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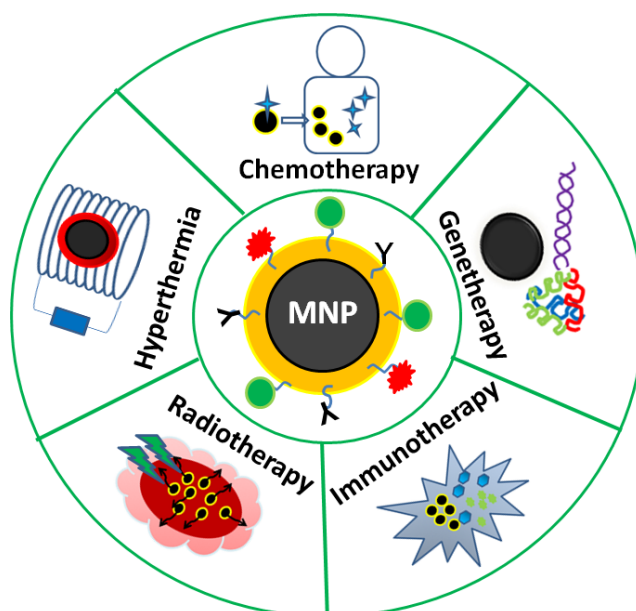
## Magnetic nanoparticles: Multifunctional tool for cancer therapy

Sumera Khizar, Eslam Elkalla, Nadia Zine, Nicole Jaffrezic-Renault, Abdelhamid Errachid, Abdelhamid Elaissari\*

Univ Lyon, University Claude Bernard Lyon-1, CNRS, ISA-UMR 5280, F-69100 Lyon, France

\*Corresponding author. ISA, University Claude Bernard Lyon-1, 5 rue de La Doua, Villeurbanne 69100, France. Email address: [abdelhamid.elaissari@univ-lyon1.fr](mailto:abdelhamid.elaissari@univ-lyon1.fr)

### 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

26 biodegradable properties.

27

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

30

### 31 **Article highlights**

32

33 • Among various nanoparticles, magnetic nanoparticles (MNPs) emerged as innovative  
34 treatment agents modernizing therapeutic usages in cancer therapy.

35

36 • MNPs modified with various coatings are developed to improve physico-chemical  
37 features.

38

39 • Commonly, SPIONs (superparamagnetic iron oxide nanoparticles) are engaged in  
40 tailored medicine intended for cancer theranostics.

41

42 • MNPs are being incorporated with immunotherapy, radiotherapy, chemotherapy,  
43 hyperthermia, and gene therapy to treat cancer effectively.

44

45 • Despite the benefits of consuming MNPs in cancer therapy, there is still space for  
46 improvement in engineering MNPs for targeting tumor cells more effectively.

47

### 48 **1. Introduction**

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

59 Magnetic nanoparticles (MNPs) possess exceptional characteristics, for instance, small  
60 dimensions, high surface area, and superparamagnetic nature, and are therefore useful for a  
61 variety of applications [5]. Nanoparticles of iron oxide are the most commonly consumed  
62 nanostructured materials used for targeted therapeutic applications. They comprise nanoparticles  
63 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,  
64 delivery of a drug, plus hyperthermia [6]. Furthermore, the superparamagnetic behavior of MNPs  
65 can efficiently extravasate and target diseased and infected tissue (lesions) or cancerous sites [7].

