Fe_3O_4 nanoparticles. This method does not require long stages and the waste produced does not need to be recycled. The nanoparticles formed are low in contamination and non-monodisperse [63]. Various research conducted utilising this method are included in **Table 4**.

Table 2 Research using wire explosion method.

Synthesis process	Specification	Characteristics	Ref.
Wire explosion	- Iron wire diameter: 0.3 mm - Iron wire length: 65 mm - Voltage: 28.5 kV - Capacitance: 1.6 μF	- Spherical - Ms: 180 emu/g - Particle size: 65 - 81 nm - High stability oxidation by hydrochloric acid solution	[64]
Wire explosion	- High density impulse: 10^4 A/mm^2 to 10^6 A/mm^2 - Iron wire diameter: 1 mm	- The crystallite size: 14.6 nm - Particle size: 15 nm - Cubic phase - Lattice parameter (a): 8.36 Å - Ms : 45.2 emu/g	[65]
Wire explosion	- Various size in diameter: 0.2, 0.3, 0.4 and 0.5 nm - Power supply: 80 V DC	- Particle size: 10.3, 17.7, 26.25 and 35.5 nm - Ms: 53.97, 54.27, 58.30 and 65.01 emu/g	[66]

Synthesis of Fe_3O_4 magnetic nanoparticles using chemical methods

Chemical synthesis of Fe_3O_4 magnetic nanoparticles can be carried out using several methods including co-precipitation, thermal decomposition, hydrothermal and sol-gel. Fe_3O_4 magnetic nanoparticles can be obtained using anhydrous precursors such as $FeCl_3.6H_2O$ and $FeCl_2.4H_2O$. The co-precipitation method is the most commonly used for synthesizing Fe_3O_4 magnetic nanoparticles.

The co-precipitation method is included in the type of wet chemical method with the simplest synthesis stages [67]. The synthesis process can be carried out at low temperatures (T < 120 °C) to produce large yields [68]. Anhydrous metals can be used as a source of metal ions during the synthesis process, and basic compounds such as NH_4OH, NaOH or KOH are used as precipitating agents [69]. The characteristics of the Fe_3O_4 magnetic nanoparticles produced can be influenced by several parameters including pH, metal ions, concentration, salt properties and reaction temperature during the co-precipitation process [70]. **Table 5** shows the characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the coprecipitation method.

The co-precipitation process consists of 3 main stages. The precursor is prepared using a metal salt solution in the 1st stage. Synthesis of Fe_3O_4 magnetic nanoparticles using iron sand requires 12 M HCl metal salt dissolved in iron sand at a temperature of around 70 °C. A basic alkalization procedure was used in the 2nd stage to prepare Fe_3O_4 magnetic nanoparticles. The base alkalization reaction is carried out by slowly adding Fe solution to the precipitating solution while stirring at a temperature below 120 °C. The 3rd stage involves washing the Fe_3O_4 magnetic nanoparticle slurry and drying it in an oven at 90 °C for 4 h [71]. This

method is still susceptible to the size distribution of nanoparticles which often agglomerate. Research has been carried out to overcome the limitations of using the co-precipitation method by adding a capping agent [72].

Table 5 Characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the co-precipitation method.

Precipitation agent	Characteristics							Ref.
	T (°C)	Time (h)	Crystallize isze (nm)	Particle size (nm)	Ms (emu/g)	Hc (Oe)	Shape	
NH_4OH	40	NE	5.6	7.2	41.5	478	Cubic	[73]
	50		6.3	7.8	41.2	496		
	60		6.3	8.3	39.7	471		
NH_4OH	60	2	8	10	27.35	32.09	Spherical	[74]
NaOH	60	2	25	32	45.14	129.73	Cubic	
NH_4OH	70	6	12.98	NE	NE	NE	Spherical	[75]
NH_4OH	60	1	14.35	16,51	77.26	NE	Spherical	[76]
NaOH	28	NE	11	11,22	63.51	0,36	Spherical	[77]
KOH	90	NE	8.19	65	68.45	NE	Spherical	[78]

Note: NE = Not explained.

The thermal decomposition method uses organometallic precursors and surfactants to produce Fe_3O_4 magnetic nanoparticles [79]. This method produces nanoparticles with characteristics of large crystallinity, controlled size and suitable shape [80]. The use of stabilizers is necessary during the synthesis process to slow down the nucleation of Fe_3O_4 magnetic nanoparticles [81]. Stabilizers that can be used include fatty acids, hexadecylamine and oleic acid [82]. Thermal decomposition methods are still limited in their use due to the production of toxic solvents that dissolve in organic substances, thus limiting their application in the biomedical field [83]. **Table 6** shows the characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the thermal decomposition method.

Table 6 Characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the thermal decomposition method.

Synthesis process	Characteristics					Ref.
	Surfactan	T (°C)	Crystallize size (nm)	Particle size (nm)	Ms (emu/g)	
Thermal decomposition	Benzyl ether	220	NE	4.9	46	[84]
	Oleylamine	265	NE	5.8	51	
	Phenyl ether	300	NE	9.4	60	
	1-Octadecene	330	NE	14.3	74	
	Phenyl ether	260	12	12	NE	[85]
	Polyacrylamide	200	27.75	46.5	3.9	[86]

Note: NE = Not explained.

The hydrothermal method utilizes high pressure and temperature reactions in an aqueous environment. The synthesis process is carried out in a sealed reactor which can withstand the high pressure inside [87]. The reaction that occurs involves hydrolysis and oxidation processes to produce Fe_3O_4 magnetic nanoparticles [88]. This method produces Fe_3O_4 magnetic nanoparticles with a high surface area and excellent magnetic properties at room temperature [89]. The hydrothermal method uses low-cost raw materials and produces little waste [90,91]. The use of high temperatures and pressure causes this method to require special handling and equipment [92].

Table 3 Characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the hydrothermal and sol-gel method.

Synthesis Process	Characteristics						Ref.
	T (°C)	Time (h)	Surface area (m^2/g)	Particle size (nm)	Ms (emu/g)	H_c (Oe)	
Hydrothermal	170	18	84.756	20	129.38	NE	[93]
	214	6	4.687	220	79.4	65	[94]
	185	18	NE	15,6	51.91	NE	[95]
	200	2	NE	20 - 30	NE	NE	[96]
	100	3	NE	22	46	50	[97]
Sol-gel	26.85	-	-	3 - 20	79.7	278.6	[98]
	150	4	35.27	4.71	21.97	11.1	
	170	2	51.64	5.81	26.24	26.2	[99]
	170	8	36.61	5.91	14.77	9.4	

Note: NE = Not explained.

The sol-gel method uses a mixture of active chemical compounds in a liquid phase environment. Gels can be produced through hydrolysis and polycondensation reactions of metal alkoxides. Sol solutions can be produced by dissolving metal salts until homogeneous in water or other solvents [100]. The sol-gel method has a complex procedure in the process. Several aspects must be considered when using this technique, such as hydrolysis rate, metal oxide precursor conditions, pH, synthesis temperature, stirring method, oxidation rate, concentration and nature of precursor anions [38]. The sol-gel method is generally used for the synthesis of ceramic materials and still needs further development if it is to be used in the synthesis of Fe_3O_4 magnetic nanoparticles [101]. This method has several limitations in use, including, the calcination process can produce a lot of alcohol, requires additional treatment at high temperatures, high nanoparticle permeability with weak binding power, and requires a long reaction time [102]. **Table 7** shows the characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the hydrothermal and sol-gel method.

Synthesis of Fe_3O_4 magnetic nanoparticles using biological methods

Biological synthesis of nanoparticles is carried out using living organisms, including plants [103] and microbes such as fungi, viruses, bacteria and actinomycetes [104]. The use of this method is still being developed to increase its advantages [105]. Zhang *et al*. [24] have conducted research that successfully achieved the biological synthesis of Fe_3O_4 magnetic nanoparticles. These nanoparticles are then used as catalysts in the photocatalysis process. In addition, biological methods able to produce nanoparticles that have biodegradation capabilities, making them suitable for use in the biomedical field. However, because this method is relatively new, more research is needed to investigate the characteristics of nanoparticles

production [106]. **Table 8** shows the characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the biological methods.

Fe_3O_4 magnetic nanoparticles have been successfully synthesized using *Allium sativum*. Research shows that biological methods can provide a cost-effective, biocompatible and environmentally friendly approach [107]. In addition, Darmawan *et al*. [108] has conducted research on the production of magnetic nanoparticles from *Moringa oleifera* extract. This research shows the potential for utilizing moringa extract to advance magnetic hyperthermia therapy. Yusefi *et al*. [109] has succeeded in synthesizing Fe_3O_4 magnetic nanoparticles using pomegranate peel extract. The obtained nanoparticles were then used for the treatment of ovarian cancer, which showed that cancer cells were reduced as the dose of Fe_3O_4 magnetic nanoparticles increased.

Table 8 Characteristics of synthesizing Fe_3O_4 magnetic nanoparticles by the biological methods.

Biological synthesis	Characteristics				Application	Ref.
	Crystallite size (nm)	Particle size (nm)	Ms (emu/g)	Shape		
Water hyacinth	NE	13.5	67.41	Spherical	Fermentative hydrogen production	[110]
Archidendron pauciflorum peel extract	20.9	294	12.9	NE	Methylene blue adsoprtion	[111]
Citrus Sinensis peel extract	23.4	20 - 24	120	Spherical	Biological activities and magnetic-hyperthermia	[112]
Silky hairs of corn	84.81	NE	0.135	Cubic	Antibacterial and anticandidal drugs	[113]
Outer leaves of Chinese cabbage	48.91	NE	23.036			
Moringa oleifera	19.9	20.8	54.2	Round	Magnetic hyperthermia	[108]

From the previous description regarding the synthesis of Fe_3O_4 magnetic nanoparticles, we can analyze and argue that each method has its advantages and disadvantages. Physical synthesis offers precise control of particle size and morphology, a rapid process, and does not involve hazardous chemicals. However, this method requires expensive specialized equipment and may yield Fe_3O_4 magnetic nanoparticles of subpar purity if not executed with care.

Chemical synthesis offers flexibility in controlling the characteristics of Fe_3O_4 magnetic nanoparticles, including size and composition, and can utilize readily accessible chemicals. Nevertheless, several chemical techniques require the utilization of dangerous substances and stringent reaction conditions. Biological synthesis is more environmentally friendly as they utilize natural biocatalysts like plants and microbes. Nevertheless, this method requires a profound comprehension of biology and may require more time. Contamination by biological byproducts or alterations in the characteristics of the nanoparticles may present challenges when using this technology. Hence, when choosing a synthesis process for Fe_3O_4 magnetic nanoparticles to be used as a cancer detector, one must consider the application's requirements, the desired control over the nanoparticles' properties, environmental considerations and cost.

Fe_3O_4 magnetic nanoparticles in medical imaging

One of the most effective early cancer detection techniques in the medical field is MRI. MRI is the best medical imaging technique compared to other medical imaging techniques including Computed Tomography (CT), Positron Emission Tomography (PET), Radiological Imaging and Optical Imaging. MRI utilizes magnetic fields and radio waves to examine various soft tissues, including muscles, blood flow in blood vessels and the density of body tissues.

Fe_3O_4 magnetic nanoparticles as a contrast agent in MRI technology are carried out by placing them inside the body. Fe_3O_4 nanoparticles exhibit a magnetic response and interfere with the surrounding magnetic field when exposed to an external magnetic field generated by an MRI device. The MRI imaging system then detects these responses and converts them into observable images [114]. Fe_3O_4 magnetic nanoparticles can amplify signals in certain areas of the body, which can help differentiate cancer cells from surrounding tissue.

Magnetic nanoparticles can be used in MRI for early detection of atherosclerosis, MRI-guided photodynamic treatment, stem cell labelling and cancer diagnosis. Research by Bai *et al*. [114] used modified Bull Serum Albumin (BSA) with Fe_3O_4 magnetic nanoparticles as an MRI contrast agent in liver tumors of rabbits (**Figure 1**). According to this study, Fe_3O_4 magnetic nanoparticles offer great promise to improve MRI sensitivity and diagnostic accuracy. This is due to the reticuloendothelial system's (RES) ability to phagocytose Fe_3O_4 magnetic nanoparticles and rapidly absorb them into the liver. Due to the enhanced T_2 relaxation caused on by this absorption, the T_2-weighted MRI image becomes darker. On T_2-weighted MRI images, localised liver lesions may look brighter or hyperintense due to a decreased capacity to absorb Fe_3O_4 magnetic nanoparticles. Thus, the contrast between dark normal liver tissue and light localised liver lesions can be increased by using Fe_3O_4 magnetic nanoparticles.

