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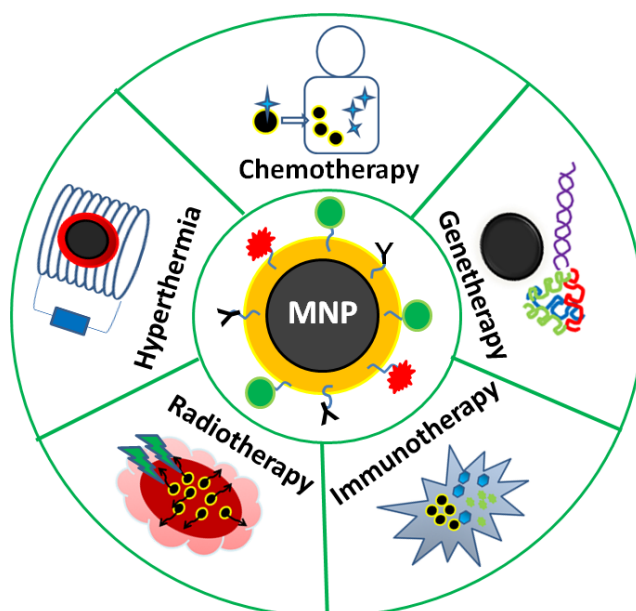
# Magnetic nanoparticles: Multifunctional tool for cancer therapy

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## Graphical Abstract:



## ABSTRACT

**Introduction:** Cancer is among the most diseases resulting in massive deaths globally. Traditional therapies used to treat cancer possess harmful adverse effects. Taking these facts into consideration, researchers explored new-fangled therapeutic possibilities with enhanced benefits. Nanoparticle development used in cancer detection in addition to therapy showed substantial progress over the past few years.

**Area covered:** Herein, the latest research regarding cancer treatment employing MNPs in chemo-, immuno-, gene-, and radio- therapy along with hyperthermia is summarized in addition to their physio-chemical feature, advantages, and limitations for clinical translation have also been discussed.

**Experts opinion:** MNPs are being extensively investigated and get developed into effective therapeutic modules in cancer therapies. MNPs are extremely functionalizable tools aimed at cancer therapy owing excellent superparamagnetic, chemical, biocompatible, physical, and

biodegradable properties.

**Keywords:** Cancer, chemotherapy, gene therapy, hyperthermia, immunotherapy, magnetic nanoparticles, radiotherapy

## Article highlights

- Among various nanoparticles, magnetic nanoparticles (MNPs) emerged as innovative treatment agents modernizing therapeutic usages in cancer therapy.
- MNPs modified with various coatings are developed to improve physico-chemical features.
- Commonly, SPIONs (superparamagnetic iron oxide nanoparticles) are engaged in tailored medicine intended for cancer theranostics.
- MNPs are being incorporated with immunotherapy, radiotherapy, chemotherapy, hyperthermia, and gene therapy to treat cancer effectively.
- Despite the benefits of consuming MNPs in cancer therapy, there is still space for improvement in engineering MNPs for targeting tumor cells more effectively.

## 1. Introduction

Anti-cancerous drugs delivered to targeted sites are one of the effective treatment methods used to treat cancer along with fewer adverse effects. For targeted therapeutics, nanoparticles emerged as a new generation of multi-functional control tools at the micro-nano level. A more effective method is recognized with the functionalization of nano-vehicles with target molecules. These functional moieties assist in which interaction of these nanoparticles with particular receptors present in specific tumors, permitting their attachment to the tumor [1,2]. Another encouraging approach is magnetic cancer therapy intended for improvement regarding imaging-guided delivery along with therapeutic action [3]. Magnetic cancer therapy possibly is employed to treat various kinds of tumors; in which magnetic drug delivery vehicles are manipulated by applying a strong magnetic field [4].

Magnetic nanoparticles (MNPs) possess exceptional characteristics, for instance, small dimensions, high surface area, and superparamagnetic nature, and are therefore useful for a variety of applications [5]. Nanoparticles of iron oxide are the most commonly consumed nanostructured materials used for targeted therapeutic applications. They comprise nanoparticles of  $\text{Fe}_3\text{O}_4$  (magnetite) and  $\gamma\text{-Fe}_2\text{O}_3$  (maghemite), which perform a vital part in cancer diagnosis, delivery of a drug, plus hyperthermia [6]. Furthermore, the superparamagnetic behavior of MNPs can efficiently extravasate and target diseased and infected tissue (lesions) or cancerous sites [7].

All these MNPs properties are entirely employed in cancer therapy, where drugs encapsulated with them or attached to their surface possibly are directed to preferred particular *in vivo* locate by applying a magnetic field externally [8].

Various shapes have been synthesized for improving magnetization by reducing surface anisotropy and increasing exchange anisotropy [9]. Different methodologies are accessible for fabricating MNPs in various forms like nanowires, nanorods, and nanocubes. These techniques include wet chemistry or “bottom-up” methods namely solvothermal, hydrothermal, co-precipitation, sol-gel, electrochemical, flow injection synthesis, and laser pyrolysis procedures [10]. In the last era, the core/shell morphology of MNPs containing a core of iron has been extensively used from the perspective of magnetic influence and loading/release of particular drugs [11]. MNPs attain controllable as well as precise release of the drugs by bonding drug moieties through linkers having the ability to be cleaved or to shell of polymer enclosing them having capability regarding releasing of drugs [12].

There are different approaches for improving some features for instance bad biodegradability, biocompatibility as well as chemical inconstancy in biological environments. All this depends on the functionalization of the MNPs surface. MNPs can be modified covalently by biocompatible and biodegradable polymers [13]. MNPs can be combined with additional functional nanomaterials by coating or successive growth particularly antibodies, ligands, or receptors to create them interacting with biomolecules with considerable affinity, consequently giving controlled “tagging” that deliberate high sensitivity for various biomedical applications [14]. Or MNPs can be integrated with other metallic nanoparticles that give distinctive properties permitting dissimilar functional molecules to get bonded to definite parts of particles and act as diagnostic and therapeutic agents [15].

Researchers have been investigating the usage of MNPs for targeted cancer therapy since late 1970s due to improvement of behavior in therapeutic agents as well as their delivery to targeted sites without any adverse effects [16,17]. Frequently, chemotherapeutic drugs, antibodies, and drugs related to other diseases are attached to MNPs and are delivered to targeted areas inside human body [18]. The employment of MNPs in drug delivery systems enhances their safety, biocompatibility, targeting ability regarding other particular drugs, and less toxicity [19]. Large surface area/volume is mainly beneficial and because of that large number of therapeutic molecules can be attached to them easily, in addition to their manipulation by magnetic field aid imaging of delivery of drugs to the targeted sites [20]. Consequently, MNPs have been coupled for therapy along with diagnosis, mainly in cancer [21]. MNPs in drug delivery systems increase the drug accumulation at the desired sites through magnetic manipulation or hyperthermia can be induced in them by a magnetic field, causing cell death or triggering drug release from thermo-responsive magnetic carriers [22].

Recently, MNPs are comprehensively employed in experimental investigations for treating cancer and consequently different magnetic formulations have been developed, presenting optimistic therapeutic impacts on various cancer types [23]. Different magnetic nanoparticles with different coatings have been synthesized to improve their non-toxicity, biocompatibility,

safety, bio-distribution, stability, etc. Therefore, here we focused on MNPs and deliver an inclusive review, considering detailed aspects of cancer treatment by integrating immunotherapy, radiotherapy, chemotherapy, hyperthermia, and gene therapy with MNPs.

## **2. Physio-chemical features and mechanism of magnetic nanoparticles (MNPs)**

MNPs have been synthesized consuming cobalt, nickel, and gadolinium, however iron oxide (typically  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> or Fe<sub>3</sub>O<sub>4</sub>) nanoparticles (IONPs) are most broadly investigated nanoparticles in cancer therapeutics because of their less systemic toxicity and intense contrast features. Generally MNPs consist of a magnetic core with and a polymer shell [24]. The surface coating and modification of MNPs improves colloidal stability that permits electrostatic or covalent binding of therapeutic payload, targeting constituents, in addition to imaging probes. It plays a vital role in modifying properties of MNPs for instance general toxicity, pharmacokinetics, and rate of clearance, non-specific adsorption of protein or interactions with cells, and persistent release of drugs [25]. MNPs incorporation with polymer coating prevents their agglomeration, and subsequently, offers a prolonged half-life, well-regulated drug release and, concurrently, provides functional groups for conjugation of biomolecules [26].