66 All these MNPs properties are entirely employed in cancer therapy, where drugs encapsulated  
67 with them or attached to their surface possibly are directed to preferred particular *in vivo* locate  
68 by applying a magnetic field externally [8].  
69 Various shapes have been synthesized for improving magnetization by reducing surface  
70 anisotropy and increasing exchange anisotropy [9]. Different methodologies are accessible for  
71 fabricating MNPs in various forms like nanowires, nanorods, and nanocubes. These techniques  
72 include wet chemistry or “bottom-up” methods namely solvothermal, hydrothermal, co-  
73 precipitation, sol-gel, electrochemical, flow injection synthesis, and laser pyrolysis procedures  
74 [10]. In the last era, the core/shell morphology of MNPs containing a core of iron has been  
75 extensively used from the perspective of magnetic influence and loading/release of particular  
76 drugs [11]. MNPs attain controllable as well as precise release of the drugs by bonding drug  
77 moieties through linkers having the ability to be cleaved or to shell of polymer enclosing them  
78 having capability regarding releasing of drugs [12].  
79 There are different approaches for improving some features for instance bad biodegradability,  
80 biocompatibility as well as chemical inconstancy in biological environments. All this depends on  
81 the functionalization of the MNPs surface. MNPs can be modified covalently by biocompatible  
82 and biodegradable polymers [13]. MNPs can be combined with additional functional  
83 nanomaterials by coating or successive growth particularly antibodies, ligands, or receptors to  
84 create them interacting with biomolecules with considerable affinity, consequently giving  
85 controlled “tagging” that deliberate high sensitivity for various biomedical applications [14]. Or  
86 MNPs can be integrated with other metallic nanoparticles that give distinctive properties  
87 permitting dissimilar functional molecules to get bonded to definite parts of particles and act as  
88 diagnostic and therapeutic agents [15].  
89 Researchers have been investigating the usage of MNPs for targeted cancer therapy since late  
90 1970s due to improvement of behavior in therapeutic agents as well as their delivery to targeted  
91 sites without any adverse effects [16,17]. Frequently, chemotherapeutic drugs, antibodies, and  
92 drugs related to other diseases are attached to MNPs and are delivered to targeted areas inside  
93 human body [18]. The employment of MNPs in drug delivery systems enhances their safety,  
94 biocompatibility, targeting ability regarding other particular drugs, and less toxicity [19]. Large  
95 surface area/volume is mainly beneficial and because of that large number of therapeutic  
96 molecules can be attached to them easily, in addition to their manipulation by magnetic field aid  
97 imaging of delivery of drugs to the targeted sites [20]. Consequently, MNPs have been coupled  
98 for therapy along with diagnosis, mainly in cancer [21]. MNPs in drug delivery systems increase  
99 the drug accumulation at the desired sites through magnetic manipulation or hyperthermia can be  
100 induced in them by a magnetic field, causing cell death or triggering drug release from thermo-  
101 responsive magnetic carriers [22].  
102 Recently, MNPs are comprehensively employed in experimental investigations for treating  
103 cancer and consequently different magnetic formulations have been developed, presenting  
104 optimistic therapeutic impacts on various cancer types [23]. Different magnetic nanoparticles  
105 with different coatings have been synthesized to improve their non-toxicity, biocompatibility,

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

109

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

111 MNPs have been synthesized consuming cobalt, nickel, and gadolinium, however iron oxide  
112 (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  
113 in cancer therapeutics because of their less systemic toxicity and intense contrast features.  
114 Generally MNPs consist of a magnetic core with and a polymer shell [24]. The surface coating  
115 and modification of MNPs improves colloidal stability that permits electrostatic or covalent  
116 binding of therapeutic payload, targeting constituents, in addition to imaging probes. It plays a  
117 vital role in modifying properties of MNPs for instance general toxicity, pharmacokinetics, and  
118 rate of clearance, non-specific adsorption of protein or interactions with cells, and persistent  
119 release of drugs [25]. MNPs incorporation with polymer coating prevents their agglomeration,  
120 and subsequently, offers a prolonged half-life, well-regulated drug release and, concurrently,  
121 provides functional groups for conjugation of biomolecules [26].