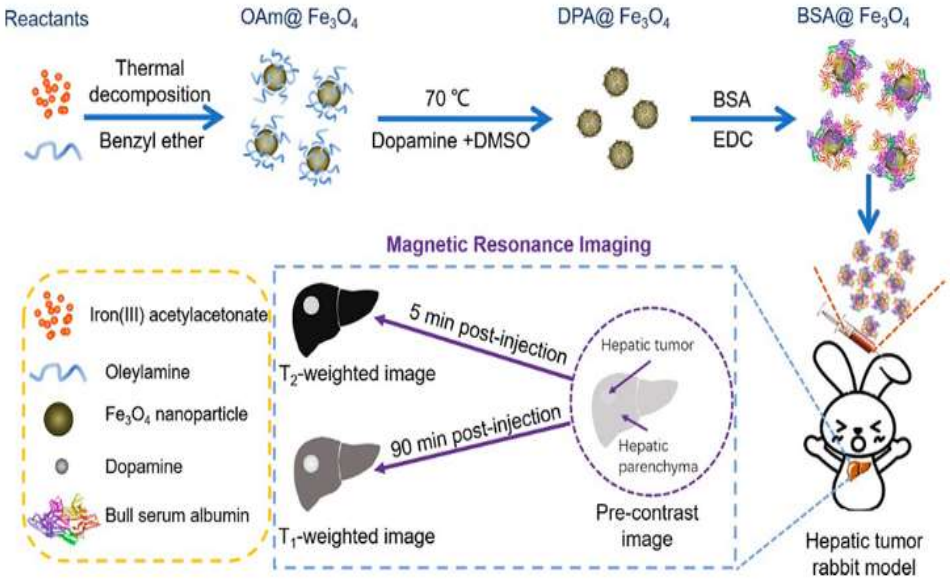

Figure 1 Utilization of Fe_3O_4 magnetic nanoparticles modified with Bull Albumin Serum as an MRI contrast agent. Reprinted from [114], with permission from ACS Publications.

This conclusion is in line with the research findings reported by Zhang *et al*. [115], which showed that Fe_3O_4 magnetic nanoparticles have high relativity r_2 and can be used effectively as a contrast agent. The surface of Fe_3O_4 magnetic nanoparticles is coated with hyaluronic acid (HA) to ensure the particles remain stable in a colloidal state and enhance tumor contrast in MRI imaging. Furthermore, the use of Fe_3O_4 magnetic nanoparticles combined with Au-BSA showed the capacity to decrease the transverse relaxation time (T_2) [116].

Fe_3O_4 magnetic nanoparticles used in medical imaging must have maximum saturation magnetization (Ms), minimum coercive field (H_c) values and high residual magnetization (Mr). The contrast enhancement effect in MRI can also be achieved by adjusting the nanostructure, magnetic properties of Fe_3O_4 magnetic nanoparticles and surface functionalization. Recent research on Fe_3O_4 magnetic nanoparticles has been carried out using various functional groups or micro morphologies as contrast agents. This research demonstrated higher-resolution images on MRI [117].

Research has shown that Fe_3O_4 magnetic nanoparticles modified with polyethylenimine (PEI) and polyethylene glycol (PEG) have higher imaging characteristics compared to unmodified Fe_3O_4 magnetic nanoparticles [118]. This is caused by PEI-PEG's ability to extend proton relaxation time and increase the MRI signal. Research has also reported the use of noble metal ion-doped Fe_3O_4 magnetic nanoparticles as a contrast agent. This research demonstrated the potential of contrast agents for detecting tumours in acidic environments [119]. Noble metal compounds have local surface plasmon resonance (LSPR) capabilities. This significantly increases the X-ray absorption coefficient and therefore improves imaging capabilities.

Biomarker detection

Biomarkers offer important information about the presence of cancer, cancer characteristics (such as cancer subtype and degree of malignancy), treatment response and the risk of disease relapse. A variety of biological substances or features, including proteins, nucleic acids, hormones, metabolites, cells, or specific anatomical structures linked to specific biological processes, might serve as biomarkers. Cancer biomarkers include various proteins, such as prostate-specific antigen (PSA) for prostate cancer, CA-125 for ovarian cancer and HER2/neu for breast cancer.

Utilization of Fe_3O_4 magnetic nanoparticles in detecting cancer biomarkers can use surface functionalization techniques. Fe_3O_4 magnetic nanoparticles are modified with certain chemicals or molecules that can interact with cancer biomarkers. The functionalization process involves the integration of antibodies, peptides, or other receptors that have a specific affinity for a particular cancer biomarker. Thus, nanoparticles have the ability to specifically identify and attach to the desired biomarker [120].

An external magnetic field delivers the functionalized Fe_3O_4 magnetic nanoparticles to cancer biomarkers. It also can separate magnetic Fe_3O_4 nanoparticles that have bound cancer biomarkers from other elements in biological tissue [121]. Measuring their signal allows spectroscopy to detect Fe_3O_4 magnetic nanoparticles attached to cancer biomarkers. The identified signals confirm the presence and levels of cancer biomarkers in the samples. This interpretation can provide information regarding early diagnosis, monitoring and further research related to cancer [122].

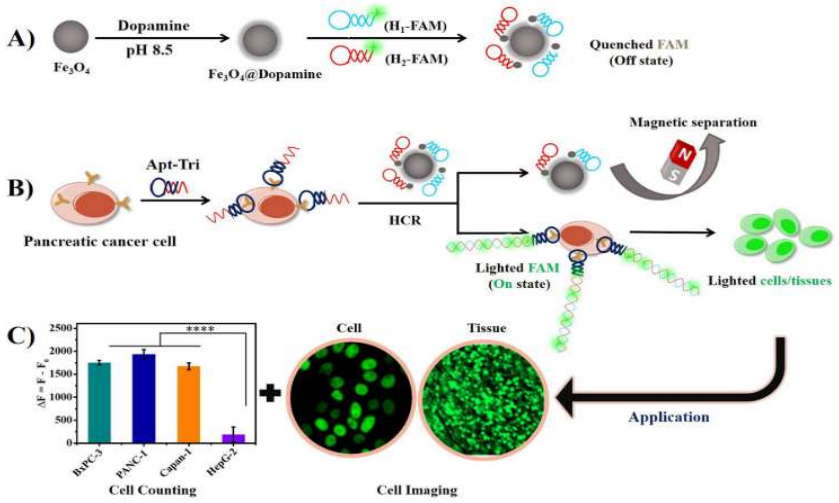

Figure 2 (A) The synthesis of Fe_3O_4 magnetic nanoparticles coated with dopamine and subsequently attached to Fluorescein Amidite (FAM). (B) The attraction of Fe_3O_4 magnetic nanoparticles coated with dopamine and FAM to cancer biomarkers results in the emission of light by FAM. (C) Imaging instruments are used to detect and measure the emitted light. Reprinted from [123], with permission from Springer.

Foroozandeh *et al*. [124] conducted research using Fe_3O_4 magnetic nanoparticles as a biomarker detector for ovarian cancer antigen 125 (CA125). The results show that the nano biosensor shows sensitivity and stability in differentiating between normal samples and samples with ovarian cancer. The research results of Ni *et al*. [125] also showed the ability of Fe_3O_4 magnetic nanoparticles to detect the CA125 biomarker. Based on the research that has been carried out, it can be seen the potential of Fe_3O_4 magnetic nanoparticles as a method for early detection of ovarian cancer.

Fe_3O_4 magnetic nanoparticles coated with dopamine have been studied to detect the presence of the pancreatic cancer biomarker MUC1 (**Figure 2**). Determination of detection sensitivity depends on the amplification signal produced by the hybridization chain reaction (HCR). This approach shows excellent sensitivity, specificity and promise for diagnosing pancreatic cancer [123]. Fe_3O_4 magnetic nanoparticles are utilized not only for direct detection of cancer biomarkers but also through the implementation of aptasensors or immunosensors. Fe_3O_4 magnetic nanoparticles facilitate the coating, binding and enhancing the sensitivity of detecting cancer biomarkers in blood [126]. Further research and modifications are needed to utilize Fe_3O_4 magnetic nanoparticles to detect various cancer biomarkers.

Magnetic therapy and drug delivery

Fe_3O_4 magnetic nanoparticles have shown significant potential in improving medical technology, particularly in the fields of magnetic therapy and drug delivery applications [127]. Magnetic fields can be utilized to function and guide Fe_3O_4 magnetic nanoparticles to specific locations in the body. This allows the application of nanoparticles in targeted drug delivery [76], more specific destruction of cancer cells [128,129], antibacterial [130], tissue engineering [131], as well as biomolecule and DNA detection [132].

Fe_3O_4 magnetic nanoparticles can produce heat when exposed to a magnetic field, known as magnetic hyperthermia. Magnetic hyperthermia is used to kill cancer cells by increasing the local temperature in the cancer area. Various applications in cancer treatment using magnetic hyperthermia include biotherapy [133], therapeutic hyperthermia [134], photothermal therapy [135] and photodynamic therapy [136].

Figure 3 illustrates the utilization of Fe_3O_4 magnetic nanoparticles for magnetic hyperthermia. Fe_3O_4 magnetic nanoparticles have shown excellent biocompatibility, efficient targeting and the ability to alter the tumour immune micro environment (TIME) when used in magnetic hyperthermia therapy [137].

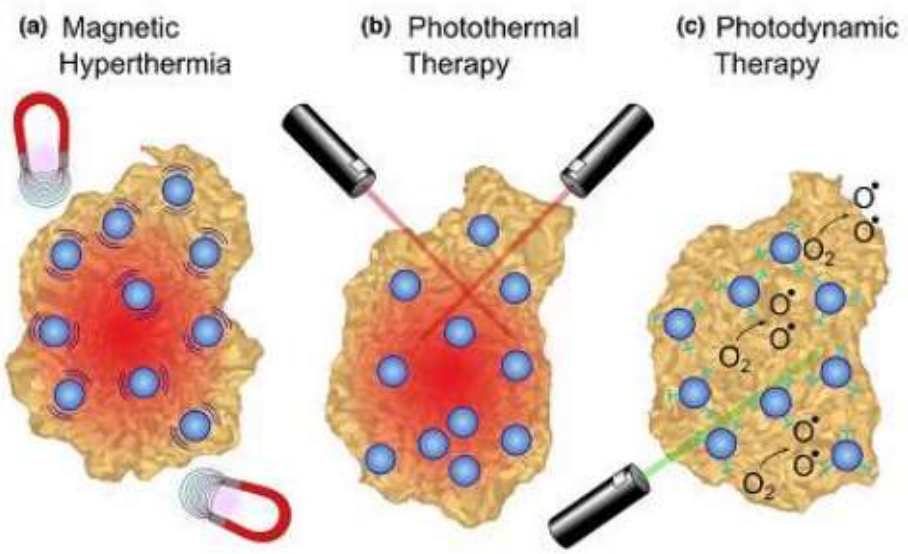

Figure 3 (a) Magnetic hyperthermia causes tumor necrosis using oscillating magnetic fields to induce heat generation by Fe_3O_4 magnetic nanoparticles, (b) photothermal therapy and (c) photodynamic therapy uses an external light source to activate photosensitizing chemicals attached to Fe_3O_4 magnetic nanoparticles. This activation process produces singlet oxygen species that are cytotoxic to cells. Reprinted from [138], with permission from Elsevier.

Hyperthermia therapy using Fe_3O_4 was introduced in patients diagnosed with prostate cancer and glioblastoma [139]. This research showed the efficacy of using Fe_3O_4 for interstitial heating in patients suffering from locally recurrent prostate cancer [140]. In addition, patients suffering from recurrent glioblastoma multiform who underwent hyperthermia treatment had a median survival rate twice as long as other patients [141]. Fe_3O_4 magnetic nanoparticles have been used in the treatment of metastatic bone cancer to reduce lesions and bone formation through hyperthermia therapy [142].