Traditionally MNPs are synthesized by co-precipitation, hydrothermal, solvothermal, sonochemistry, reverse microemulsion, and thermal decomposition techniques [10]. In recent times, microfluidic and biogenic synthetic methods have been developed as novel approaches for MNPs. Microfluidic systems offer a large number of benefits namely automation, process screening, and constant synthesis. It provides control over reaction time, temperature, and concentration, in addition to the final size, shape, and uniformity of MNPs [27]. However, biogenic methods provide control over nanoparticle's size and shape through biological routes of the organism, or biomineralization. Though, biogenic synthesis still suffers from low yields [28]. Dimensions, morphology, and charge on the MNPs surface could be tuned according to numerous cancer therapeutic applications [29]. Ultimate charges on the surface of synthesized MNPs are utilized used to attach nucleic acids to them electrostatically or increase circulation times [30]. Mostly MNPs with spherical morphology is used in cancer treatment, but few investigations have been conducted using different morphologies such as nanocubes or hollow rods. During the last few years, MNPs especially IONPs gained incredible importance in cancer therapeutics through drug/gene delivery, hyperthermia, radio- and immune- therapy. MNPs are excellent nanomaterials owing to their high magnetic moments, superparamagnetism, magnetic anisotropy, irreversibility regarding high-field magnetization, large surface area, magnetothermal effect, and idyllic biocompatibility [31]. Furthermore, MNPs are present in different constructs: single-phase particle form, core-shell comprising core with polymer coating, multicore, or leaning chain arrangements [32]. A high aspect ratio concerning MNPs is favorable for cellular internalization and surface functionalization, that permits high deformability and prolonged bloodstream circulation time [33].

Among various magnetic configurations accessible for multipurpose cancer therapy, MNPs are mainly designed with core shell morphology that sustains therapeutic and targeting and moieties.

Cancer therapeutic through MNPs also depends on shell functionality that not only protects the core but also overcome limitations regarding immunogenicity and biocompatibility. Delivery of drugs through MNPs systems have been an effective approach for cancer therapeutics due to the tunable physicochemical characteristics of MNPs [26]. They can be fabricated to instruct functionality for therapy for instance conjugation of bio/chemotherapeutics non-covalently or covalently enhances biocompatibility and systemic circulation, employing active and passive targeting mechanisms to the therapeutic site [34]. Immunotherapy to treat cancer utilizes the patient's immunity system for identifying cancer cells, constraining their proliferation, and attacking solid tumors even directly. Combining it with MNPs provides advantages such as targeted delivery that can be tuned to have the required shape, size, charge, and modifications for maximum delivery efficiency [35]. In addition, MNPs generate heat by thermal fluctuations of spins in an AC magnetic field (hyperthermia), by irradiation with light (photothermal therapy), or by conjugating it with photosensitizing agents (photodynamic therapy), which is used for thermal ablation of cancer cells [36]. This heat is transferred to the cells and raises the temperature of cancerous cells more than normal cells and causes death of cancerous cells [37]. The same heat can be used to control the release of drugs encapsulated in magnetic nanocomposites with light or temperature responsive polymer coatings. Magnetic based cancer theranostics is the integration of numerous moieties in single platform that could provide influential paradigm designed for effectual treatment of cancers [38]. MNPs provide a way to track the location of therapeutic agents or target the site by applying external magnetic field, to control therapy process continuously, and ultimately evaluate efficacy of treatment [39].

### **3. Applications of magnetic nanoparticles (MNPs) in cancer therapeutics**

MNPs are been permitted by FDA (Food and Drug Administration) as contrast agent (CA) in MRI, to treat iron deficiency, bio-therapeutic transport, as transporter for drug regarding magnetic targeted therapy in various parts of body, in hyperthermia, and photo-dynamic and -thermal therapy [26]. Cancer therapy through diagnosis and monitoring depends on imaging or using chemo/bio therapeutic agents for instance drugs, proteins, and nucleic acids. A tumor with a clear image is beneficial to know the response of the patient when it is removed surgically and further treatment is suggested. For imaging, CT scans (computerized tomography), magnetic resonance imaging (MRI), echography, X-ray radiography, and PET (positron emission tomography) are employed [7]. Amongst them, MRI possesses a strong effect in timely cancer diagnosis, and SPIONs are the most effective contrast agent for MRI in comparison to other contrast agents (for instance gadolinium-based contrast agents) because of their facile and controlled synthesis regarding size and shape, easy surface decoration, low toxicity, good biodegradability, reduced risk of accumulation, and tissue damage during MRI [40]. Presently gadolinium-based contrast agents (GBCAs) are mostly used in clinical trials. However, gadolinium is toxic to humans in its free form ( $Gd^{3+}$ ). Free gadolinium is excreted very slowly owing to its insolubility at physiological pH, and has an ionic radius close to calcium allowing it to compete with it various physiological processes [41]. As a result, GBCAs remain in the body

for a long time, increasing their probability to dissociate and deposit in the body. IONPs based contrast agents were chosen over gadolinium-based contrast agents due to their low toxicity and researchers have found that they can produce similar MRI contrast with SPIONs [42]. The literature results show clinical research on SPIONs remains robust, particularly fuelled by the approval of ferumoxytol for intravenously administration. SPIONs have been tested on MR angiography, sentinel lymph node detection, lymph node metastasis evaluation; inflammation evaluation; blood volume measurement; as well as liver imaging. The risk of accumulation and tissue damage is reduced when compared to GBCAs. Therefore in comparison to GBCAs, SPIONs are the most effective contrast agents for MRI [43]. MNPs for drug delivery applications are impossible to be unobserved. They are employed to carry drug carriers via attaching chemotherapeutic drugs or antibodies. Usually, MNPs are loaded with chemotherapeutic drugs for cancer therapy. MNPs for cancer therapy are typically employed in numerous ways to attain an enhanced therapeutic efficiency, integrated with chemotherapy, radiotherapy, magnetic hyperthermia, photothermal therapy (PTT), and photodynamic therapy [44]. An immediate treatment observation is possible by specific integration of various drugs with SPIONs that have revealed encouraging potential providing adaptable and sensitive platform for point-of-care (POC) therapeutic applications. SPIONs can be injected immediately into infected tissue, controlled by magnetic field, externally applied for generating heat with aid of Néel and Brownian relaxation processes [45,46]. The section discusses the MNPs employment for cancer therapeutics. Table 1 summarizes some of the information about magnetic nanocomposites in cancer treatment.

**Table 1.** Different magnetic nanocomposites for cancer treatment

Type of MNP	Size	Therapeutic applications	Ref
Iron oxide nanoparticles	10-100 nm	Breast, epithelial colorectal cancers	[47-49]
SPIONs	10-50 nm	Breast, brain, prostate, and lung cancers	[50,51]
Bismuth-iron oxide nanoparticles	55- 150 nm	Breast cancer	[52-54]
Silica-coated iron oxide nanoparticles	150-170 nm	Liver and breast cancers	[55,56]
Iron oxide/gold nanocomposites	50-70 nm	Breast cancer	[57-59]
Zinc oxide/iron oxide nanocomposites	20-80 nm	Breast cancer	[60,61]

Graphene oxide/iron oxide nanocomposites	100-300 nm	Breast, liver, cervical, and blood cancer	[62-65]
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### 3.1. Chemotherapy

MNPs conjugation with chemotherapeutic drugs for obtaining nanosystems for delivery possesses numerous benefits counting magnetic targeting, magnetic thermotherapy, *in vivo* imaging, and collective delivery regarding chemotherapeutic agents. To increase drug targeting efficiency further for chemotherapy via MNPs, particularly SPIONs [66], other targeting molecules comprising antibodies, transferrin, aptamers, folate, hyaluronic acid, and targeting peptides can be coated on SPIONs surface [67]. Magnetic nanoparticles have been widely studied and gradually emerged as another method of tumor treatment, having great potential to assist in the treatment of cancers, especially liver, breast, prostate, and pancreatic cancers [68]. There is no continuous optimization in the treatment process. Magnetic carriers possessing therapeutic doses regarding adsorbed Tc99, doxorubicin, and paclitaxel, have been investigated for cancer treatment [69].