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

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

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

167

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

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

186 for a long time, increasing their probability to dissociate and deposit in the body. IONPs based  
 187 contrast agents were chosen over gadolinium-based contrast agents due to their low toxicity and  
 188 researchers have found that they can produce similar MRI contrast with SPIONs [42]. The  
 189 literature results show clinical research on SPIONs remains robust, particularly fuelled by the  
 190 approval of ferumoxytol for intravenously administration. SPIONs have been tested on MR  
 191 angiography, sentinel lymph node detection, lymph node metastasis evaluation; inflammation  
 192 evaluation; blood volume measurement; as well as liver imaging. The risk of accumulation and  
 193 tissue damage is reduced when compared to GBCAs. Therefore in comparison to GBCAs,  
 194 SPIONs are the most effective contrast agents for MRI [43]. MNPs for drug delivery  
 195 applications are impossible to be unobserved. They are employed to carry drug carriers via  
 196 attaching chemotherapeutic drugs or antibodies. Usually, MNPs are loaded with  
 197 chemotherapeutic drugs for cancer therapy. MNPs for cancer therapy are typically employed in  
 198 numerous ways to attain an enhanced therapeutic efficiency, integrated with chemotherapy,  
 199 radiotherapy, magnetic hyperthermia, photothermal therapy (PTT), and photodynamic therapy  
 200 [44]. An immediate treatment observation is possible by specific integration of various drugs  
 201 with SPIONs that have revealed encouraging potential providing adaptable and sensitive  
 202 platform for point-of-care (POC) therapeutic applications. SPIONs can be injected immediately  
 203 into infected tissue, controlled by magnetic field, externally applied for generating heat with aid  
 204 of Néel and Brownian relaxation processes [45,46]. The section discusses the MNPs employment  
 205 for cancer therapeutics. Table 1 summarizes some of the information about magnetic  
 206 nanocomposites in cancer treatment.

207 **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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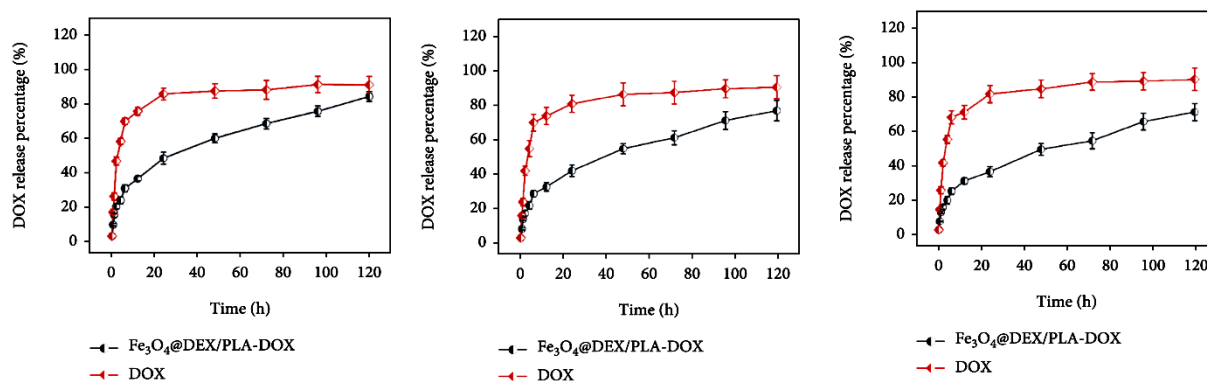
### 209 **3.1. Chemotherapy**