Fe_3O_4 magnetic nanoparticles have fulfilled the characteristics for use in *in-vivo* systems, such as chemotherapy drugs [143]. Fe_3O_4 magnetic nanoparticles have the potential to improve the pharmacokinetic and pharmacodynamic characteristics of drugs used in cancer therapy [128,129]. The process involves integrating chemotherapy drugs into magnetic Fe_3O_4 nanoparticles, which are then directed to the cancer site by utilizing an external magnetic field [144]. Fe_3O_4 magnetic nanoparticles can efficiently reach the lesion site due to their nanoscale size and specific surface area [145].

The research conducted by Ayyanaar *et al*. [146] (**Figure 4**) utilized Fe_3O_4 magnetic nanoparticles combined with poly (l-lactic acid) (PLA) and filled with the antibiotic Ciprofloxacin (CIF) for *in vitro* research. The study showed a significant increase in cytotoxicity against HeLa-S3 cancer cells *in vitro*, with an IC_{50} of 0.8 ± 0.03 µg/mL. The results show that Fe_3O_4 magnetic nanoparticles have the potential to be efficient drug carriers for targeted cancer therapy that responds to multi-stimuli. Further research is required to determine the mechanism working and confirm the targeted drug delivery route of this method.

Fe_3O_4 magnetic nanoparticles must exhibit high biocompatibility with minimal toxicity to be used as medical materials in the body [147]. Additionally, they should be capable of synthesis in various shapes and sizes [148], exhibiting high encapsulation efficiency and the ability to accommodate hydrophilic and hydrophobic drugs [149]. Fe_3O_4 magnetic nanoparticles should be well tolerated when entering the capillaries of targeted cancer cells [150,151] and must have a hydrodynamic size smaller than 5 nm to be excreted in urine [152-153].

Drug delivery using magnetic materials can increase the therapeutic efficacy of drugs and minimize side effects due to conventional cancer treatments [154]. Drug carrier agents at the nanoscale can be categorized into 3 groups, including organic, inorganic and organo-inorganic hybrids [155]. Organic drug carriers include solid lipid nanoparticles (SLNs), polymer nanoparticles and biomimetic virus-based nanoparticles. SLNs exhibit a spherical morphology with sizes ranging from 50 nm to 1 μm and can be digested by the body include diglycerides, triglycerides, phospholipids and fatty acids. SLNs can provide easy delivery of active drugs to cancer cells, the ability to reduce resistance, the ability to control drug exposure and the synergistic effect of mixed loading [156]. SLNs exhibit stability characteristics under acidic conditions and enhances cancer cell cytotoxicity.

Polymer nanoparticles can be synthesized with sizes from 10 to 1000 nm using chitosan, poly(lactide-glycolide), poly (lactic acid), polyacrylic acid and alginate [157]. Synthesis of polymer nanoparticles is carried out using several methods such as solvent evaporation, salting and dialysis. Polymeric nanoparticles have biocompatibility, provide protection against drug degradation, are non-immunogenic, show great efficacy in encapsulating lipophilic drugs, and can be rapidly excreted from the body [158].

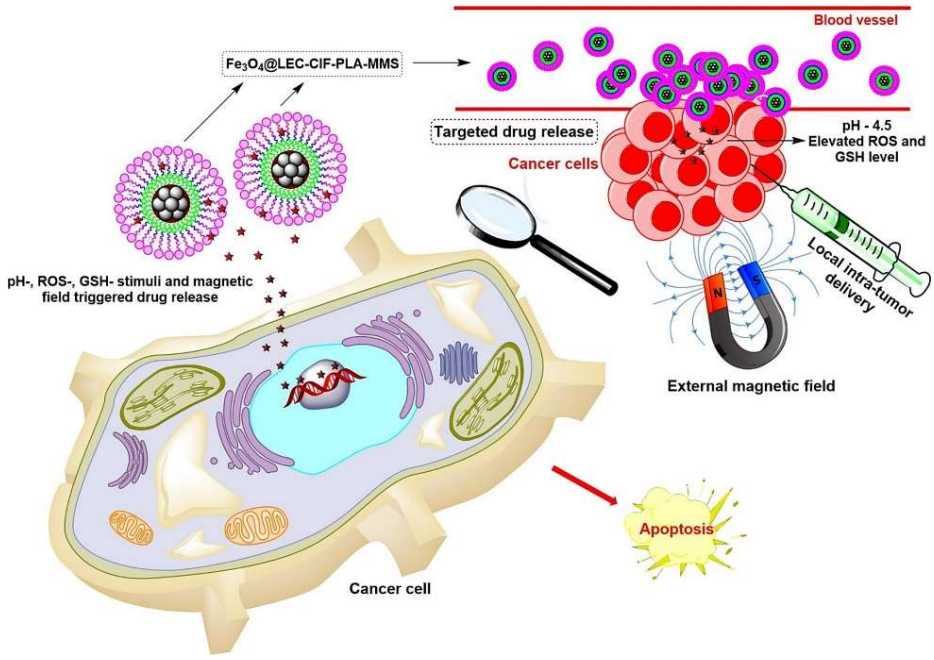

Figure 4 Illustrates the drug release process of Fe_3O_4 established with poly (l-lactic acid) (PLA) and loaded with the antibiotic medication CIF. Reprinted from [146], with permission from Elsevier.

Inorganic drug carriers have a spherical or cylindrical shape with sizes ranging from 10 to 500 nm. Basic materials often used include gold, silver, silica and iron. Chemicals are used to modify the inorganic base material, allowing its conjugation with antibodies, ligands and other pharmaceutical compounds [159].

Research shows that inorganic materials actively interact with drug solutions [160]. Additionally, nanoparticles show a dual response to glutathione and pH when used as drug carriers [161].

Fe_3O_4 magnetic nanoparticles used directly can cause premature damage to the drug delivery agent before it reaches the cancer area. This causes the amount of drug that can be delivered to be reduced, and it is not effective in treating cancer [162]. Research continues to be carried out to increase the efficiency of using Fe_3O_4 magnetic nanoparticles as a drug delivery vehicle. **Figure 5** shows a drug delivery system using Fe_3O_4 magnetic nanoparticles.

Andronescu *et al*. [163] investigated drug delivery in bone cancer using COLL/HA- Fe_3O_4@cisplatin material implanted in the bone defect. This research enables targeted delivery in specific areas using external controls to prevent harmful effects on the entire system. In addition, the Fe_3O_4@SiO_2@tannic acid alloy can function as a pH-responsive drug carrier for the simultaneous release of the anticancer drugs methotrexate (MTX) and doxorubicin (DOX). This suggests that double-shell nano-drug delivery can be used to treat cancer [164].

Dai *et al*. [165] investigated the use of Fe_3O_4@SiO_2 with DOX utilizing the solvothermal technique. Research shows that a DOX concentration of 10 µg/mL resulted in the death of 82.8 % of lung cancer cells, while a DOX concentration of 0.5 µg/mL during an incubation period of 15 min of NIR irradiation caused the death of 81.3 % of lung cancer cells. This shows the potential of photothermal effects in chemotherapy treatment.

Utilization of Fe_3O_4 magnetic nanoparticles in drug delivery offers the advantage of being an easy-to-use, cost-effective and recyclable separator. In addition, various research has been carried out to determine its potential for detecting cancer cells [166]. The utilization of Fe_3O_4 magnetic nanoparticles is hampered by their susceptibility to acid and oxidative damage. The presence of strong Van Der Waals forces and magnetic attraction between particles results in high agglomeration, thereby limiting the practical usefulness of these nanoparticles [167]. Current research is still limited in terms of its applicability to humans, as it can only be evaluated in small animal models [168].

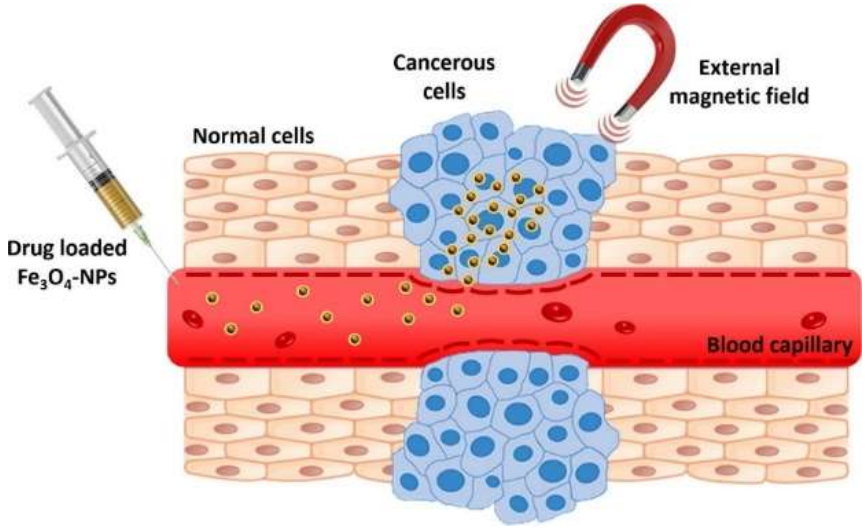

Figure 5 Illustrates the drug delivery process using Fe_3O_4 magnetic nanoparticles. Medicines containing nanoparticles are injected into the blood capillaries. Then, an external magnetic field positions the drug at the cancer site. Reprinted from [104], with permission from Elsevier.

Surface modification of Fe_3O_4 magnetic nanoparticles

Surface modification of Fe_3O_4 magnetic nanoparticles is very important for accurate and targeted cancer detection. Various chemicals or molecules can functionalize the surface of Fe_3O_4 magnetic nanoparticles. The choice of materials used must be able to interact with cancer biomarkers without causing major toxicity effects. One frequently performed surface modification technique involves the application of an external protective coating. The presence of an outer protective layer on Fe_3O_4 magnetic nanoparticles can maintain the stability of the magnetic components and prevent excessive agglomeration [169]. **Table 9** shows modification of magnetic Fe_3O_4 nanoparticles and medical applications.

Applying a biocompatible coating to targeted cancer tissue can increase the specificity of Fe_3O_4 nanoparticles [170]. Biocompatible coatings can provide a variety of multifunctional methods using Fe_3O_4 magnetic nanoparticles [171]. Fe_3O_4 magnetic nanoparticles can be coated with an inorganic layer (e.g. C, SiO_2, ZnO) or an organic layer (e.g. PEG) [123]. This protective layer is expected to provide benefits as a strong binding medium [172]. Inorganic protective layers on Fe_3O_4 magnetic nanoparticles for cancer therapy are still limited. The hydrophobic and chemically inert nature of most inorganic protective coatings can have negative effects in aqueous environments [15].

Organic protective layers are more promising for further use because they can cover the weaknesses of inorganic protective layers [173]. Fe_3O_4 magnetic nanoparticles coated with an organic shield enable hydrophilic interactions with a loading capacity comparable to that of a sponge. Additionally, organic shields can aid in the functionalization of antibodies for targeted delivery, ensuring biocompatibility to evade the immune system and the ability to deceive cancer cells as a defense mechanism [174-176]. Polyethylene glycol (PEG) is an organic coating that has been widely reported in various literature sources [177].

Polyethylene Glycol (PEG) is a hydrophilic polymer that is easily soluble in water, biocompatible, non-antigenic and resistant to proteins [167]. Tai *et al*. [178] conducted research showing that Fe_3O_4 magnetic nanoparticles coated with PEG, showed high colloidal stability for up to 21 days. This finding exceeds the stability of unmodified Fe_3O_4 magnetic nanoparticles. However, long-term colloid stability is not always necessary, because cytostatic release only occurs within a few days. Therefore, additional investigations are needed to explore potential materials that can serve as a protective layer on Fe_3O_4 magnetic nanoparticles.

Research has been carried out to examine the toxicity of Fe_3O_4 magnetic nanoparticles without a protective layer and Fe_3O_4 magnetic nanoparticles with various protective layers [179]. Fe_3O_4 magnetic nanoparticles show minimal cytotoxicity when given at concentrations below the threshold of 100 μg/mL [180]. The surface of nanoparticles can be coated with antibodies, small molecules, peptides, aptamers and other components due to the unique properties of nanoparticles [181]. Fe_3O_4 magnetic nanoparticles can negatively impact cell behaviour through various mechanisms, such as disruption of the cytoskeleton, induction of oxidative stress, generation of free radicals, decreased mitochondrial function, DNA damage and changes in cell pathways [182]. Research has shown that the toxicity of Fe_3O_4 magnetic nanoparticles is influenced by their shape (e.g. spheres, rods and beads) and the mass ratio of the protective layer. These factors have a direct and significant impact on toxicity [183].