Polydopamine (PDA)-coated MNPs modified by SH- $\beta$ CD (mono-6-thio- $\beta$ -cyclodextrin) were prepared and loaded with doxorubicin. Cellular internalization of the prepared particles in liver cancer was imaged by confocal microscopy. The developed nanomaterials with chemotherapeutical drug and PDA layer could absorb NIR (near-infrared) light. They showed significant effectiveness in a combined photo, chemo, and thermal treatment of liver cancer. Furthermore, they also exhibit enhanced T2 contrast, verified by MRI of these nanoparticles. Consequently, the prepared nanomaterial is an effective nanosystem having significant theranostic potential [70]. A multimodal nanoplatform to treat hepatocellular carcinoma (HCC) *in vitro* was developed. The nanoplatforms were based on polydopamine (PDA)-coated Fe<sub>3</sub>O<sub>4</sub> nanoparticles and spheres (sMAG) with PAMAM dendrimers and functionalized with NHS-PEG-Mal (N-hydroxysuccinimide–polyethylene glycol–maleimide) linker that permits their functionalization with a folic acid derivative. The nanomaterials with folic acid-targeting moiety displayed high efficiency in killing cancer cells in the dual chemo- and photothermal therapy (CT-PTT) of the liver cancer cells as compared to modalities implemented separately. Materials have activity comparable to free doxorubicin (DOX) with a concentration above 10  $\mu$ g/mL. It is worth mentioning that a functionalized magnetic sphere with DOX more intensely affected the HepG2 cells than smaller functionalized nanoparticles with DOX in the performed chemotherapy [71]. In another work multifunctional nanocarriers based on PAMAM dendrimers generation (G) 4.0, 5.0 and 6.0 fixed to polydopamine (PDA) coated Fe<sub>3</sub>O<sub>4</sub> nanoparticles were synthesized and applied in combined chemo- and photothermal therapy (CT-PTT) of liver cancer cells. The combined effect of the above-mentioned modalities results in higher mortality of cancer cells in contrast to their individual performance. Additionally, *in vitro* studies exposed that dual therapy was more effective in triggering desired cell death mechanism apoptosis. The integration of MNPs with dendrimers increases the functionality of dendrimers leading to hybrid



multifunctional nanostructures that are promising smart drug delivery systems to treat cancer [72]. Nanocarrier dextran/polylactic acid (DEX/PLA) and  $\text{Fe}_3\text{O}_4$  (magnetite) nanoparticles carrying the drug were prepared for improving DOX targeting in the treatment of liver cancer and decreasing its possible toxicity to organs. Drug release from prepared nanoparticles inside the body was carried in different pH solutions. The drug is released rapidly in first 24 hours and successive release was slow (Figure 1). At the same time, release of the drug in acidic medium is better from nanoparticles compared with free drug. As cancerous tissues have acidic surroundings, drug can precisely reach cancerous site and inhibit its growth. The *ex vivo* besides *in vivo* results found prepared nanocarriers have intense targeting regarding liver cancerous tissue and could be applied in targeted therapy providing a novel approach for clinical therapy regarding liver cancer [73].

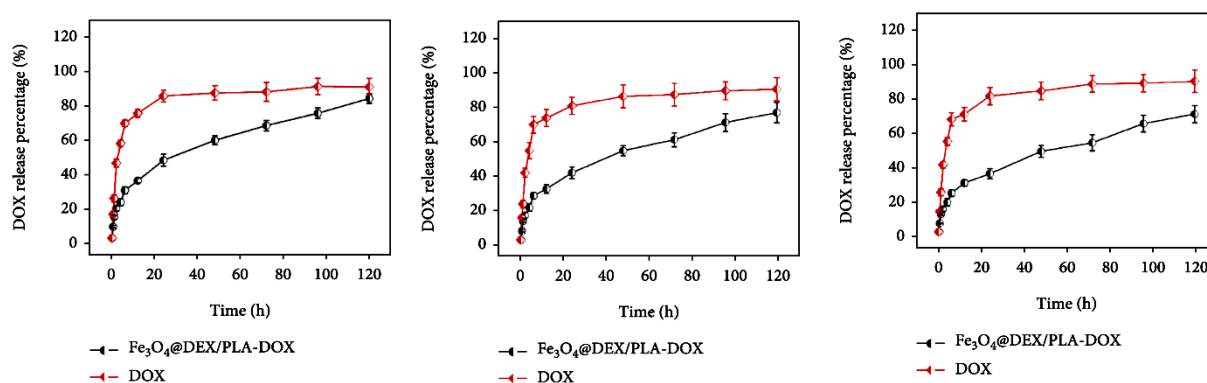


Figure 1. Releasing ability of drug from magnetite nanoparticles loaded with drug (DOX) at (a) pH of 4 (b) pH of 6.28, and (c) pH of 7.4. Reprinted with permission from the reference [73].

Magnetite ( $\text{Fe}_3\text{O}_4$ ) nanoparticles covered by HPG (hyperbranched polyglycerol) along with FA (folic acids) loaded with curcumin were prepared to treat cervical cancer. Functionalized nanoparticles ( $\text{FA@HPG@Fe}_3\text{O}_4$ ) aggregates less compared with non-functionalized ( $\text{HPG@Fe}_3\text{O}_4$ ) nanoparticles. These nanoparticles showed maximum loading capacity for drug found to be equal to 82 and 88%, respectively. Functionalized nanocarriers were captivated by L929 mouse fibroblasts as well as HeLa cells more as compared to  $\text{HPG@Fe}_3\text{O}_4$  nanoparticles. Thus they have potential to be engaged within systems regarding delivery of drugs for cancer treatment. For diagnosis, HeLa cells incubation with prepared nanoparticles reduces MRI signal intensity and biggest variation was perceived after their incubation with functionalized nanoparticles [74]. Paclitaxel (PTX) is a strong chemotherapeutic drug to treat solid advanced carcinomas. Yet, its limited medical consumption is due to its poor solubility in water. A formulation (NP-PTX-FA) involving core of SPIONs coated with polyethylene glycol to conjugate hydrophobic PTX and folic acid (FA). This formulation targets breast cancerous cells and permits controllable PTX release. NP-PTX-FA holds high capacity regarding drug loading equals to 22.8 wt%. Drug is released in acidic conditions similar to intracellular pH concerning

breast cancerous cells. FA bonding results in higher uptake by target sites, increasing cytotoxicity, compared with free drug, to target cells. This formulation possesses significant perspective for improving therapy regarding breast cancer as well as potential for delivering hydrophobic drugs to treat different types of cancer [75]. A versatile nanocomposite was designed to target breast cancer. It comprised of docetaxel (DXL), polyvinyl alcohol (PVA) network intended for controllable release, and silica-coated MNPs for targeted delivery. The developed nanocomposite is directed magnetically for cancer therapy. 10% DXL loaded into pH/thermal PVA responsive gel. 96 % DXL is selectively released through interaction of green and near-infrared (NIR) light and caused 75% of cell death in *in vitro* studies. 70% growth inhibition regarding tumor was displayed by *in vivo* experiments with biosafety investigations verifying less adverse side effects to other organs [76].

An innovative thermal/pH responsive amphiphilic copolymer comprising magnetite nanoparticles with biodegradable and hydrophobic block of PLA and hydrophilic P(NIPAAm-co-HEMA-co-MAA-co-TMSPMA) section had been developed for combined chemotherapy. Cationic (doxorubicin) and anionic (methotrexate) anti-cancerous drugs were loaded instantaneously to nanoparticles for combined cancer therapy. Efficiency of encapsulation regarding DOX was 95.04% and for MTX was 97.29%. Double profile related to release of drugs exposed tumor aided release behavior. They are non-toxic to MCF-7 cell lines shown by cytotoxicity studies. Antitumor characteristics concerning DOX/MTX-loaded nanoparticles were considerably greater than free drugs verified via MTT analysis and immediate analysis by PCR consuming cell MCF7 lines. Consequences showed that such engineered particles possibly are efficiently consumed in directed DOX as well as MTX delivery to cancerous sites besides for more usages in *in vivo* applications [77].

### 3.2. Immunotherapy

Cancer immunotherapy is leading-edge approach eliminating cancerous cells via increasing immunity of host. Conversely, low rate of response along with risks of persuading toxicity elevated improbability in therapy. MNPs are multipurpose theranostic device used for targeted delivery concerning numerous immunotherapeutics in addition to observe cell/tissue reactions. Immunotherapy inhibits tumor resistant elusion demonstrates noteworthy clinical realization. Though, therapeutic reaction is inadequate to definite number of patients, and immunotoxicity in addition to autoimmunity are bargained therapeutic advantages [78].