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

221 Polydopamine (PDA)-coated MNPs modified by SH- $\beta$ CD (mono-6-thio- $\beta$ -cyclodextrin) were  
222 prepared and loaded with doxorubicin. Cellular internalization of the prepared particles in liver  
223 cancer was imaged by confocal microscopy. The developed nanomaterials with  
224 chemotherapeutical drug and PDA layer could absorb NIR (near-infrared) light. They showed  
225 significant effectiveness in a combined photo, chemo, and thermal treatment of liver cancer.  
226 Furthermore, they also exhibit enhanced T2 contrast, verified by MRI of these nanoparticles.  
227 Consequently, the prepared nanomaterial is an effective nanosystem having significant  
228 theranostic potential [70]. A multimodal nanoplatform to treat hepatocellular carcinoma (HCC)  
229 *in vitro* was developed. The nanoplatforms were based on polydopamine (PDA)-coated Fe<sub>3</sub>O<sub>4</sub>  
230 nanoparticles and spheres (sMAG) with PAMAM dendrimers and functionalized with NHS-  
231 PEG-Mal (N-hydroxysuccinimide–polyethylene glycol–maleimide) linker that permits their  
232 functionalization with a folic acid derivative. The nanomaterials with folic acid-targeting moiety  
233 displayed high efficiency in killing cancer cells in the dual chemo- and photothermal therapy  
234 (CT-PTT) of the liver cancer cells as compared to modalities implemented separately. Materials  
235 have activity comparable to free doxorubicin (DOX) with a concentration above 10  $\mu$ g/mL. It is  
236 worth mentioning that a functionalized magnetic sphere with DOX more intensely affected the  
237 HepG2 cells than smaller functionalized nanoparticles with DOX in the performed chemotherapy  
238 [71]. In another work multifunctional nanocarriers based on PAMAM dendrimers generation (G)  
239 4.0, 5.0 and 6.0 fixed to polydopamine (PDA) coated Fe<sub>3</sub>O<sub>4</sub> nanoparticles were synthesized and  
240 applied in combined chemo- and photothermal therapy (CT-PTT) of liver cancer cells. The  
241 combined effect of the above-mentioned modalities results in higher mortality of cancer cells in  
242 contrast to their individual performance. Additionally, *in vitro* studies exposed that dual therapy  
243 was more effective in triggering desired cell death mechanism apoptosis. The integration of  
244 MNPs with dendrimers increases the functionality of dendrimers leading to hybrid



245 multifunctional nanostructures that are promising smart drug delivery systems to treat cancer  
 246 [72]. Nanocarrier dextran/polylactic acid (DEX/PLA) and  $\text{Fe}_3\text{O}_4$  (magnetite) nanoparticles  
 247 carrying the drug were prepared for improving DOX targeting in the treatment of liver cancer  
 248 and decreasing its possible toxicity to organs. Drug release from prepared nanoparticles inside  
 249 the body was carried in different pH solutions. The drug is released rapidly in first 24 hours and  
 250 successive release was slow (Figure 1). At the same time, release of the drug in acidic medium is  
 251 better from nanoparticles compared with free drug. As cancerous tissues have acidic  
 252 surroundings, drug can precisely reach cancerous site and inhibit its growth. The *ex vivo* besides  
 253 *in vivo* results found prepared nanocarriers have intense targeting regarding liver cancerous  
 254 tissue and could be applied in targeted therapy providing a novel approach for clinical therapy  
 255 regarding liver cancer [73].  
 256



257  
 258 Figure 1. Releasing ability of drug from magnetite nanoparticles loaded with drug (DOX) at (a)  
 259 pH of 4 (b) pH of 6.28, and (c) pH of 7.4. Reprinted with permission from the reference [73].  
 260

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

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

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

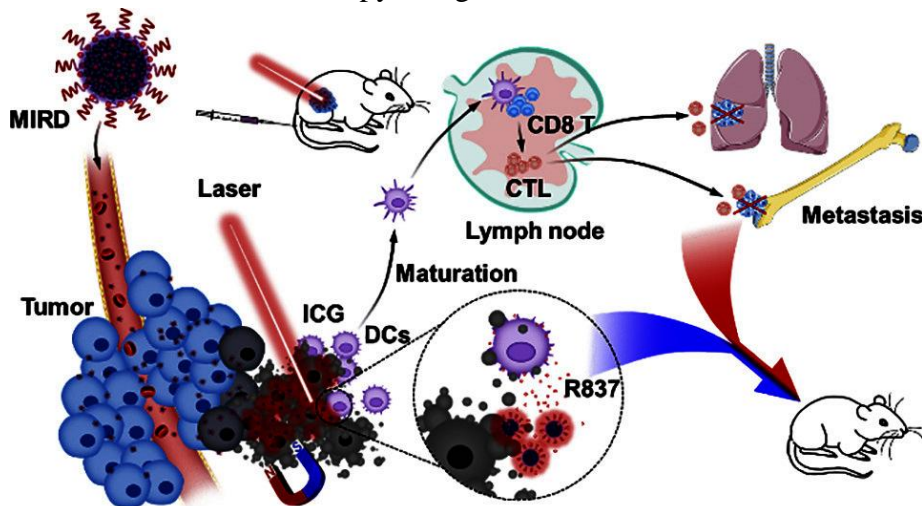
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### 300 **3.2. Immunotherapy**