Kandasamy *et al*. [184] conducted research on the application of protective coatings on Fe_3O_4 magnetic nanoparticles. The research was carried out using a multifunctional magnetic polymer made by combining ferrofluid and hydrophobic Fe_3O_4 magnetic nanoparticles with oleylamine as a stabilizer. The results showed that nanoparticles used with 2 drugs (curcumin or verapamil) could significantly improve stability with minimal toxicity. Additionally, research has developed polycaprolactone (PCL)-coated Fe_3O_4 magnetic nanoparticles as a new therapeutic drug that exhibits improved thermo sensitivity and

cytocompatibility. Nanomedicines show important benefits in terms of excellent stability, effective dispersion, compatibility with living cells and controllable heating [185].

Applying citric acid and chitosan in the coating process of Fe_3O_4 magnetic nanoparticles enables curcumin transportation into cells as a drug carrier (**Figure 6**). The application of a coating including citric acid and chitosan is conducted to provide pH stability during the drug release process, hence facilitating the efficient cellular uptake of curcumin for its therapeutic effects. The cellular uptake of curcumin has been seen to have a significant inhibitory impact on the proliferation, invasion and migration of SGC-7901 cells. Furthermore, the SGC-7901 cells exhibited oxidative damage and apoptosis via caspase and ferroptosis processes, while causing minimal harmful side effects on the normal GES-1 cell tissue. This study presents a prospective medication delivery system capable of traversing the blood-brain barrier (BBB) [186].

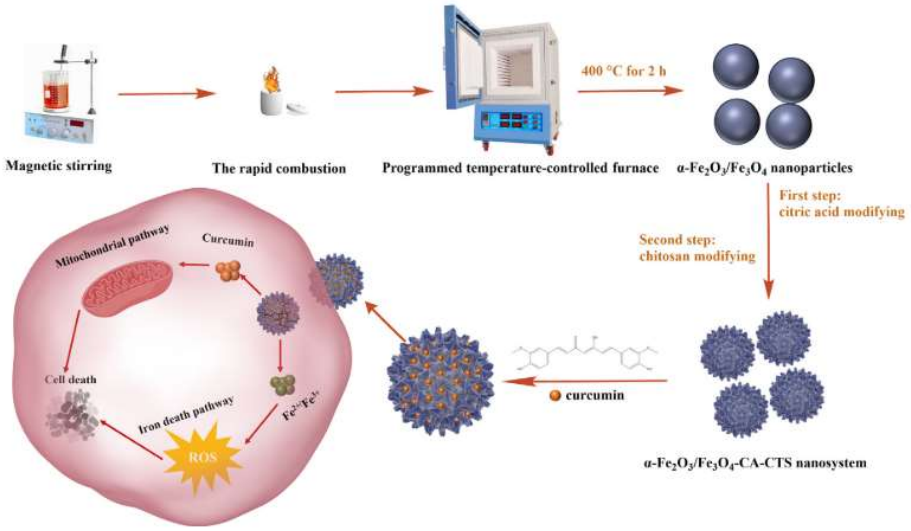

Figure 6 Illustration of applying citric acid and chitosan in the coating process of Fe_3O_4 magnetic nanoparticles enables curcumin transportation into cells as a drug carrier. Reprinted from [186], with permission from Elsevier.

Table 4 Modification of magnetic Fe_3O_4 nanoparticles and medical applications.

Surface modification	Medical applications	Principal discoveries	Ref.
PEG	Magnetic hyperthermia, drug delivery system and MRI.	Surface modification of the magnetic nanoparticle Fe_3O_4 layer caused magnetic saturation to decrease from 51.9 to 38.8 emu/g. This method can also reduce the explosive effect by 32 % of administering the anticancer drug, Tamoxifen.	[187]
Ag/Fe_3O_4@CS@PVA	Multifunctional wound healing.	This method exhibits an inhibitory impact on both Gram-positive and Gram-negative bacteria when used in low doses. Rapid wound healing is demonstrated through *in vivo* experimentation with excellent biocompatibility.	[188]

Surface modification	Medical applications	Principal discoveries	Ref.
Polyethyleneimine (PEI) and Hyaluronic Acid (HA)	Drug delivery, and targeted therapy.	Fe_3O_4 nanoparticles selectively target cancer cells through an external magnetic field. The use of HA on the surface of Fe_3O_4 nanoparticles showed high stability and uniform dispersion in the acidic cancer environment. This method can deliver drugs through the ferroptosis process in hepatocellular carcinoma (HCC).	[189]
ZIF-8	Targeted drug release.	Fe_3O_4 nanoparticles can be applied to targeted drug release using external magnetic fields. ZIF-8 administration facilitates the release of drugs of pH-sensitive and biocompatible medicines.	[190]
SiO_2	Plasmid DNA purification.	The application of SiO_2 coating on Fe_3O_4 magnetic nanoparticles can enhance the adsorption efficiency of plasmid DNA and encourage a high elution rate, while also providing resistance to acidic conditions.	[191]

Conclusions

Fe_3O_4 magnetic nanoparticles show great potential for future cancer detection applications. Previous research has shown that nanoparticles offer significant potential in various and efficient diagnostic and therapeutic applications. Fe_3O_4 magnetic nanoparticles are effective as sensitive contrast agents for accurately detecting cancer in MRI images. Fe_3O_4 magnetic nanoparticles enhance early cancer diagnosis, leading to improved patient prognosis. Improvements are needed to enhance the research outcomes, such as doing comparison studies on different forms of cancer to assess the benefits and drawbacks of Fe_3O_4 magnetic nanoparticles under diverse settings.

The synthesis method of Fe_3O_4 magnetic nanoparticles can impact the properties, morphology and dimensions of the nanoparticles. Nanoparticles provide adaptable surface properties and the ability to target cancer biomarkers, allowing for precise and sensitive detection. The nanoscale size enables improved tissue penetration and serves as a contrast agent in medical imaging to enhance diagnostic accuracy. Fe_3O_4 magnetic nanoparticles can target therapeutic drugs to the tumor location, minimizing damage to healthy tissue and enhancing treatment efficacy. Additional research is required to enhance delivery efficiency and address the growing issue of medication resistance. Further research on the pharmacokinetics and pharmacodynamics of Fe_3O_4 magnetic nanoparticles in drug administration could enhance comprehension of their distribution, metabolism and pharmacological impacts in the human body.

The main focus of research on Fe_3O_4 magnetic nanoparticles remains on investigating their toxicity and biocompatibility. The need for a detailed evaluation of the interaction between Fe_3O_4 magnetic nanoparticles and biological systems to ensure their safe utilization in medical environments. Future study should concentrate on enhancing the biocompatible qualities of Fe_3O_4 magnetic nanoparticles. This may entail altering the surface of Fe_3O_4 magnetic nanoparticles with a coating that minimizes immunological reactions and biological harm.

Further research is required to evaluate the toxicity of Fe_3O_4 magnetic nanoparticles using *in vitro* and *in vivo* studies to comprehend their effects on human cells and organs. For understanding the removal and metabolism of Fe_3O_4 magnetic nanoparticles from the human body, it is crucial to identify the physiological pathways affected by these nanoparticles. This review paper aims to offer valuable insights to researchers regarding the possible use of Fe_3O_4 magnetic nanoparticles as a cancer detector. To enable future research on creating Fe_3O_4 magnetic nanoparticles for safer and more efficient use in medical applications.

Acknowledgements

The authors are gratefully acknowledged the Posgraduate Program of Physics, FMIPA, Universitas Sumatera Utara, Indonesia and Departement of Physics, FMIPA, Universitas Sumatera Utara, Indonesia for the support and encouragement to complete this project through facilities provided. Tulus Na Duma thanks to PMDSU Program Batch VII Year of 2023.

References

[1] KJ Hiam-Galvez, BM Allen and MH Spitzer. Systemic immunity in cancer. *Nat. Rev. Cancer* 2021; **21**, 345-59.

[2] IO Wulandari, LB Rahayu, I Riva, H Sulistyarti and A Sabarudin. Sintesis dan karakterisasi nanopartikel Fe_3O_4 termodifikasi biokompatibel polimer serta potensinya sebagai penghantar obat (*in Indonesian*). *Indones. Green Tech. J*. 2021; **10**, 1-8.

[3] D Menasco and Q Wang. *Nanoparticles as drug delivery vehicles*. *In*: B Wang, L Hu and TJ Siahaan (Eds.). Drug delivery: Principles and applications. 2nd eds. John Wiley & Sons, New Jersey, 2016, p. 299-335.

[4] G Bharath, K Rambabu, F Banat, N Ponpandian, E Alsharaeh, AH Harrath, A Alrezaki and S Alwasel. Shape-controlled rapid synthesis of magnetic nanoparticles and their morphological dependent magnetic and thermal studies for cancer therapy applications. *Mater. Res. Express* 2019; **6**, 66104.

[5] F Malega, IPT Indrayana and E Suharyadi. Synthesis and characterization of the microstructure and functional group bond of Fe_3O_4 nanoparticles from natural iron sand in Tobelo North Halmahera. *Jurnal Ilmiah Pendidikan Fisika Al-BiRuNi* 2018; **7**, 129-38.

[6] Q Wu, M Chen, K Chen, S Wang, C Wang and G Diao. Fe_3O_4-based core/shell nanocomposites for high-performance electrochemical supercapacitors. *J. Mater. Sci*. 2016; **51**, 1572-80.

[7] S Humaidi, M Hamid and H Wijoyo. Study and characterization of $BaFe_{12}O_{19}$/PVDF composites as electrode materials for supercapacitors. *Biosens. Bioelectron.* 2024; **19**, 100507.

[8] MR Ghazanfari, M Kashefi, SF Shams and MR Jaafari. Perspective of Fe_3O_4 nanoparticles role in biomedical applications. *Biochem. Res. Int*. 2016; **2016**, 7840161.

[9] SS Khiabani, M Farshbaf, A Akbarzadeh and S Davaran. Magnetic nanoparticles: Preparation methods, applications in cancer diagnosis and cancer therapy. *Artif. Cells Nanomed. Biotechnol*. 2017; **45**, 6-17.

[10] J Dulińska-Litewka, A Łazarczyk, P Hałubiec, O Szafrański, K Karnas and A Karewicz. Superparamagnetic iron oxide nanoparticles-current and prospective medical applications. *Materials* 2019; **12**, 617.

[11] Wahajuddin and S Arora. Superparamagnetic iron oxide nanoparticles: Magnetic nanoplatforms as drug carriers. *Int. J. Nanomed*. 2012; **7**, 3445-71.

[12] S Liu, B Yu, S Wang, Y Shen and H Cong. Preparation, surface functionalization and application of Fe_3O_4 magnetic nanoparticles. *Adv. Colloid Interface Sci*. 2020; **281**, 102165.

[13] Kritika and I Roy. Therapeutic applications of magnetic nanoparticles: Recent advances. *Mater. Adv*. 2022; **3**, 7425-44.

[14] I Rosenberger, A Strauss, S Dobiasch, C Weis, S Szanyi, L Gil-Iceta, E Alonso, MG Esparza, V Gómez-Vallejo, B Szczupak, S Plaza-García, S Mirzaei, LL Israel, S Bianchessi, E Scanziani, JP Lellouche, P Knoll, J Werner, K Felix, L Grenacher, T Reese, J Kreuter and M Jiménez-González. Targeted diagnostic magnetic nanoparticles for medical imaging of pancreatic cancer. *J. Controlled Release* 2015; **214**, 76-84.

[15] LS Ganapathe, MA Mohamed, RM Yunus and DD Berhanuddin. Magnetite (Fe_3O_4) nanoparticles in biomedical application: From synthesis to surface functionalisation. *Magnetochemistry* 2020; **6**, 68.

[16] R Rahmawati, A Taufiq, S Sunaryono, A Fuad, B Yuliarto, S Suyatman and D Kurniadi. Synthesis of magnetite (Fe_3O_4) nanoparticles from iron sands by coprecipitation-ultrasonic irradiation methods. *J. Mater. Environ. Sci*. 2018; **9**, 155-60.