Immunotherapy for cancer has appeared as extremely hopeful therapeutic technique for a number of cancers. Fucoidan and dextran based MNPs (IO@FuDex<sub>3</sub>) were linked with anti-PD-L1 (checkpoint inhibitor) and anti-CD3 also anti-CD28 (T-cell activators). They possess ability to repair immunosuppressive cancer microenvironment via reviving tumor sensitive lymphocytes. Off targets impacts can be minimalized via magnetic navigation regarding tumor. Therapy that integrates IO@FuDex<sub>3</sub> with magnetic navigation decreases adverse happenings as well as prolongs average survival from 32 days to 63 days with less than 1% dosage in comparison to soluble anti-PD-L1. Therefore, incorporating T-cell activators and anti-PD-L1 with MNPs in

nanomedicine form enhance therapy index of immunotherapy [79]. A MNP delivery system was developed loaded with ICG (indocyanine green) and R837 (immunostimulator hydrochloride) aimed at spatial and temporal immunotherapy/PTT combination in cancer (Figure 2). It comprises core of magnetite nanoparticles to load ICG coated with layer of DPA-PEG (polyethylene glycol polyphenols) for loading R837, forming MIRDs. The developed MIRDs lead to prolong circulation, guiding agents for MRI, as well as magnetic targeting. MIRDs targeted towards tumors, on irradiation with near-infrared (NIR) triggered ablation of tumor and give rise to release of antigens related to tumor inducing immunological reaction. Here, combined PTT and immunotherapy repressed growth of tumors, metastasis, as well as recurrence that lead to effective anticancerous therapy along fewer adverse effects [80].

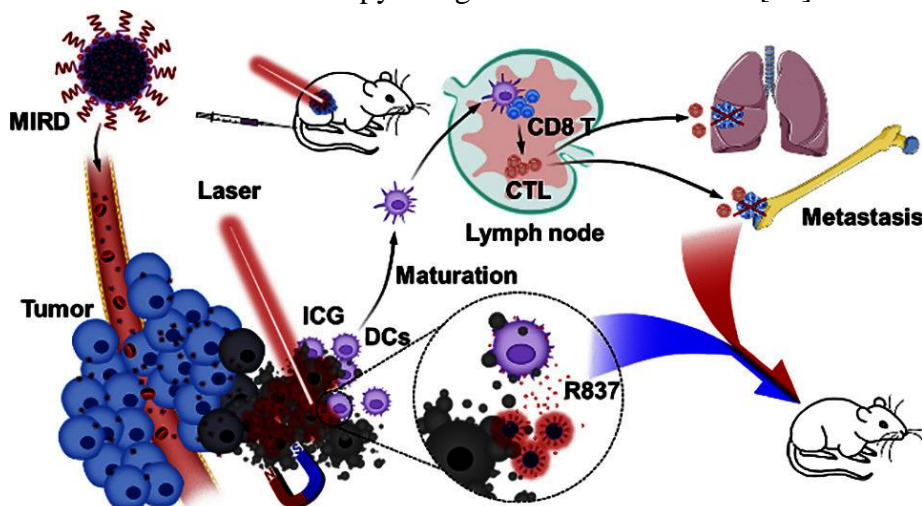


Figure 2. MNPs functionalized by polyphenols aimed at spatial- sequential controllable immunothermal/phototherapy regarding cancer. Reprinted with permission from the reference [80].

A biomimetic  $\text{Fe}_3\text{O}_4$  (magnetite)-SAS (sulfasalazine)@PLT (platelet) are established as different method for sensitizing active ferroptosis and produce slight immunogenicity, improving rate of response regarding non-inflamed cancer aimed at immunotherapy. They activated ferroptotic cell death by preventing glutamate-cystine antiporter method Xc-path. It considerably increases effectiveness of planned cell death 1 immune checkpoint blockade treatment in addition to attaining constant elimination of tumor in model of mouse having metastatic 4T1 tumors. Investigations performed in proteomics also exposed induction of immune reaction specific to tumor and efficient repolarization of macrophages from M2 immuno-suppressive phenotype into M1 antitumor phenotype. Accordingly, ferroptosis facilitated by  $\text{Fe}_3\text{O}_4$ -SAS@PLT related to immunotherapy possess pronounced prospective for medical handling regarding tumor metastasis [81].

A simple system founded on combined stimulation of immunity and killing of cancerous cells directly via integrated TLR (Toll like receptor) ligation consuming R837 (imiquimod) as TLR7 agonist and polyIC as TLR3, with OVA (ovalbumin) and micelles of

phospholipids enclosing MNPs doped with zinc. TLR agonists activated immune reaction in LNs (lymph nodes) with no pro-inflammatory cytokines release. It presented exceptional effectiveness against violent melanoma B16-F10 cells testifying OVA had been enhanced by immunity checkpoint abolition concerning immune-oppressive automated death-ligand 1 (PD-L1) on cancerous cells. This vaccine can be tracked with magnetic field along with nuclear imaging from injection site of injection to tumor and LNs. Generally, collective TLR agonists with MNPs and immune obstruction have substantial probability aimed at preclinical as well as clinical vaccines formulation for cancer treatment by immunotherapy [82]. Hollow magnetite nanoparticles have also been employed for reprogramming M2 TAMs to M1 TAMs, intended for releasing proinflammatory cytokines in addition to employee T cells for killing cancer cells. MNPs were enclosed by poly (acrylic acid) (PAA) after being loaded by l-arginine (l-Arg). Then they were modified as LPMNPs that has ability of releasing l-Arg depending on pH of PAA. *In vivo* as well as *in vitro* investigations validate that the develop MNPs efficiently do the reprogramming of M2 into M1 macrophages, triggering T cells, discharging TNF- $\alpha$ , besides generating extraordinary NO, resulting in immunotherapy [83].

### 3.3. Hyperthermia

Hyperthermia is encouraging method to treat cancer. The usage of MNPs as heating mediators delivers an innovative approach to improve treatment regarding tumor and, subsequently, quality of patient's life [84,85]. In current clinical trials of hyperthermia using MNPs to treat tumors, AC (alternating current) magnetic field of 100 kHz is safe to be applied on patient. Though, systematic magnetic hyperthermia as temperature function on therapeutic efficacy is scarcely examined [86].

MNPs coated by biocompatible poly-L-lysine had been developed aimed at magnetic hyperthermia to determine their therapeutic efficacy. They were verified for hyperthermia appropriateness via calorimetric estimations and SAR (specific absorption rate) was also measured. SAR value at 8 kAm<sup>-1</sup> field and 190 kHz frequency were 14 to 15 Wg<sup>-1</sup>. These particles were also tested in MRI. The heating characteristics along with parameters of MRI possess pronounced ability for advancement of targeted cancer therapy in future [87]. A magnetic guanidinylation chitosan (MGC) nanobiocomposite was designed and evaluated by *in vitro* hyperthermia for the cancer therapy. Size distribution of prepared composite was found to be in between 30-34 nm during synthesis process with a core-shell structure. By using AC magnetic field SAR and saturation magnetization value were 70.59 w/g and 43.66 emu/g respectively [88].

*In vivo* as well as *in vitro* comparative analysis reliant upon temperature regarding effectiveness concerning nanoparticles of cobalt ferrites was done in two models of murine tumors that is 4T1 (breast) and CT26 (colon) cancer. *In vitro* killing capacity by using these nanoparticles gets increased with increase in temperature (Figure 3). CT26 cancer cells have more sensitivity than 4T1 on heating to 43 °C. Similarly *in vivo* data also revealed curing of non-metastatic CT26 cells, whereas only preventing growth of metastatic 4T1 tumor with no improvement of complete

survival. Higher temperature that is greater than 47 °C lead to whole clearance of 4T1 primary tumor, 25 to 40% prolong rates of survival, in addition to active inhibition concerning metastasis compared with surgical abstraction. Therefore, particular temperature should be well-defined for ensuring positive antitumor therapy [89].

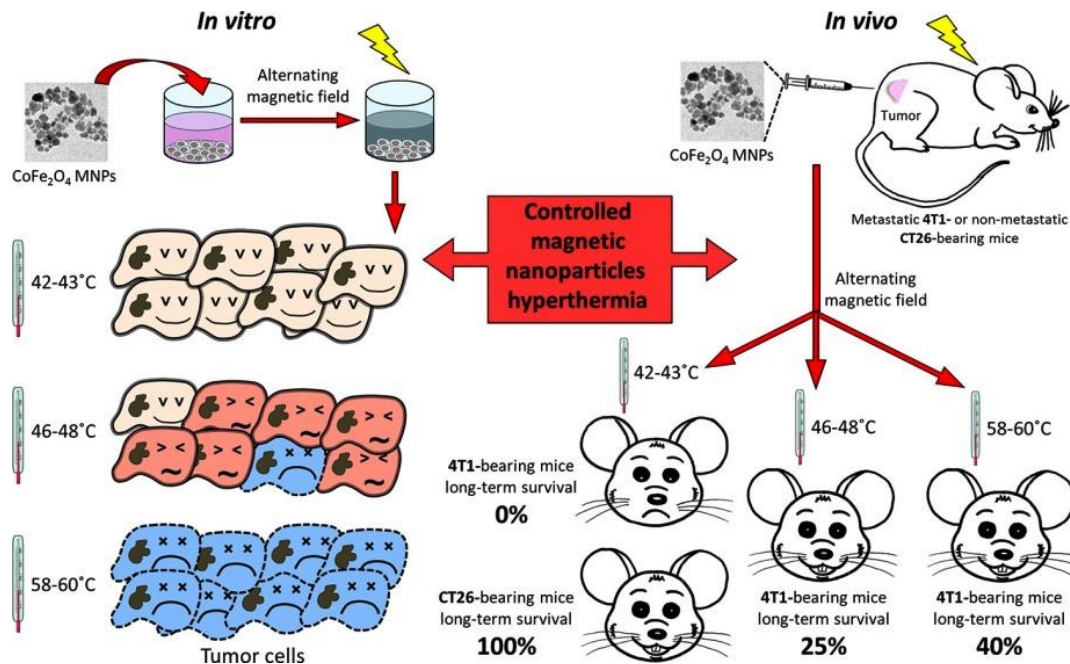


Figure 3. MNPs prevent primary growth of tumor in addition to metastases propagation through temperature-controllable hyperthermia. Reprinted with permission from the reference [89].