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

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

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



326  
 327 Figure 2. MNPs functionalized by polyphenols aimed at spatial- sequential controllable  
 328 immunothermal/phototherapy regarding cancer. Reprinted with permission from the reference  
 329 [80].

330  
 331 A biomimetic  $\text{Fe}_3\text{O}_4$  (magnetite)-SAS( sulfasalazine)@PLT (platelet) are established as  
 332 different method for sensitizing active ferroptosis and produce slight immunogenicity, improving  
 333 rate of response regarding non-inflamed cancer aimed at immunotherapy. They activated  
 334 ferroptotic cell death by preventing glutamate-cystine antiporter method Xc-path. It considerably  
 335 increases effectiveness of planned cell death 1 immune checkpoint blockade treatment in  
 336 addition to attaining constant elimination of tumor in model of mouse having metastatic 4T1  
 337 tumors. Investigations performed in proteomics also exposed induction of immune reaction  
 338 specific to tumor and efficient repolarization of macrophages from M2 immuno-suppressive  
 339 phenotype into M1 antitumor phenotype. Accordingly, ferroptosis facilitated by  $\text{Fe}_3\text{O}_4$ -  
 340 SAS@PLT related to immunotherapy possess pronounced prospective for medical handling  
 341 regarding tumor metastasis [81].

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

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

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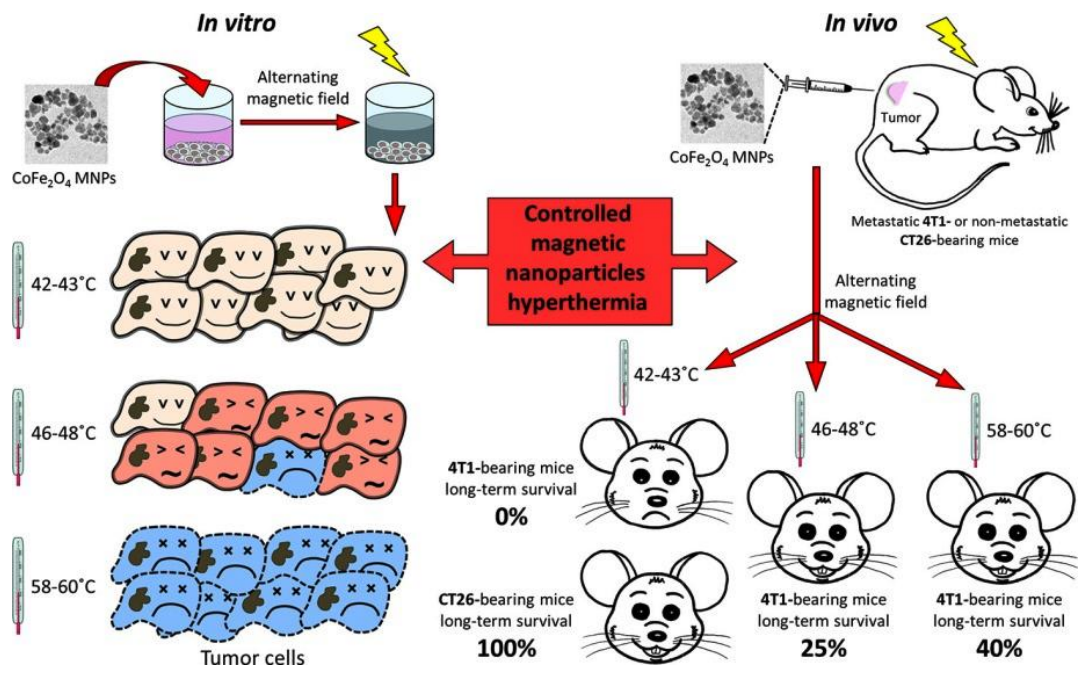
### 361 **3.3. Hyperthermia**