[17] M Hamid, M Rianna, WR Rangkuti, T Sembiring and P Sebayang. Study and characterization rGO/Fe_3O_4 in microstructure and magnetic properties. *S. Afr. J. Chem. Eng*. 2022; **42**, 280-2.

[18] SK Giri, NN Das and GC Pradhan. Synthesis and characterization of magnetite nanoparticles using waste iron ore tailings for adsorptive removal of dyes from aqueous solution. *Colloids Surf. A Physicochem. Eng. Aspects* 2011; **389**, 43-9.

[19] S Wu, A Sun, F Zhai, J Wang, W Xu, Q Zhang and AA Volinsky. Fe_3O_4 magnetic nanoparticles synthesis from tailings by ultrasonic chemical co-precipitation. *Mater. Lett*. 2011; **65**, 1882-4.

[20] S Febriyani and S Aini. Synthesis of magnetite (Fe_3O_4) nanoparticles from iron ore with the addition of lauric acid. *Nat. Sci. Jurnal Penelitian Bidang IPA Pendidikan* 2023; **9**, 57-69.

[21] R Prasetyowati, D Widiawati, PE Swastika, A Ariswan and W Warsono. Synthesis and characterization of magnetite (Fe_3O_4) nanoparticles based on iron sands at Glagah Beach Kulon Progo with coprecipitation methods at various NH_4OH concentrations (*in Indonesian*). *Jurnal Sains Dasar* 2021; **10**, 57-61.

[22] VM Chakka, B Altuncevahir, ZQ Jin, Y Li and JP Liu. Magnetic nanoparticles produced by surfactant-assisted ball milling. *J. Appl. Phys*. 2006; **99**, 08E912.

[23] TP Yadav, RM Yadav and DP Singh. Mechanical milling: A top down approach for the synthesis of nanomaterials and nanocomposites. *Nanosci. Nanotechnol*. 2012; **2**, 22-48.

[24] Q Zhang, X Yang and J Guan. Applications of magnetic nanomaterials in heterogeneous catalysis. *ACS Appl. Nano Mater*. 2019; **2**, 4681-97.

[25] M Song, Y Zhang, S Hu, L Song, J Dong, Z Chen and N Gu. Influence of morphology and surface exchange reaction on magnetic properties of monodisperse magnetite nanoparticles. *Colloids Surf. A Physicochem. Eng. Aspects* 2012; **408**, 114-21.

[26] S Taib and E Suharyadi. Sintesis nanopartikel magnetite (Fe_3O_4) dengan template silika (SiO_2) dan karakterisasi sifat kemagnetannya (*in Indonesian*). *Indones. J. Appl. Phys*. 2015; **5**, 23.

[27] M Sheikholeslami and SA Shehzad. Numerical analysis of Fe_3O_4-H_2O nanofluid flow in permeable media under the effect of external magnetic source. *Int. J. Heat Mass Transfer* 2018; **118**, 182-92.

[28] D Azarifar, O Badalkhani and Y Abbasi. Silica-modified magnetite Fe_3O_4 nanoparticles grafted with sulfamic acid functional groups: An efficient heterogeneous catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-one and tetrahydrobenzo[b]pyran derivatives. *J. Sulfur Chem*. 2016; **37**, 656-73.

[29] K Hardani, F Buazar, K Ghanemi, M Kashisaz, MH Baghlani-Nezhad, A Khaledi-Naseb and M Badri. Removal of toxic mercury (II) from water *via* Fe_3O_4/hydroxyapatite nanoadsorbent: An efficient, economic and rapid approach. *AASCIT J. Nanosci*. 2015; **1**, 11-8.

[30] M Liu, C Liu, H Chen, X Huang, X Zeng, J Zhou and S Mi. Prevention of cholesterol gallstone disease by schaftoside in lithogenic diet-induced C57BL/6 mouse model. *Eur. J. Pharmacol*. 2017; **815**, 1-9.

[31] HE Ghandoor, HM Zidan, MMH Khalil and MIM Ismail. Synthesis and some physical properties of magnetite (Fe_3O_4) nanoparticles. *Int. J. Electrochem. Sci*. 2012; **7**, 5734-45.

[32] I Karimzadeh, M Aghazadeh, T Doroudi, MR Ganjali and PH Kolivand. Superparamagnetic Iron oxide (Fe_3O_4) nanoparticles coated with PEG/PEI for biomedical applications: A facile and scalable preparation route based on the cathodic electrochemical deposition method. *Adv. Phys. Chem*. 2017; **2017**, 9437487.

[33] MS Kandelousi and R Ellahi. Simulation of ferrofluid flow for magnetic drug targeting using the lattice boltzmann method. *Zeitschrift Für Naturforschung A* 2015; **70**, 115-24.

[34] C Wang, C Bao, S Liang, L Zhang, H Fu, Y Wang, K Wang, C Li, M Deng, Q Liao, J Ni and D Cui. HAI-178 antibody-conjugated fluorescent magnetic nanoparticles for targeted imaging and simultaneous therapy of gastric cancer. *Nanoscale Res. Lett*. 2014; **9**, 274.

[35] J Chen, M Shi, P Liu, A Ko, W Zhong, WJ Liao and MMQ Xing. Reducible polyamidoamine-magnetic iron oxide self-assembled nanoparticles for doxorubicin delivery. *Biomaterials* 2014; **35**, 1240-8.

[36] BWC Tse, GJ Cowin, C Soekmadji, L Jovanovic, RS Vasireddy, MT Ling, A Khatri, T Liu, B Thierry and PJ Russell. PSMA-targeting iron oxide magnetic nanoparticles enhance MRI of preclinical prostate cancer. *Nanomedicine* 2015; **10**, 375-86.

[37] P Orlowski, M Zmigrodzka, E Tomaszewska, K Ranoszek-Soliwoda, M Czupryn, M Antos-Bielska, J Szemraj, G Celichowski, J Grobelny and M Krzyzowska. Tannic acid-modified silver nanoparticles for wound healing: The importance of size. *Int. J. Nanomed*. 2018; **13**, 991-1007.

[38] KN Koo, AF Ismail, MHD Othman, MA Rahman and TZ Sheng. Preparation and characterization of superparamagnetic magnetite (Fe_3O_4) nanoparticles: A short review. *Malays. J. Fundam. Appl. Sci*. 2019; **15**, 23-31.

[39] US Khan, NS Khattak, A Rahman and F Khan. Historical development of magnetite nanoparticles synthesis. *J. Chem. Soc. Pak*. 2011; **33**, 793-804.

[40] H Lubis. Perbandingan karakterisasi morfologi Fe_3O_4 terhadap Fe_3O_4 merck melalui metode kopresipitasi (*in Indonesian*). *Jurnal Insitusi Politeknik Ganesha Medan Juripol* 2022; **5**, 458-63.

[41] AS Teja and PY Koh. Synthesis, properties, and applications of magnetic iron oxide nanoparticles. *Prog. Cryst. Growth Charact. Mater*. 2009; **55**, 22-45.

[42] Y Wei, B Han, X Hu, Y Lin, X Wang and X Deng. Synthesis of Fe_3O_4 nanoparticles and their magnetic properties. *Procedia Eng*. 2012; **27**, 632-7.

[43] DT Nurrohman and JS Pribadi. Kajian struktur kristal, lattice strain, dan komposisi kimia nanopartikel pasir besi yang disintesis dengan metode ball milling (*in Indonesian*). *Konstan Jurnal Fisika Pendidikan Fisika* 2018; **3**, 94-101.

[44] P Simamora and Krisna. Sintesis dan karakteristik sifat magnetik nanokomposit Fe_3O_4-montmorilonit berdasarkan variasi suhu (*in Indoenesian*). *Prosiding Seminar Nasional Fisika* 2015; **4**, 75-80.

[45] SS Staniland, A Rawlings, J Bramble, J Tolosa, O Wilson, JC García-Martínez and C Binns. *Novel methods for the synthesis of magnetic nanoparticles*. *In*: C Binns (Ed.). Nanomagnetism: Fundamentals and applications. Elsiver, Amsterdam, Netherlands, 2014, p. 85-128.

[46] Z Jalil, A Rahwanto, Mustanir, Akhyar and E Handoko. Magnetic behavior of natural magnetite (Fe_3O_4) extracted from beach sand obtained by mechanical alloying method. *AIP Conf. Proc*. 2017; **1862**, 30023.

[47] JE Muñoz, J Cervantes, R Esparza and G Rosas. Iron nanoparticles produced by high-energy ball

milling. *J. Nanopart. Res*. 2007; **9**, 945-50.

[48] L Mohammed, HG Gomaa, D Ragab and J Zhu. Magnetic nanoparticles for environmental and biomedical applications: A review. *Particuology* 2017; **30**, 1-14.

[49] A Erwin, S Salomo, P Adhy, N Utari, W Ayu, Y Wita and S Nani. Magnetic iron oxide particles (Fe_3O_4) fabricated by ball milling for improving the environmental quality. *In*: Proceedings of the International Conference on Chemical Engineering and Applied Sciences, Banda Aceh, Indonesia. 2019, p. 12051.

[50] Y Pratiwi, Ramli and Ratnawulan. Pengaruh waktu milling terhadap struktur kristal magnetite (Fe_3O_4) berbahan dasar mineral vulkanik dari gunung talang sumatera barat (*in Indonesian*). *Pillar Phys*. 2017; **10**, 102-8.

[51] MF Elmahaishi, RS Azis, I Ismail, MS Mustaffa, Z Abbas, KA Matori, FD Muhammad, NK Saat, R Nazlan, IR Ibrahim, NH Abdullah and N Mokhtar. Structural, electromagnetic and microwave properties of magnetite extracted from mill scale waste via conventional ball milling and mechanical alloying techniques. *Materials* 2021; **14**, 7075.

[52] MM Can, S Ozcan, A Ceylan and T Firat. Effect of milling time on the synthesis of magnetite nanoparticles by wet milling. *Mater. Sci. Eng. B* 2010; **172**, 72-5.

[53] PAC Bedoya, PM Botta, PG Bercoff and MA Fanovich. Magnetic iron oxides nanoparticles obtained by mechanochemical reactions from different solid precursors. *J. Alloys Compd*. 2021; **860**, 157892.

[54] LA Melinia, E Puspita, M Naibaho, Ramlan and M Ginting. Analisa pasir besi alam dari sungai musi sumatera selatan (*in Indonesian*). *Jurnal Penelitian Sains* 2022; **24**, 122-6.

[55] AA Velásquez, CC Marín and JP Urquijo. Synthesis and characterization of magnetite-maghemite nanoparticles obtained by the high-energy ball milling method. *J. Nanopart. Res*. 2018; **20**, 72.

[56] M Rianna, M Hamid, F Handayani, AMS Sebayang, WR Rangkuti, M Situmorang, T Sembiring, EA Setiadi, AP Tetuko and P Sebayang. Study and characterization of Fe_3O_4 synthesized from natural iron sand in Sumatera Utara. *J. Aceh Phys. Soc*. 2022; **11**, 45-8.

[57] P Biehl, MVD Lühe, S Dutz and FH Schacher. Synthesis, characterization, and applications of magnetic nanoparticles featuring polyzwitterionic coatings. *Polymers* 2018; **10**, 91.

[58] HD Kurland, J Grabow, G Staupendahl, W Andrä, S Dutz and ME Bellemann. Magnetic iron oxide nanopowders produced by CO_2 laser evaporation. *J. Magn. Magn. Mater*. 2007; **311**, 73-7.

[59] V Amendola and M Meneghetti. Laser ablation synthesis in solution and size manipulation of noble metal nanoparticles. *Phys. Chem. Chem. Phys*. 2009; **11**, 3805-21.

[60] FH Alkallas, SM Alghamdi, EA Rashed, ABG Trabelsi, SS Nafee, WB Elsharkawy, E Alsubhe, SH Alshreef and AM Mostafa. Nanocomposite Fe_3O_4-MWCNTs based on femtosecond pulsed laser ablation for catalytic degradation. *Diamond Relat. Mater*. 2023; **140**, 110445.

[61] M Al-Salih, S Samsudin and SS Arshad. Synthesis and characterizations iron oxide carbon nanotubes nanocomposite by laser ablation for anti-microbial applications. *J. Genet. Eng. Biotechnol*. 2021; **19**, 76.