Cancer cells possess distinctive metabolic feature that had been explored for biosynthesizing MNPs for possible hyperthermia uses. Cancerous cells were mixed mixture of zinc gluconate and FeCl<sub>2</sub> that significantly increase intracellular iron and zinc measure inside cells. There is rise in temperature after thirty minutes exposure to alternating magnetic field. Nanoparticles of iron and zinc oxide were formed. MNPs are SPIONs with magnetite and maghemite mixture. Optimizing conditions for treatment lead to a rise in temperature of about 5 to 6 °C on applying magnetic field to treated cells. The simple treatment procedure, cell specificity able to synthesize SPIONs, and hyperthermia perceived in cancerous cells specified a hopeful approach towards achieving operative hyperthermia aimed at cancer therapy [90]. Ultrasmall SPIONs (USPIONs) are prepared via single-step method. Discrete nanoparticles were separated from unstable agglomerated nanoparticles by post-synthetic purification, resulting in USPIONs preserving colloidal and chemical stability for long time. The improved nanoparticles displayed higher saturation magnetization along with better heating efficacy for hyperthermia measurements. Unusually, these nanoparticles showed notable double T1/T2 signal improvement, therefore could be employed as MRI contrast agents. Such encouraging results established that these nanoparticles are outstanding candidates to develop theranostic nanosystems having potential in hyperthermia and imaging applications [91]. A three dimensional cross-linked chitosan hydrogel

was fabricated consuming chitosan polymeric chains and synthetic terephthaloyl diisothiocyanate. It had high stability and uniformity in aqueous solution and high porosity was applied as new substrate to generate novel nanocomposite comprising magnetic terephthaloyl thiourea cross-linked chitosan and evaluated for hyperthermia process. The size distribution of nanocomposites was estimated in between 30 to 40 nm. Under AC magnetic field, the SAR was found to be 66.92 w/g with saturation magnetization of 78.43 emu/g [92]. A novel magnetic nanocomposite made of aromatic polyamide was investigated in hyperthermia aimed at cancer therapy. The magnetite nanoparticles were modified by phenylenediamine derivatives and terephthaloyl chloride via polymerization reaction. Exceptional morphologies of rose flower and spheres were observed of the developed nanocomposites. On exposure to external AC magnetic field, SAR was measured was 191.97 w/g for 0.5 mg/mL of a sample, with saturation magnetization of 4.3 emu/g [93].

Hydrophilic surface modified SPIONs were prepared to treat liver cancer by hyperthermia. Short-chain molecules, for instance 4-aminobenzoic acid (4ABA), 1,4-diaminobenzene (14DAB), plus 3,4-diaminobenzoic acid (34DABA) along molecules of terephthalic acid (TA)/2-aminoterephthalic acid (ATA)/trimesic acid (TMA)/pyromellitic acid (PMA) were used to functionalize SPIONs. Heating abilities of SPIONs were evaluated by calorimeter regarding their surface coatings, concentrations, medium for dispersion, besides applied alternating magnetic fields. All SPIONs were superparamagnetic in behavior, but SPIONs coated with 14DAB- 4ABA-, 4ABA-TA-, and 34DABA- displayed greater magnetization ( $M_s = 55$  to  $71$  emu/g) with good dispersibility in water. 34DABA-coated SPIONs exposed rapid thermal reaction on applying magnetic field and extended therapy temperature to low concentration equals to  $0.5 \text{ mg (mL)}^{-1}$  in comparison to 4ABA-, 14DAB-, and 4ABA-TA-coated SPIONs. Furthermore, 34DABA-coated SPIONs showed great heating efficiencies with SAR of  $432.1 \text{ W/g}$  and killing efficacy of about 61 to 88% in liver HepG2 cancer cells in comparison to water/magnetic field based thermotherapy. Thus, 34DABA-coated SPIONs are favorable heating mediators for hyperthermia and could be utilized as operative nanomedicines aimed at treatments of cancer [94]. The thermal reaction of tumor tissue to hyperthermia depends on the MNPs configuration setup along with its different parameters. Injection approach effects mass transfer during treatment, which is related to the success of hyperthermia cancer treatment. In one of the study mechanical response of tumor tissue to single and three site injections was compared. The results indicated that increasing injection sites enhances heat and mass transfer fluxes slightly; but more expressively influenced by rate of injection. The three-point injection improved distribution of nanoparticles and heat uniformly, which increased tissue damage and reduced the risk of tissue necrosis [95].

### 3.4. Radiotherapy

Tumor radio-sensitization could possibly get improved by integrating classical radiotherapy with various drugs or MNPs. Currently, MNPs are being investigated to be applied in radionuclides delivery,  $\alpha$ - or  $\beta$ - emitters, as well as radiosensitizers for inducing damage to DNA of cancerous

cells by generating ionic radiation or free radicals [96]. They propose distinctive benefits over existing radiotherapy practices via decreasing damage to off-target tissues because of non-particular treatment nature via active and passive targeting [97]. Additionally, MNPs holds high atomic number (Z) as well as display significant absorption of X-ray photons, resulting in increase in production of secondary electrons for DNA destruction on increasing dose of radiations. SPIONs enhance radiotherapy effectiveness and specificity regarding DNA destruction via catalyzing production of ROS through ionizing rays causing considerably strong oxidative pressure, particularly hydroxyl radicals which destroy DNA of cells [98,99].

Currently, MNPs coated with gold (Au@IONPs) gained significant consideration towards cancer therapeutics. *In vitro* studies were carried out to find out anti-cancerous impact regarding Au@IONPs nanoparticles with core-shell morphology in thermo-radiotherapy. Furthermore, apoptosis level stimulated in glioma U87-MG human cells was examined after getting combined therapy (hyperthermia + Au@IONPs + radiotherapy). After incubating nanoparticles with cells, hyperthermia was done for one hour (43 °C) and after that they were instantaneously exposed to 6 megavolts of X-ray. The MTT results showed no substantial cytotoxicity regarding nanoparticles at below concentration of 10 µg/mL and also enhanced cytotoxic effect concerning radiation and hyperthermia was observed. Reason of cell death had been apoptosis due to combined effect of nanoparticles, radiation, and hyperthermia on cancerous cells. Thus, prepared nanoparticles are good radio-thermo-sensitizer that activates noteworthy apoptosis levels for cancer treatment [100]. A novel platform based on MNPs modified with cationic polymer for promoting radiotherapy to treat glioma. Modified MNPs induced cytotoxicity to in glioma cells on radiations besides encouraging substantial survival advantages in athymic and immunocompetent mice having glioma. Taking advantage of magnetic features of MNPs, it was discovered that nanoparticles were taken up by MDSC (myeloid derived suppressor cells) inside tumor of brain. Efficiency of nanoparticles was estimated by glioma cells destructions in addition to repolarization of MDSCs from immuno-suppressive to pro-inflammatory phenotype that helped antitumor impact as well as radio-therapeutic impacts synergistically (Figure 4). These nanoparticles offers fast targeting dual platform aimed at radiotherapy of glioma through immediate tumor abolition and management of myeloid phenotypes in central nervous system [101].



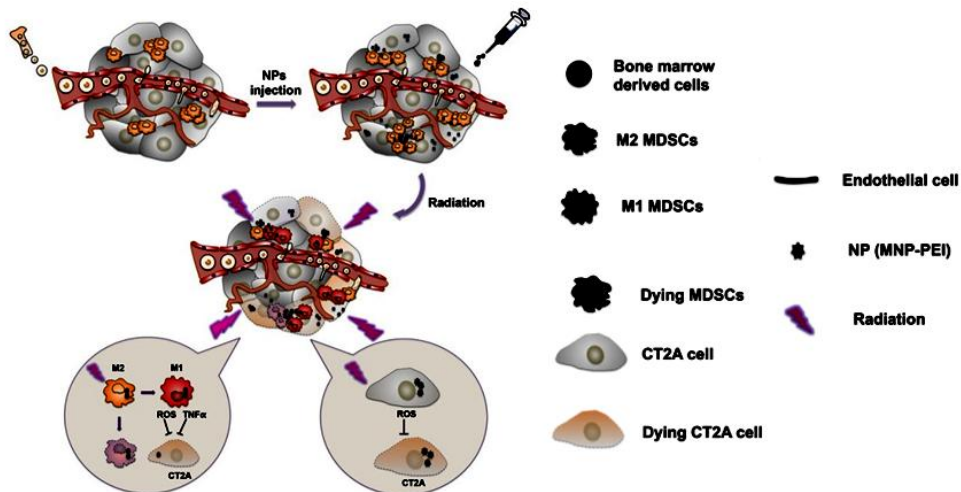


Figure 4. MNPs resulting in extreme cytotoxicity specific to cancer. MDSCs, incompletely exposed in addition to repolarized in M1-like phenotype producing anti-cancerous impact after radiation therapy along with MNPs. The combined influence showed positive efficacy. Reprinted with permission from the reference [101].

Magnetite nanoparticles coated with PEG are favorable candidate as radiation sensitizer for radiotherapy. They improved cancer therapy and decreases adverse impacts regarding radiations. On exposition to radiations surface coating of PEG possibly be fully or partially destroyed. This makes iron ions more accessible and perform as a catalyst to produce ROS species that improves the cancer radiation therapy. Cytotoxicity studies revealed percentage killing of cells employing  $\text{Fe}_3\text{O}_4$  coated with PEG is greater for MCF-7 in comparison with L929. However, percentage with bare MNPs is greater for both when compared with PEG coated MNPs. Thus, PEG coating enhanced biocompatibility of MNPs that makes them appropriate for radiotherapy and also upholds innovative opportunities in field of cancer radiotherapy for improving clinical effectiveness in dissimilar cancer types [102]. MNPs conjugated with quercetin (QMNP) were prepared to investigate their sensitivity towards breast cancer in radiotherapy treatment. *In vitro* results presented that HePG-2, MCF-7, and A459 cancerous cells incubation along these nanoparticles effectively for twenty-four hours prevented cancerous cell growth depending on concentration with values of  $\text{IC}_{50}$  equal to 77.5, 11, and 104  $\text{nmol}(\text{mL})^{-1}$ , correspondingly. Irradiation (IR) coupling with QMNPs powerfully blocked proliferation of MCF-7 cancerous cells. QMNPs had no toxicity assessed by renal, hepatic, and hematological markers. In addition, in white albino female rats, they prevented cancer growth and persuasively improved adjacent radiotherapy inside MNU (N-methyl-N-nitrosourea) prompted breast cancer. Such radio-sensitizing along anti-cancerous happenings had been because of immunomodulation, cell cycle detention, cytotoxicity, in addition to effectiveness by apoptosis generation. Conclusively, MNPs with radiotherapy possess prospective targeted therapy for treating breast cancer [103]. SPIONs have demonstrated fascinating characteristics beneficial for diagnostic and therapeutic application. Radio-sensitizing properties regarding SPIONs in brachytherapy and electron beam



radiotherapy had been investigated. *In vitro* investigations were performed consuming HeLa cells with SPIONs. Irradiations doses ranged from 0 to 10 Gy were done by 0.38 MeV  $^{192}\text{Ir}$  brachytherapy as well as electron beams of 6 and 12 MeV energy. Radio-sensitization classification was done through evaluating improvement in ratio of sensitization (SER), gained from survival loops. Results showed SPIONs encourage radio-sensitization in electron beams particularly at low energy having value of SER of 1.5. It is further noticeable in brachytherapy having SER of 2. High concentration of SPIONs increases radio-sensitization impacts more. In summary, radio-sensitization is influenced by energy of radiation as well as SPIONs concentration. Additional categorization concerning radio-sensitization persuaded by SPIONs might permit medical translation regarding SPIONs as per radio-sensitizer for radiotherapy [104].

### 3.5. Gene therapy

Gene therapy signifies a different substitute to manage diseases with no adequate cure. Gene therapy to treat cancer made good progress in the last three decades. Comparatively gene therapy has better safety with tolerable adverse effects than chemotherapy for the treatment of cancer [105]. The major dissimilarity between gene therapy and chemotherapy is that in chemotherapy drugs are being delivered, whereas in gene therapy targeted biological moieties for instance RNA, DNA, or else siRNA, peptides, and proteins are been delivered to cancer site, and by this manner death of the cells possibly is induced. When one part of the body has cancer, human damaged DNA is categorized by presence of atypical proteins. This could be treated by replacing defected gene in cancer cells [106]. On the other hand, siRNA suppressed protein activities, occurring because of cancer cells. siRNA integrated with nanoparticles could be carried and delivered to cells, since medicinal RNA are very degradable when injected directly in bloodstream. siRNA-MNP complex becomes practically unidentifiable for human body. Their cellular uptake gets improved with longer circulation time. Because of vascular nature of tumor, MNPs enter and accumulates in tumor [107].

Magnetite nanoparticles coated with polydiacetylenes ( $\text{Fe}_3\text{O}_4@\text{PDA}$ ) possess better photothermal ability and could be applied for efficient loading and delivery of siRNA. They are further coated with mesenchymal stem cells (MSCs), forming membrane.  $\text{Fe}_3\text{O}_4@\text{PDA}$ -siRNA@MSCs (MSCs membrane with nanoparticles of  $\text{Fe}_3\text{O}_4@\text{PDA}$ -siRNA) conserved photothermal effectiveness besides MRI ability received from nanoparticles of  $\text{Fe}_3\text{O}_4@\text{PDA}$ . Prepared nanocomposites displayed unique capabilities to deliver siRNA to cells (DU145). Additionally, they deliver siRNA opposing gene Plk1 restricts endogenous gene Plk1 expression in addition apoptosis in cells DU145. Combined photothermal therapy with gene silencing presented clear antitumor efficiency in xenograft DU145 mice model. Primary *in vivo* and *in vitro* examinations revealed that the developed nanocomposites have substantial potential as carrier aimed at photothermal and gene therapy [108]. Suicide-gene therapy is hopeful method to treat uterine leiomyoma (UL), tumor occurring in women categorized via specific localization. The competence regarding  $\alpha\text{v}\beta 3$  integrin-targeted arginine-rich peptide carrier R6p-cRGD

attached electrostatically to MNPs aimed at targeted delivery of DNA to UL cells. MNPs addition caused decrease in required time for fruitful transfection by immediate escalation in efficacy. After plasmid delivery, therapeutic impact onto prime UL cells was evaluated. It encodes simple herpes virus 1 (HSV-1) thymidine kinase gene. Treating by ganciclovir, increases efficiency to twenty percent in suicide-gene treatment inside UL cells introduced by pPTK-1 plasmid. Finally, consumption of MNPs with cationic peptides are promising carriers to develop non-viral modular carriers aimed at suicide-gene delivery in UL cells [109].

Magnetically mediated suicide-gene therapy is favorable for suicide gene therapy. M-MSNs comprising MNPs with nanoparticles of mesoporous silica were synthesized. Then carboxyl-modified M-MSNs had been loaded with PEG-g-PLL and GCV. After that they were attached to M-MSNs surface that offered positively charged surface for absorption of TK plasmid (Figure 5). They were evaluated for their role in MRI, magnetically targeted as well as hyperthermia-assisted suicide gene therapy of hepatocellular carcinoma (HCC). Rod-shaped MSNs showed greater capacity for loading, rapid release of pro-drug, improved magnetic gene delivery, in addition to enhanced hyperthermia in comparison with spherical MSNs. M-MSNs showed extremely active double magnetic improved *in vivo* suicide-gene therapy along reduced methodical toxicity. It also has capability for monitoring therapy outcome via MRI. Attributed to magnetic targeting and hyperthermia, developed M-MSNs are possibly better candidate aimed at HCC suicide gene therapy [110].