[62] S Dadashi, R Poursalehi and H Delavari. Structural and optical properties of pure iron and iron oxide nanoparticles prepared via pulsed Nd:YAG laser ablation in liquid. *Procedia Mater. Sci*. 2015; **11**, 722-6.

[63] G Kawamura, S Alvarez, IE Stewart, M Catenacci, Z Chen and YC Ha. Production of oxidation-resistant Cu-based nanoparticles by wire explosion. *Sci. Rep*. 2015; **5**, 18333.

[64] AS Lozhkomoev, AV Pervikov, SO Kazantsev, AF Sharipova, NG Rodkevich, NE Toropkov, KV Suliz, NV Svarovskaya, AM Kondranova and MI Lerner. Synthesis of Fe/Fe_3O_4 core-shell nanoparticles by electrical explosion of the iron wire in an oxygen-containing atmosphere. *J.*

Nanopart. Res. 2021; **23**, 73.

[65] S Singh and N Goswami. Structural, optical, magnetic and dielectric properties of magnetite (Fe_3O_4) nanoparticles prepared by exploding wire technique. *J. Mater. Sci. Mater. Electron*. 2021; **32**, 26857-70.

[66] F Shahbazi, M Noghani and R Ahmadi. Effect of synthesis conditions on the morphology, composition and magnetic properties of the iron oxide nanoparticles prepared via electric discharge method. *J. Magn. Magn. Mater*. 2021; **536**, 168090.

[67] LPS Sagala, S Humaidi, K Tarigan, AMS Soehada and P Sebayang. Synthesis and characterization of nanoparticles $Zn_{0.7}Ni_{0.15}Cu_{0.15}Fe_2O_4$ using the co-precipitation method. *In*: Proceedings of the 1st South East Asia Science, Technology, Engineering and Mathematics International Conference, Banda Aceh, Indonesia. 2021, p. 12012.

[68] M Hamid, Susilawati, SA Amaturrahim, IB Dalimunthe and A Daulay. Synthesis of magnetic activated carbon-supported cobalt (II) chloride derived from pecan shell (*Aleurites moluccana*) with co-precipitation method as the electrode in supercapacitors. *Mater. Sci. Energy Tech*. 2023; **6**, 429-36.

[69] SNK Tarigan, S Humaidi, M Rianna and NMR Nasution. Effect of NaOH concentrationon magnetic properties and structural studies of $MgFe_2O_4$ based on natural iron sand synthesized by coprecipitation method. *Prisma Sains* 2023; **11**, 636-41.

[70] J Mosayebi, M Kiyasatfar and S Laurent. Synthesis, functionalization, and design of magnetic nanoparticles for theranostic applications. *Adv. Healthcare Mater*. 2017; **6**, 1700306.

[71] FC Nalle, R Wahid, IO Wulandari and A Sabarudin. Synthesis and characterization of magnetic Fe_3O_4 nanoparticles using oleic acid as stabilizing agent. *Rasayan J. Chem*. 2019; **12**, 14-21.

[72] AG Magdalena, IMB Silva, RFC Marques, ARF Pipi, PN Lisboa-Filho and MJ Jafelicci. EDTA-functionalized Fe_3O_4 nanoparticles. *J. Phys. Chem. Solids* 2018; **113**, 5-10.

[73] FV Gutierrez, IS Lima, AD Falco, BM Ereias, O Baffa, CDDA Lima, LIM Sinimbu, PDL Presa, C Luz-Lima and JFDF Araujo. The effect of temperature on the synthesis of magnetite nanoparticles by the coprecipitation method. *Heliyon* 2024; **10**, e25781.

[74] MM Ba-Abbad, A Benamour, D Ewis, AW Mohammad and E Mahmoudi. Synthesis of Fe_3O_4 nanoparticles with different shapes through a co-precipitation method and their application. *J. Miner. Met. Mater. Soc.* 2022; **74**, 3531-9.

[75] FDD Irianti, H Sutanto, P Priyono, AA Wibowo, AN Syahida and I Alkian. Characterization structure of Fe_3O_4@PEG-4000 nanoparticles synthesized by co-precipitation method. *In*: Proceedings of the 10th International Seminar on New Paradigm and Innovation on Natural Science and Its Application, Semarang, Indonesia. 2021, p. 12014.

[76] G Antarnusa, PD Jayanti, YR Denny and A Suherman. Utilization of co-precipitation method on synthesis of Fe_3O_4/PEG with different concentrations of PEG for biosensor applications. *Materialia* 2022; **25**, 101525.

[77] I Nkurikiyimfura, Y Wang, B Safari and E Nshingabigwi. Temperature-dependent magnetic properties of magnetite nanoparticles synthesized *via* coprecipitation method. *J. Alloys Compd*. 2020; **846**, 156344.

[78] MJ Eskandari and I Hasanzadeh. Size-controlled synthesis of Fe_3O_4 magnetic nanoparticles via an alternating magnetic field and ultrasonic-assisted chemical co-precipitation. *Mater. Sci. Eng. B* 2021; **266**, 115050.

[79] VVN Girija and S Vasu. Synthesis and characterization of iron oxide nanoparticles by thermal decomposition method of iron (III) chelates. *Int. J. Nanosci. Nanotechnol*. 2019; **15**, 65-73.

[80] FB Effenberger, RA Couto, PK Kiyohara, G Machado, SH Masunaga, RF Jardim and LM Rossi. Economically attractive route for the preparation of high quality magnetic nanoparticles by the thermal decomposition of iron (III) acetylacetonate. *Nanotechnology* 2017; **28**, 115603.

[81] B Ren, AE Kandjani, M Chen, MR Field, DK Oppedisano, SK Bhargava and LA Jones. Preparation of Au nanoparticles on a magnetically responsive support via pyrolysis of a Prussian blue composite. *J. Colloid Interface Sci*. 2019; **540**, 563-71.

[82] V Patsula, L Kosinová, M Lovrić, LF Hamzić, M Rabyk, R Konefal, A Paruzel, M Šlouf, V Herynek, S Gajović and D Horák. Superparamagnetic Fe_3O_4 nanoparticles: Synthesis by thermal decomposition of Iron (III) glucuronate and application in magnetic resonance imaging. *ACS Appl. Mater. Interfaces* 2016; **8**, 7238-47.

[83] M Faraji, Y Yamini and M Rezaee. Magnetic nanoparticles: Synthesis, stabilization, functionalization, characterization, and applications. *J. Iran. Chem. Soc.* 2010; **7**, 1-37.

[84] D Maity, J Ding and JM Xue. Synthesis of magnetite nanoparticles by thermal decomposition: Time, temperature, surfactant and solvent effects. *Funct. Mater. Lett*. 2008; **1**, 189-93.

[85] U Klekotka, S Boratyńska, D Satuła and B Kalska-Szostko. Influence of long-term thermal treatment of magnetite nanoparticles on its physicochemical properties. *J. Magn. Magn. Mater*. 2023; **585**, 171099.

[86] EA Bakr, MN El-Nahass, WM Hamada and TA Fayed. Facile synthesis of superparamagnetic Fe_3O_4@noble metal core-shell nanoparticles by thermal decomposition and hydrothermal methods: Comparative study and catalytic applications. *RSC Adv*. 2020; **11**, 781-97.

[87] P Zhang, Y Zhang, M Gao and X Zhang. Dendrimer-assisted hydrophilic magnetic nanoparticles as sensitive substrates for rapid recognition and enhanced isolation of target tumor cells. *Talanta* 2016; **161**, 925-31.

[88] I Campos, A Espindola, C Chagas, E Barbosa, CE Castro, C Molina, FLA Fonseca and PS Haddad. Biocompatible superparamagnetic nanoparticles with ibuprofen as potential drug carriers. *SN Appl. Sci*. 2020; **2**, 456.

[89] M Hamid, S Humaidi, IR Saragi, C Simanjuntak, I Isnaeni, Azizah and H Wijoyo. The effectiveness of activated carbon from nutmeg shell in reducing ammonia (NH_3) levels in fish pond water. *Carbon Trends* 2024; **14**, 100324.

[90] J Siregar, K Sebayang, B Yuliarto and S Humaidi. XRD characterization of Fe_3O_4-ZnO nanocomposite material by the hydrothermal method. *AIP Conf. Proc*. 2020; **2221**, 110008.

[91] EO Sari, A Fadli and A Amri. The 3 hours-hydrothermal sunthesis of high surface area superparamagnetic Fe_3O_4 core-shell nanoparticles. *Jurnal Sains Materi Indonesia* 2017; **19**, 9-13.

[92] M Zahid, N Nadeem, MA Hanif, IA Bhatti, HN Bhatti and G Mustafa. *Metal ferrites and their graphene-based nanocomposites: Synthesis, characterization, and applications in wastewater treatment*. *In*: K Abd-Elsalam, M Mohamed and R Prasad. Springer, Cham, Switzerland, 2019, p. 181-212.

[93] T Liu, S Zhang and Y Xu. Preparation and characterization of Fe_3O_4 nanoparticles via a hydrothermal process with propanediol as the solvent. *Mater. Res. Express* 2022; **9**, 125001.

[94] JMM Silva, PE Feuser, R Cercená, M Peterson and AG Dal-Bó. Obtention of magnetite nanoparticles via the hydrothermal method and effect of synthesis parameters. *J. Magn. Magn. Mater*. 2023; **580**, 170925.

[95] SF Rafie, H Sayahi, H Abdollahi and N Abu-Zahra. Hydrothermal synthesis of Fe_3O_4 nanoparticles at different phs and its effect on discoloration of methylene blue: Evaluation of alternatives by TOPSIS method. *Mater. Today Commun*. 2023; **37**, 107589.

[96] F Shabani and A Khodayari. Structural, compositional, and biological characterization of Fe_3O_4 nanoparticles synthesized by hydrothermal method. *Synth. React. Inorg. Met.-Org. Nano-Met. Chem*. 2015; **45**, 356-62.

[97] LM Cursaru, RM Piticescu, DV Dragut, R Morel, C Thébault, M Carrière, H Joisten and B Dieny. One-step soft chemical synthesis of magnetite nanoparticles under inert gas atmosphere. Magnetic properties and *in vitro* study. *Nanomaterials* 2020; **10**, 1500.

[98] P Hu, T Chang, WJ Chen, J Deng, SL Li, YG Zuo, L Kang, F Yang, M Hostetter and AA Volinsky. Temperature effects on magnetic properties of Fe_3O_4 nanoparticles synthesized by the sol-gel explosion-assisted method. *J. Alloys Compd*. 2019; **773**, 605-11.

[99] MB Polla, JL Nicolini, J Venturini, ADC Viegas, MAZ Vasconcellos, ORK Montedo and S Arcaro. Low-temperature sol-gel synthesis of magnetite superparamagnetic nanoparticles: Influence of heat treatment and citrate-nitrate equivalence ratio. *Ceram. Int*. 2023; **49**, 7322-32.

[100] SAMK Ansari, E Ficiarà, FA Ruffinatti, I Stura, M Argenziano, O Abollino, R Cavalli, C Guiot and F D'Agata. Magnetic iron oxide nanoparticles: Synthesis, characterization and functionalization for biomedical applications in the central nervous system. *Materials* 2019; **12**, 465.

[101] IPT Indrayana. Review Fe_3O_4 dari pasir besi: Sintesis, karakterisasi, dan fungsionalisasi hingga aplikasinya dalam bidang nanoteknologi maju (*in Indonesian*). *Jurnal UNIERA* 2019; **8**, 65-75.

[102] SF Hasany, I Ahmed, J Ranjan and A Rehman. Systematic review of the preparation techniques of iron oxide magnetic nanoparticles. *Nanosci. Nanotechnol*. 2013; **2**, 148-58.

[103] M Hamid, M Rianna, MDE Vania, ID Yanti, FAA Manurung, R Afriandani and A Daulay. Sweet potato-derived carbon nanosheets incorporate $NiCo_2O_4$ nanocomposite as electrode materials for supercapacitors. *Mater. Sci. Energy Tech*. 2023; **6**, 382-7.

[104] YP Yew, K Shameli, M Miyake, NBBA Khairudin, SEB Mohamad, T Naiki and KX Lee. Green biosynthesis of superparamagnetic magnetite Fe_3O_4 nanoparticles and biomedical applications in targeted anticancer drug delivery system: A review. *Arabian J. Chem*. 2020; **13**, 2287-308.