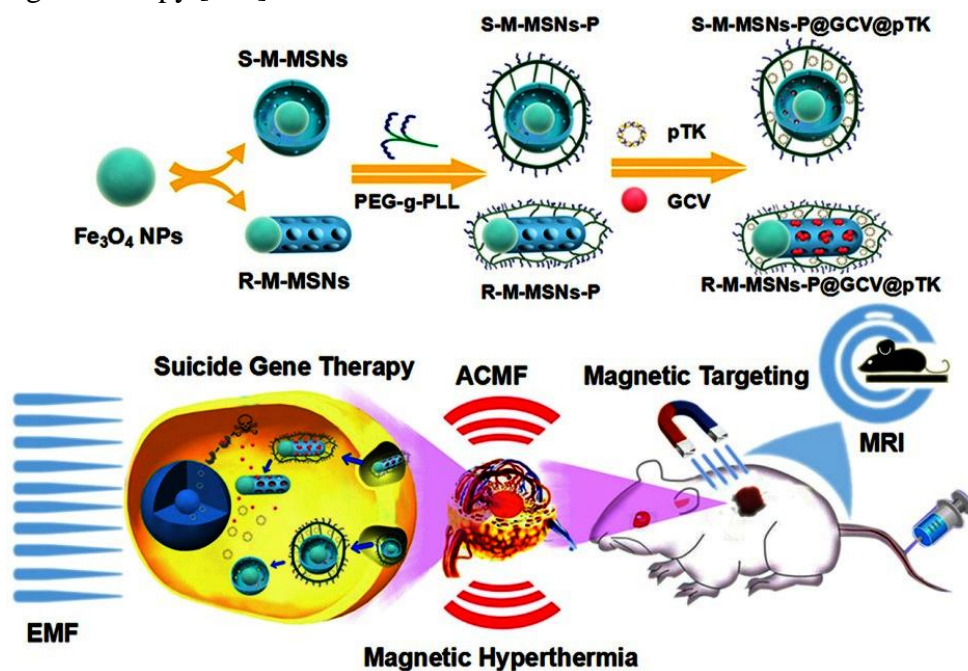


Figure 5. M-MSNs aimed at suicide-gene therapy regarding hepatocellular carcinoma cells mediated magnetically. Reprinted with permission from the reference [110].

SPIONs functionalized with galactose (Gal) and polyethylenimine (PEI) bonded siRNA tightly, defend siRNA from nuclease decomposition in system. Encapsulation of siRNA with SPIONs prolongs its half-life and its transfection in cancerous cells with no *in vitro* cytotoxicity. Also,

encapsulated siRNA can be accumulated instantaneously, precisely target siRNA to targeted cells, prolonging time of siRNA in tumor in addition to inhibition of growth of tumor. Consequently, it provides a newfangled targeting approach to liver cancer therapy. The developed nanoparticles hold pronounced potential for gene therapy of tumor [111]. In another work, MNPs (magnetite) functionalized with polyethyleneimine (PEI) were synthesized for delivering siRNAs targeting BCL2 (B-cell lymphoma-2) and BIRC5 (Baculoviral IAP repeat-containing 5) to oral Ca9-22 cancerous cells aimed at therapeutics. Nanoparticles blocked siRNA depending on concentration analyzed via gel retardation. Higher gene silencing efficacies were observed through measurable immediate western blotting and PCR. Additionally, the developed nanocomplex delivering siRNAs to target BIRC5 and BCL2 inhibit considerably Ca9-22 cells migration and viability. Thus developed siRNA-based approach was novel and promising therapy to target BIRC5 and BCL2 regarding oral cancer [112]. A new approach was developed towards RNA interference therapy of glioblastoma multiforme based on MNPs delivery of double-stranded RNA (dsRNA) with homological sequences to mRNA of tenascin-C (TN-C), named ATN-RNA. Polyethyleneimine (PEI) coated MNPs conjugated to dsRNA were synthesized that showed high efficiency in ATN-RNA delivery. These nanocomposites results in significant suppression of TN-C expression level and weakened migration of the tumor cells. Furthermore, developed nanocomposites possess high contrast characteristics in magnetic resonance imaging (MRI) and less cytotoxicity combining with lack of induction of interferon response. This work is an effective combination of functional and non-immunostimulatory dsRNA delivery system based on MNPs with high prospective for further application in Glioblastoma multiforme (GBM) therapy [113].

#### **4. Advantages and limitations of magnetic nanoparticles for cancer therapy**

MNPs are amongst widely investigated nanostructured material, by reason of their possible usages in different research fields wavering from data storing to catalyzing applications, including cancer detection and therapy [114,115]. MNPs have many benefits, particularly high ratio to surface area to volume, size of pores, modified surfaces, more than one interaction or binding sites, making them greatly appropriate to be utilized for treatments of diverse diseases [116].

Moreover, MNPs holds benefit over substitute metallic nanoparticles due to their control in size, definite interaction as well as dispersion, prevention of accumulation via coating, in addition to permeation of tissue and cell barriers [66]. Generally, MNPs attained substantial consideration attributed to their exclusive behavior, configuration, and differentiated applications. In particular, their separate magnetic characteristics and variable size, ease of functionalizing surface by different molecules, compatibility with various cell and biomolecules, inductive magnetic moment, chemical constancy holding enlarged surface area, large magnetic susceptibility, besides superparamagnetism [117].

One of the major limitations in employing MNPs in therapeutic applications is impossibility to concentrate them in 3-D (three-dimensional) area. Since by applying magnetic field externally,

MNPs organizes in 2-D (two-dimensional) space [118]. Furthermore, to retain MNPs in the targeted region is difficult after the removal of magnetic field. Another problem is related is time of exposure to applied magnetic field, it is not possible to expose patients for unlimitedly external magnetic field. This all reduced therapeutic effectiveness and limits it to intensity, frequency, as well as exposure time of applied field [24]. Toxicity of MNPs depends mainly on administration method, surface chemistry, biodegradability, etc. Normally shape, composition, surface area, coating, and dimensions MNPs are considered to determine cytotoxicity. MNPs functionalization is vital for confirming minimum toxic impacts [119]. In some cases, controlled release of ions for instance, cobalt ions from MNPs surface is helpful and can be consumed as toxic agents for cells, like chemotherapeutic drugs [120]. Therefore a comprehensive valuation regarding therapeutic and safety efficiency concerning MNPs must be executed before any treatment for clinical usage [121]. Another issue is lasting effects of MNPs inside the body. Commercially available MNPs are not biodegradable and their prolonged accumulation in tissues can be dangerous for healthy cells. It is important to know how MNPs interacts with cancerous and healthy cells in human body as well as their excretion [115,122].

SPIONs (superparamagnetic iron oxide nanoparticles) accumulation becomes unstable inside biological medium or solutions that are same as body fluids [123]. They possess diverse adverse effects, for instance deterioration in functioning of brain, liver, skin, stomach that might persist for ten years [124]. MNPs faced different physiological barriers lessening therapeutics localization at targeted site, which limit their use in cancer theranostics. Another limitation is particular targeting to cancer bearing site that reduces dosage and effectiveness regarding MNPs [125]. Few of the advantages along with disadvantages are illustrated in Figure 6.

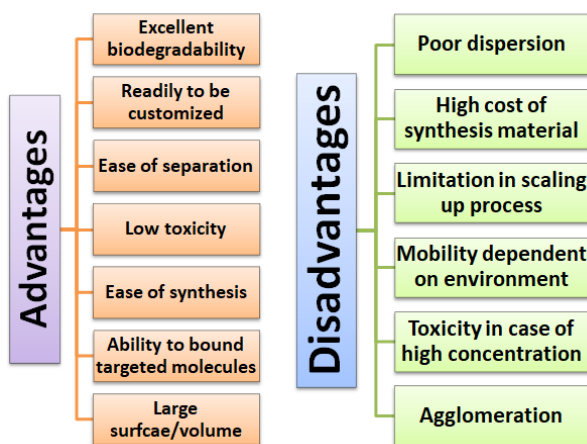


Figure 6. Some of the advantages and disadvantages regarding MNPs.

## 5. Conclusions

Magnetic nanoparticles are being extensively explored for cancer therapeutics in combination with various therapies. Different MNPs are synthesized and functionalized with various coatings to enhance non-toxicity, biocompatibility, safety, bio-distribution, stability, etc. Massive consideration to MNPs was had been given because of their utilization in primary cancer

recognition and, hence, offer novel prospects for medicating cancer along with other diseases. MNPs bonding to drugs, genes, antibodies, enzymes, and proteins assist in direct targeting of definite cancerous site employing magnetic field that is externally applied. Current advancement has focused to increase three-dimensional accuracy in activated release of drug, in addition to improvement in magnetic targeting regarding drug to deeper tissues. In this review, we highlight recent development in cancer therapy by integrating MNPs with chemo-, immune-, gene-, radio-therapy in addition to hyperthermia. Since together they lead forward in a better way to amend or treat cancer. Noteworthy progress was made utilizing with MNP platforms for pre-clinical cancer therapy. Additionally, MNPs display pronounced potential to be used for monitoring cancer treatment and providing critical evidence to doctors permitting them for adapting treatment approaches to deliver optimum care.

In future work critical information is still needed to develop better MNPs properties in addition to technologies aimed at economical magnetic systems. Moreover, researchers tried to overcome difficulties particularly knowing bio-nano interactions inside humans, crossing biological as well as methodological barriers particular to cancer kind, evading late lysosome/endosome system in cytosol inside cells, besides prolong toxicity. MNPs synthesis along their functionalization with biotherapeutic as well as chemotherapeutic agents are being under progress to develop multi-module therapeutic tactics by unifying MNPs with different therapies in addition to consuming numerous drugs in different formulation aimed at cancer therapy. Fusion of immunomodulatory and other targeting ligands assisted in cancer targeting and ultimately its therapy. Better laboratory practices need to be industrialized to overcome industrial barriers. For scaling up magnetic systems for cancer therapy, advancement in coil technology is mandatory for making resource-effectual system.

In spite of many positive results gained from consuming MNPs as theranostic agent, there are still some features to be improved for instance capacity to load drug and enhancing affinity for targeting tumor cells. MNPs might be suitable for medical usage through integrated multimodal treatment in future and vividly influence treatment regarding cancer. Numbers of pre-clinical tests with MNPs have been perceived, though, no single formulation comprising MNPs being accepted aimed at cancer therapeutic till date. However, it's been anticipated that it would evolve into medical investigations, on account of their pronounced potential to treat cancer. We have confidence that delay in fruitful consumption of MNPs for clinics are motivated by making new formulations for cancer therapy.

## **6. Experts opinion**

MNPs are explored broadly during last few years but still it is a great challenge to engineer them to improve diagnosis and treatment of diseases. With respect to MNPs, central idea has been to attach conventional anti-cancerous drugs to magnetic small spheres superficially, before directing them inside human body. After getting inside to the body, drug loaded MNPs accumulated in tumor by means of externally applied strong magnetic fields. By employing MNPs, drug payload would be significantly reduced. Hence, unwanted and adverse effects

related to systematic chemotherapeutics delivery, particularly nausea, loss of hair, in addition to destabilized immunity, was prohibited. In spite of these facts, drug loaded MNPs are not in medical use, and is in developing stage at extraordinary speed.

Cancer therapeutic approaches consuming MNPs depends upon transmitting energy to MNPs, being introduced to body, from magnetic field. MNPs are favorable in medical sciences due to their stability in aqueous solutions, biocompatibility, low toxicity, over and above exceptional chemical as well as physical features particularly superparamagnetism. Among MNPs, SPIONs are commonly employed in tailored medicine aimed at cancer diagnosis and therapy. A list of SPIONs in clinical trials and already in the market is presented in Table 2. Moreover, predicting the best formulation of MNPs for humans is achieved with the help of better theoretical animal models. For “*in vivo*” application, hydrodynamic size of MNPs is important factor, being constrained by anatomical feature of human body. Due to this fact, they are mostly carried in solutions of water. Nanoparticles having size lesser than one-fifty nanometers are able to cross endothelial barrier, however MNPs with reduced size can penetrate blood–brain barrier [126]. Additionally, MNPs except with size smaller than 10 nm, don’t have fast renal clearance and would not be internalized by the reticuloendothelial system (RES) [127]. MNPs have tendency of forming aggregates that is significant in magnetic resonance examinations.

**Table 2.** A list of SPIONs in clinical trials regarding cancer therapy.

Product	Size (nm)	Morphology	Coating agent	Application	Targeting moiety	Ref
SPIONs	40-50	Roughly spherical	Poly(ethylene glycol)/Dextran	Breast/Brain cancer	Folic acid	[128]
SPIONs	9-20	Polygonal and roughly spherical	Poly(ethylene glycol)	Prostate cancer	A10 RNA aptamer	[129]
SPIONs	8-13	Spherical	3-(aminopropyl) trimethoxysilane	Brain tumors	Methotrexate	[50,130]
SPIONs	10-30	Spherical	Dextran	Liver tumors	-	[131]
Ultrasmall SPIONs	5-15	Spherical	3-(aminopropyl) trimethoxysilane	Lung cancer	Arginine-glycine-aspartic acid	[132]

MNPs toxicity is one of the serious causes regarding their biomedical applications. It reduces therapeutic efficiency along with immunity or inflammatory activation because of their agglomeration in organs. On entrance in cells, the toxicity can upset nuclear activities, leakage of cell membranes that results in adversative metabolic action, proliferation of cells, and viability consequences. Even though MNPs and SPIONs are FDA approved, but their usage in treating cancer should be wisely directed and organized, since their large amount might be unsafe. Excessive use of MNPs can cause changes in living cells because of ROS production cytoskeletal destruction, mitochondrial impairment, as well as DNA configuration alteration. One challenge is scaling up of the magnetic system. Prototypes devices for small-sized animals could be built exploiting stable magnets with benchtop amplifiers, whereas establishing large

systems need high-powered electromagnets.

MNPs display substantial promise for theranostic applications as contrast enhancers and therapeutic agents for cancers. MNPs indicate the potential to be engaged in treating cancer treatments because of their specific characteristics that deliver acute data to physicians offering ultimate care. MNPs have been investigated extensively attributed to their ease of synthesis and functionalization; still, inadequate formulations get permitted for clinical uses. However, there is room to translate MNPs from lab to clinic that requires complete understanding concerning MNPs effects on human physiological reactions. Research showed numerous formulations consisting MNPs have unsuccessful results to produce satisfactory treatment levels in large animals and humans; similar to results that were perceived in small animals. For MNPs translation to clinics, ability to load drug, improving their specificity and affinity to target cells, in addition to obtain required release of drug depending on tumor microenvironment must be considered with the help of superior animal theoretical models. Table 3 summarizes some features of the reported magnetic nanoparticles intended for cancer therapy. Taking account of countless advantages, we are confident that combine diagnostic and multimodal therapy consuming MNPs would propel forward their clinical employment and considerably influence cancer therapy in near future.

**Table 3.** Some features regarding the reported magnetic nanoparticles intended for cancer therapy.

Material	Target	Specific feature	Type of treatment	Advantages	Ref
Polycaprolactone-SPIONs	Liver cancer	Polymer (PCL)	Hyperthermia	Better dispersibility, structural stability, and cytocompatibility	[133]
Polyaspartamide-SPIONs	Cancer cells	Biotin	Hyperthermia	Better heating capability and enhanced cellular uptake	[134]
Polyacrylic acid-SPIONs	Breast cancer	Anti-HER2 antibody	Hyperthermia	Ultra-small size, High stability, and resistance to accumulation	[135]
GdPO <sub>4</sub> -CS-Fe <sub>3</sub> O <sub>4</sub>	Breast cancer	-	Photothermal therapy	Increased apoptosis and prevent cancer recurrence	[136]
SPIONs/Cur/Ver loaded PLGA nanoparticle	HepG2Liver cancer	Poly lactic co glycolic acid (PLGA)	Chemotherapy/thermotherapy	Minimum toxicity, enhanced stability and maximum treatment efficacy	[137]
Cetyltrimethyl ammonium bromide encapsulated IONPs	HeLa cells	-	Chemotherapy	Large-scale simple production, modifiable uniform size of pore size, high surface area, and pore volumes	[138]
Trastuzumab	MCF-7	Conjugated	Photothermal	Minimum cytotoxicity	[139]

conjugated porphyrin-SPIONs		antibodies	therapy	and water-solubility	
Poly-L-lysine-coated MNPs	Colorectal cancer cells	Conjugate specific antibodies	Immunotherapy	Selective targeting	[140]
Iron oxide nanoparticles FeONPs SPIONs	MCF-7	-	Radiotherapy (X- ray irradiation)	Additional oxidative stress	[141]
	Colon cancer	-	Radiotherapy (150 MeV proton beams)	Enhanced oxidative stress to damage DNA of cells	[142,143]
Cationic coated MNPs	Brain cancer	-		High efficiency, non- viral vehicles, and survival rate	[106]

Among all these therapeutic methods, chemotherapeutic and hyperthermia are most promising strategies and holds a pronounced potential to become a first line treatment for cancers. Other approaches are still in progress and could become a safe option to treat various cancers. *In vivo* or *in vitro* analysis verifies that SPIONs could modify living cells due to deterioration of cytoskeleton, generation of ROS, mitochondrial damage, and structural changes in DNA [144]. MNPs toxicity is also due to their agglomerations that become unstable in physiological media. For effective use of SPIONs, their shape, the dimensions, coating shell are vital parameters that must be considered. Some research work claims that adverse effects regarding MNPs used in chemotherapy, radiotherapy, gene therapy, immunotherapy, and hyperthermia might be effectively addressed by the body's self-defense system [145]. MNPs as a therapeutic tool is a new and important research domain, which is still in the phase of continuous development and should be, investigated more.

## Disclosure statement

Authors have no competing interest to disclose.

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