[105] S Gul, SB Khan, IU Rehman, MA Khan and MI Khan. A comprehensive review of magnetic nanomaterials modern day theranostics. *Front. Mater*. 2019; **6**, 179.

[106] M Duan, JG Shapter, W Qi, S Yang and G Gao. Recent progress in magnetic nanoparticles: Synthesis, properties, and applications. *Nanotechnology* 2018; **29**, 452001.

[107] L Liu, Y Li, AA AL-Huqail, E Ali, T Alkhalifah, F Alturise and HE Ali. Green synthesis of Fe_3O_4 nanoparticles using alliaceae waste (*Allium sativum*) for a sustainable landscape enhancement using support vector regression. *Chemosphere* 2023; **334**, 138638.

[108] MY Darmawan, NI Istiqomah, N Adrianto, RM Tumbelaka, AD Nugraheni and E Suharyadi. Green synthesis of Fe_3O_4/Ag composite nanoparticles using moringa oleifera: Exploring microstructure, optical, and magnetic properties for magnetic hyperthermia applications. *Results Chem*. 2023; **6**, 100999.

[109] M Yusefi, K Shameli, RR Ali, SW Pang and SY Teow. Evaluating anticancer activity of plant-mediated synthesized iron oxide nanoparticles using *Punica Granatum* fruit peel extract. *J. Mol. Struct*. 2020; **1204**, 127539.

[110] Q Zhang, Y Zhang, Y Li, P Ding, S Xu and J Cao. Green synthesis of magnetite nanoparticle and its regulatory effect on fermentative hydrogen production from lignocellulosic hydrolysate by *Klebsiella* Sp. *Int. J. Hydrogen Energy* 2021; **46**, 20413-24.

[111] M Rahmayanti, AN Syakina, I Fatimah and T Sulistyaningsih. Green synthesis of magnetite nanoparticles using peel extract of jengkol (*Archidendron pauciflorum*) for methylene blue adsorption from aqueous media. *Chem. Phys. Lett*. 2022; **803**, 139834.

[112] BA Eldeeb, WMA El-Raheem and S Elbeltagi. Green synthesis of biocompatible Fe_3O_4 magnetic nanoparticles using Citrus sinensis peels extract for their biological activities and magnetic-hyperthermia applications. *Sci. Rep*. 2023; **13**, 19000.

[113] JK Patra and KH Baek. Green biosynthesis of magnetic iron oxide (Fe_3O_4) nanoparticles using the aqueous extracts of food processing wastes under photo-catalyzed condition and investigation of their antimicrobial and antioxidant activity. *J. Photochem. Photobiol. B Biol*. 2017; **173**, 291-300.

[114] C Bai, P Hu, N Liu, G Feng, D Liu, Y Chen, M Ma, N Gu and Y Zhang. Synthesis of ultrasmall Fe_3O_4 nanoparticles as T_1-T_2 dual-modal magnetic resonance imaging contrast agents in rabbit hepatic tumors. *ACS Appl. Nano Mater*. 2020; **3**, 3585-95.

[115] W Zhang, Z Zhang, S Lou, Z Chang, B Wen and T Zhang. Hyaluronic acid-stabilized Fe_3O_4 nanoparticles for promoting *in vivo* magnetic resonance imaging of tumors. *Front. Pharmacol*. 2022; **13**, 918819.

[116] H Danafar, Y Baghdadchi, M Barsbay, M Ghaffarlou, N Mousazadeh and A Mohammadi. Synthesis of Fe_3O_4-Gold hybrid nanoparticles coated by bovine serum albumin as a contrast agent in MR imaging. *Heliyon* 2023; **9**, e13874.

[117] Y Yang, Y Liu, L Song, X Cui, J Zhou, G Jin, AR Boccaccini and S Virtanen. Iron oxide nanoparticle-based nanocomposites in biomedical application. *Trends Biotechnol*. 2023; **41**, 1471-87.

[118] Y Peng, Y Gao, C Yang, R Guo, X Shi and X Cao. Low-molecular-weight poly(ethylenimine) nanogels loaded with ultrasmall iron oxide nanoparticles for T_1-weighted MR imaging-guided gene therapy of sarcoma. *ACS Appl. Mater. Interfaces* 2021; **13**, 27806-13.

[119] Y Sun, H Chen, Y Huang, F Xu, G Liu, L Ma and Z Wang. One-pot synthesis of AuPd@Fe_xO_y nanoagent with the activable Fe species for enhanced Chemodynamic-photothermal synergetic therapy. *Biomaterials* 2021; **274**, 120821.

[120] D Karley, D Gupta and A Tiwari. Biomarker for cancer: A great promise for future. *World J. Oncol*. 2011; **2**, 151-7.

[121] AA Roointan, TA Mir, SI Wani, KK Hussain, B Ahmed, S Abrahim, A Savardashtaki, G Gandomani, M Gandomani, R Chinnappan and MH Akhtar. Early detection of lung cancer biomarkers through biosensor technology: A review. *J. Pharm. Biomed. Anal*. 2018; **164**, 93-103.

[122] GES Chaudhry, AM Akim, N Safdar, A Yasmin, S Begum, YY Sung and TST Muhammad. Cancer and disease diagnosis - Biosensor as potential diagnostic tool for biomarker detection. *J. Adv. Pharm. Tech. Res*. 2022; **13**, 243-7.

[123] Q Dong, X Jia, Y Wang, H Wang, Q Liu, D Li, J Wang and E Wang. Sensitive and selective detection of mucin1 in pancreatic cancer using hybridization chain reaction with the assistance of Fe_3O_4@polydopamine nanocomposites. *J. Nanobiotechnol*. 2022; **20**, 94.

[124] A Foroozandeh, M Abdouss, H SalarAmoli, M Pourmadadi and F Yazdian. An electrochemical aptasensor based on G-C_3N_4/Fe_3O_4/PANI nanocomposite applying cancer antigen_125 biomarkers detection. *Process Biochem*. 2023; **127**, 82-91.

[125] Y Ni, H Ouyang, L Yu, C Ling, Z Zhu, A He and R Liu. Label-free electrochemical aptasensor based on magnetic α-Fe_2O_3/Fe_3O_4 heterogeneous hollow nanorods for the detection of cancer antigen 125. *Bioelectrochemistry* 2022; **148**, 108255.

[126] M Braiek, Y Yang, C Farre, C Chaix, F Bessueille, A Baraket, A Errachid, A Zhang and N Jaffrezic-Renault. Boron-doped diamond electrodes modified with Fe_3O_4@Au magnetic nanocomposites as sensitive platform for detection of a cancer biomarker, interleukin-8. *Electroanalysis* 2016; **28**, 1810-6.

[127] SC McBain, HHP Yiu and J Dobson. Magnetic nanoparticles for gene and drug delivery. *Int. J.*

Nanomed. 2008; **3**, 169-80.

[128] P Tran, SE Lee, DH Kim, YC Pyo and JS Park. Recent advances of nanotechnology for the delivery of anticancer drugs for breast cancer treatment. *J. Pharm. Invest*. 2020; **50**, 261-70.

[129] T Asai. Nanoparticle-mediated delivery of anticancer agents to tumor angiogenic vessels. *Biol. Pharm. Bull*. 2012; **35**, 1855-61.

[130] YT Prabhu, KV Rao, BS Kumari, VSS Kumar and T Pavani. Synthesis of Fe_3O_4 nanoparticles and its antibacterial application. *Int. Nano Lett*. 2015; **5**, 85-92.

[131] S Sunaryono, A Taufiq, N Nurdin and D Darminto. Kontribusi *Filler* magnetik Fe_3O_4 pada efek histerisis magneto-elastisitas komposit ferogel (*in Indonesian*). *Jurnal Fisika Aplikasinya* 2013; **9**, 37.

[132] C Tang, Z He, H Liu, Y Xu, H Huang, G Yang, Z Xiao, S Li, H Liu, Y Deng, Z Chen, H Chen and N He. Application of magnetic nanoparticles in nucleic acid detection. *J. Nanobiotechnol*. 2020; **18**, 62.

[133] H Mok and M Zhang. Superparamagnetic iron oxide nanoparticle-based delivery systems for biotherapeutics. *Expert Opin. Drug Delivery* 2013; **10**, 73-87.

[134] CSSR Kumar and F Mohammad. Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. *Adv. Drug Delivery Rev*. 2011; **63**, 789-808.

[135] B Liu, J Zhou, B Zhang and J Qu. Synthesis of $Ag@Fe_3O_4$ nanoparticles for photothermal treatment of ovarian cancer. *Hindawi J. Nanomater*. 2019; **2019**, 6457968.

[136] MR Ahghari, Z Amiri-Khamakani and A Maleki. Synthesis and characterization of Se doped Fe_3O_4 nanoparticles for catalytic and biological properties. *Sci. Rep*. 2023; **13**, 1007.

[137] W Wang, F Li, S Li, Y Hu, M Xu, Y Zhang, MI Khan, S Wang, M Wu, W Ding and B Qiu. M_2 macrophage-targeted iron oxide nanoparticles for magnetic resonance image-guided magnetic hyperthermia therapy. *J. Mater. Sci. Tech*. 2021; **81**, 77-87.

[138] RA Revia and M Zhang. Magnetite nanoparticles for cancer diagnosis, treatment, and treatment monitoring: Recent advances. *Mater. Today* 2016; **19**, 157-68.

[139] D Destouches, N Page, Y Hamma-Kourbali, V Machi, O Chaloin, S Frechault, C Birmpas, P Katsoris, J Beyrath, P Albanese, M Maurer, G Carpentier, JM Strub, AV Dorsselaer, S Muller, D Bagnard, JP Briand and J Courty. A simple approach to cancer therapy afforded by multivalent pseudopeptides that target cell-surface nucleoproteins. *Cancer Res*. 2011; **71**, 3296-305.

[140] M Johannsen, U Gneveckow, K Taymoorian, B Thiesen, N Waldöfner, R Scholz, K Jung, A Jordan, P Wust and SA Loening. Morbidity and quality of life during thermotherapy using magnetic nanoparticles in locally recurrent prostate cancer: Results of a prospective phase I trial. *Int. J. Hyperthermia* 2007; **23**, 315-23.

[141] K Maier-Hauff, F Ulrich, D Nestler, H Niehoff, P Wust, B Thiesen, H Orawa, V Budach and A Jordan. Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. *J. Neuro-Oncol*. 2011; **103**, 317-24.

[142] A Matsumine, K Takegami, K Asanuma, T Matsubara, T Nakamura, A Uchida and A Sudo. A novel hyperthermia treatment for bone metastases using magnetic materials. *Int. J. Clin. Oncol*. 2011; **16**, 101-8.

[143] P Sangaiya and R Jayaprakash. A review on iron oxide nanoparticles and their biomedical applications. *J. Supercond. Novel Magn*. 2018; **31**, 3397-413.

[144] PT Yin, BP Shah and KB Lee. Combined magnetic nanoparticle-based microRNA and hypertermia therapy to enhace apoptosis in brain cancer cells. *Small* 2015; **10**, 41602-12.

[145] M Ahmed and M Douek. The role of magnetic nanoparticles in the localization and treatment of breast cancer. *BioMed Res. Int*. 2013; **2013**, 281230.

[146] S Ayyanaar and MP Kesavan. Magnetic iron oxide nanoparticles@lecithin/poly (l-lactic acid) microspheres for targeted drug release in cancer therapy. *Int. J. Biol. Macromol*. 2023; **253**, 127480.

[147] I Khmara, O Strbak, V Zavisova, M Koneracka, M Kubovcikova, I Antal, V Kavecansky, D Lucanska, D Dobrota and P Kopcansky. Chitosan-stabilized iron oxide nanoparticles for magnetic resonance imaging. *J. Magn. Magn. Mater*. 2019; **474**, 319-25.

[148] A Widoni, A Fadli and Komalasari. Sintesis komposit Fe_3O_4/hidroksiapatit menggunakan metode presipitasi dengan variasi rasio Ca/P dan kecepatan pengadukan. *Jom FTEKNIK* 2019; **6**, 2-7.

[149] DEJ Waddington, T Boele, R Maschmeyer, Z Kuncic and MS Rosen. High-sensitivity *in vivo* contrast for ultra-low field magnetic resonance imaging using superparamagnetic iron oxide nanoparticles. *Sci. Adv*. 2020; **6**, eabb0998.

[150] M Ghafari, F Haghiralsadat, SK Falahati-Pour and JZ Reza. Development of a novel liposomal nanoparticle formulation of cisplatin to breast cancer therapy. *J. Cell. Biochem*. 2020; **121**, 3584-92.

[151] Y Hui, X Yi, F Hou, D Wibowo, F Zhang, D Zhao, H Gao and CX Zhao. Role of nanoparticle mechanical properties in cancer drug delivery. *ACS Nano* 2019; **13**, 7410-24.

[152] HS Choi and JV Frangioni. Nanoparticles for biomedical imaging: Fundamentals of clinical translation. *Mol. Imaging* 2010; **9**, 291-310.

[153] VP Vu, GB Gifford, F Chen, H Benasutti, G Wang, EV Groman, R Scheinman, L Saba, SM Moghimi and D Simberg. Immunoglobulin deposition on biomolecule corona determines complement opsonization efficiency of preclinical and clinical nanoparticles. *Nat. Nanotechnol*. 2019; **14**, 260-8.

[154] Khalkhali, K Rostamizadeh, S Sadighian, F Khoeini, M Naghibi and M Hamidi. The impact of polymer coatings on magnetite nanoparticles performance as MRI contrast agents: A comparative study. *DARU J. Pharm. Sci.* 2015; **23**, 45.

[155] EM Materón, CM Miyazaki, O Carr, N Joshi, PHS Picciani, CJ Dalmaschio, F Davis and FM Shimizu. Magnetic nanoparticles in biomedical applications: A review. *Appl. Surf. Sci. Adv*. 2021; **6**, 100163.

[156] CS Kumar, R Thangam, SA Mary, PR Kannan, G Arun and B Madhan. Targeted delivery and apoptosis induction of trans-resveratrol-ferulic acid loaded chitosan coated folic acid conjugate solid lipid nanoparticles in colon cancer cells. *Carbohydr. Polym*. 2020; **231**, 115682.

[157] R Shukla, M Handa, SB Lokesh, M Ruwali, K Kohli and P Kesharwani. *Conclusion and future prospective of polymeric nanoparticles for cancer therapy*. *In*: Polymeric nanoparticles as a promising tool for anti-cancer therapeutics. Academic Press, Massachusetts, 2019, p. 389-408.

[158] JP Abriata, RC Turatti, MT Luiz, GL Raspantini, LB Tofani, RLFD Amaral, K Swiech, PD Marcato and JM Marchetti. Development, characterization and biological *in vitro* assays of paclitaxel-loaded PCL polymeric nanoparticles. *Mater. Sci. Eng. C Mater. Biol. Appl.* 2019; **96**, 347-55.

[159] B Haley and E Frenkel. Nanoparticles for drug delivery in cancer treatment. *Urol. Oncol. Semin. Orig. Invest*. 2008; **26**, 57-64.

[160] Y Alyassin, EG Sayed, P Mehta, K Ruparelia, MS Arshad, M Rasekh, J Shepherd, I Kucuk, PB Wilson, N Singh, MW Chang, DG Fatouros and Z Ahmad. Application of mesoporous silica nanoparticles as drug delivery carriers for chemotherapeutic agents. *Drug Discovery Today* 2020; **25**, 1513-20.

[161] N Lu, Y Tian, W Tian, P Huang, Y Liu, Y Tang, C Wang, S Wang, Y Su, Y Zhang, J Pan, Z Teng and G Lu. Smart cancer cell targeting imaging and drug delivery system by systematically engineering periodic mesoporous organosilica nanoparticles. *ACS Appl. Mater. Interfaces* 2016; **8**, 2985-93.

[162] L Gu, X He and Z Wu. Mesoporous Fe_3O_4/hydroxyapatite composite for targeted drug delivery. *Mater. Res. Bull*. 2014; **59**, 65-8.

[163] C Marques, JMF Ferreira, E Andronescu, D Ficai, M Sonmez and A Ficai. Multifunctional materials

for bone cancer treatment. *Int. J. Nanomed*. 2014; **9**, 2713-25.

[164] AM Demin, AV Vakhrushev, MS Valova, MA Korolyova, MA Uimin, AS Minin, VA Pozdina, IV Byzov, AA Tumashov, KA Chistyakov, GL Levit, VP Krasnov and VN Charushin. Effect of the silica-magnetite nanocomposite coating functionalization on the doxorubicin sorption/desorption. *Pharmaceutics* 2022; **14**, 2271.

[165] A Maximenko, J Depciuch, N Łopuszyńska, M Stec, Ż Świątkowska-Warkocka, V Bayev, PM Zieliński, J Baran, J Fedotova, WP Węglarz and M Parlinska-Wojtan. Fe_3O_4@SiO_2@Au nanoparticles for mri-guided chemo/NIR photothermal therapy of cancer cells. *RSC Adv*. 2020; **10**, 26508-20.

[166] Y Pang, J Shi, X Yang, C Wang, Z Sun and R Xiao. Personalized detection of circling exosomal PD-L1 based on Fe_3O_4@TiO_2 isolation and SERS immunoassay. *Biosens. Bioelectron*. 2020; **148**, 111800.

[167] M Anbarasu, M Anandan, E Chinnasamy, V Gopinath and K Balamurugan. Synthesis and characterization of polyethylene glycol (PEG) coated Fe_3O_4 nanoparticles by chemical co-precipitation method for biomedical applications. *Spectrochimica Acta A Mol. Biomol. Spectrosc*. 2015; **135**, 536-9.

[168] VJ Venditto and FC Szoka. Cancer nanomedicines: So many papers and so few drugs! *Adv. Drug Delivery Rev*. 2013; **65**, 80-8.

[169] M Sonmez, M Georgescu, L Alexandrescu, D Gurau, A Ficai, D Ficai and E Andronescu. Synthesis and applications of Fe_3O_4/SiO_2 core-shell materials. *Curr. Pharm. Des*. 2015; **21**, 5324-35.

[170] JE Rosen, L Chan, DB Shieh and FX Gu. Iron oxide nanoparticles for targeted cancer imaging and diagnostics. *Nanomed. Nanotechnol. Biol. Med*. 2012; **8**, 275-90.

[171] N Zhu, H Ji, P Yu, J Niu, MU Farooq, MW Akram, IO Udego, H Li and X Niu. Surface modification of magnetic iron oxide nanoparticles. *Nanomaterials* 2018; **8**, 810.

[172] D Istrati, A Moroșan, R Stan, BȘ Vasile, G Vasilievici, O Oprea, G Dolete, B Purcăreanu and DE Mihaiescu. Microwave-assisted sol-gel preparation of the nanostructured magnetic system for solid-phase synthesis. *Nanomaterials* 2021; **11**, 3176.

[173] C Chircov, RE Ștefan, G Dolete, A Andrei, AM Holban, OC Oprea, BS Vasile, IA Neacșu and B Tihăuan. Dextran-coated iron oxide nanoparticles loaded with curcumin for antimicrobial therapies. *Pharmaceutics* 2022; **14**, 1057.

[174] M Caciandone, AG Niculescu, V Grumezescu, AC Bîrcă, IC Ghica, BȘ Vasile, O Oprea, IC Nica, MS Stan, AM Holban, AM Grumezescu, I Anghel and AG Anghel. Magnetite nanoparticles functionalized with therapeutic agents for enhanced ENT antimicrobial properties. *Antibiotics* 2022; **11**, 623.

[175] VA Spirescu, AG Niculescu, Ș Slave, AC Bîrcă, G Dorcioman, V Grumezescu, AM Holban, OC Oprea, BȘ Vasile, AM Grumezescu, IC Nica, MS Stan and E Andronescu. Anti-biofilm coatings based on chitosan and lysozyme functionalized magnetite nanoparticles. *Antibiotics* 2021; **10**, 1269.

[176] RA Puiu, PC Balaure, E Constantinescu, AM Grumezescu, E Andronescu, OC Oprea, BS Vasile, V Grumezescu, I Negut, IC Nica and MS Stan. Anti-cancer nanopowders and maple-fabricated thin coatings based on spions surface modified with paclitaxel loaded β-cyclodextrin. *Pharmaceutics* 2021; **13**, 1356.

[177] M Caciandone, AG Niculescu, AR Roșu, V Grumezescu, I Negut, AM Holban, O Oprea, BȘ Vasile, AC Bîrcă, AM Grumezescu, MS Stan, AG Anghel and I Anghel. PEG-functionalized magnetite nanoparticles for modulation of microbial biofilms on voice prosthesis. *Antibiotics* 2022; **11**, 39.

[178] MF Tai, CW Lai and SBA Hamid. Facile synthesis polyethylene glycol coated magnetite

nanoparticles for high colloidal stability. *J. Nanomater*. 2016; **2016**, 8612505.

[179] N Singh, GJS Jenkins, R Asadi and SH Doak. Potential toxicity of superparamagnetic iron oxide nanoparticles (SPION). *Nano Rev*. 2010; **1**, 5358.

[180] S Laurent, AA Saei, S Behzadi, A Panahifar and M Mahmoudi. Superparamagnetic iron oxide nanoparticles for delivery of therapeutic agents: Opportunities and challenges. *Expert Opin. Drug Delivery* 2014; **11**, 1449-70.

[181] B Kumar, S Singh, I Skvortsova and V Kumar. Promising targets in anti-cancer drug development: Recent updates. *Curr. Med. Chem*. 2017; **24**, 4729-52.

[182] M Mahmoudi, H Hofmann, B Rothen-Rutishauser and A Petri-Fink. Assessing the *in vitro* and *in vivo* toxicity of superparamagnetic iron oxide nanoparticles. *Chem. Rev*. 2012; **112**, 2323-38.

[183] M Mahmoudi, A Simchi, AS Milani and P Stroeve. Cell toxicity of superparamagnetic iron oxide nanoparticles. *J. Colloid Interface Sci*. 2009; **336**, 510-8.

[184] G Kandasamy, A Sudame, D Maity, S Soni, K Sushmita, NS Veerapu, S Bose and CV Tomy. Multifunctional magnetic-polymeric nanoparticles based ferrofluids for multi-modal *in vitro* cancer treatment using thermotherapy and chemotherapy. *J. Mol. Liq*. 2019; **293**, 111549.

[185] Z Hedayatnasab, A Dabbagh, F Abnisa and WMAW Daud. Polycaprolactone-coated superparamagnetic iron oxide nanoparticles for *in vitro* magnetic hyperthermia therapy of cancer. *Eur. Polym. J*. 2020; **133**, 109789.

[186] M Ma, Z Lv, Y Li, Z Zhu, C Ling, D He and R Liu. Enhanced anti-cancer effects of magnetic targeted ph-sensitive curcumin delivery system based on heterogeneous magnetic α-Fe_2O_3/Fe_3O_4 nanoparticles on gastric cancer SGC-7901 cells. *Arabian J. Chem*. 2023; **16**, 105352.

[187] MA Mohammadi, S Asghari and B Aslibeiki. Surface modified Fe_3O_4 nanoparticles: A cross-linked polyethylene glycol coating using plasma treatment. *Surf. Interfaces* 2021; **25**, 101271.

[188] J Qi, J Zhang, H Jia, X Guo, Y Yue, Y Yuan and T Yue. Synthesis of silver/Fe_3O_4@chitosan@polyvinyl alcohol magnetic nanoparticles as an antibacterial agent for accelerating wound healing. *Int. J. Biol. Macromol*. 2022; **221**, 1404-14.

[189] Z Liang, Y Wang, J Wang, T Xu, S Ma, Q Liu, L Zhao, Y Wei, X Lian and D Huang. Multifunctional Fe_3O_4-PEI@HA nanoparticles in the ferroptosis treatment of hepatocellular carcinoma through modulating reactive oxygen species. *Colloids Surf. B Biointerfaces* 2023; **227**, 113358.

[190] W Cai, W Zhang and Z Chen. Magnetic Fe_3O_4@ZIF-8 nanoparticles as a drug release vehicle: PH-sensitive release of norfloxacin and its antibacterial activity. *Colloids Surf. B Biointerfaces* 2023; **223**, 113170.

[191] Q Fan, Y Guan, Z Zhang, G Xu, Y Yang and C Guo. A new method of synthesis well-dispersion and dense Fe_3O_4@SiO_2 magnetic nanoparticles for DNA extraction. *Chem. Phys. Lett*. 2019; **715**, 7-13.