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

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

379 *In vivo* as well as *in vitro* comparative analysis reliant upon temperature regarding effectiveness  
380 concerning nanoparticles of cobalt ferrites was done in two models of murine tumors that is 4T1  
381 (breast) and CT26 (colon) cancer. *In vitro* killing capacity by using these nanoparticles gets  
382 increased with increase in temperature (Figure 3). CT26 cancer cells have more sensitivity than  
383 4T1 on heating to  $43 \text{ }^\circ\text{C}$ . Similarly *in vivo* data also revealed curing of non-metastatic CT26  
384 cells, whereas only preventing growth of metastatic 4T1 tumor with no improvement of complete

385 survival. Higher temperature that is greater than 47 °C lead to whole clearance of 4T1 primary  
 386 tumor, 25 to 40% prolong rates of survival, in addition to active inhibition concerning metastasis  
 387 compared with surgical abstraction. Therefore, particular temperature should be well-defined for  
 388 ensuring positive antitumor therapy [89].  
 389



390  
 391 Figure 3. MNPs prevent primary growth of tumor in addition to metastases propagation through  
 392 temperature-controllable hyperthermia. Reprinted with permission from the reference [89].  
 393

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

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

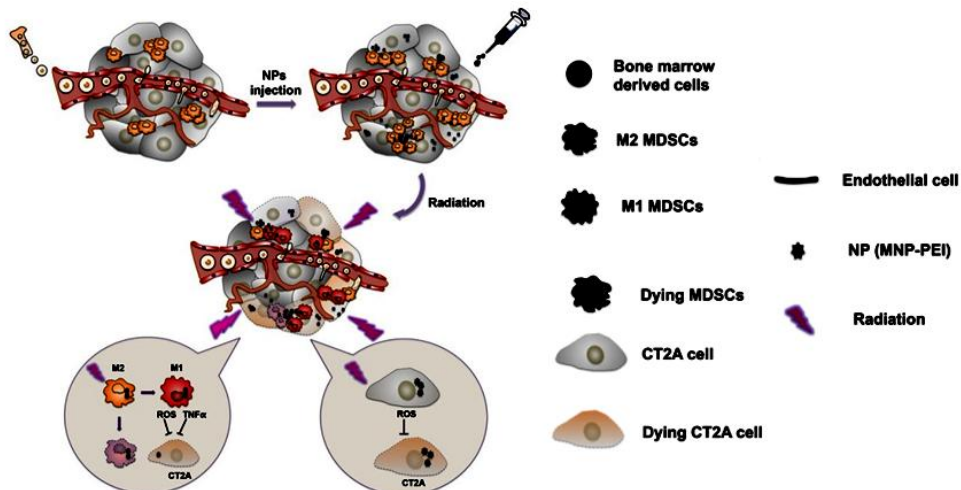
423 Hydrophilic surface modified SPIONs were prepared to treat liver cancer by hyperthermia.  
424 Short-chain molecules, for instance 4-aminobenzoic acid (4ABA), 1,4-diaminobenzene  
425 (14DAB), plus 3,4-diaminobenzoic acid (34DABA) along molecules of terephthalic acid  
426 (TA)/2-aminoterephthalic acid (ATA)/trimesic acid (TMA)/pyromellitic acid (PMA) were used  
427 to functionalize SPIONs. Heating abilities of SPIONs were evaluated by calorimeter regarding  
428 their surface coatings, concentrations, medium for dispersion, besides applied alternating  
429 magnetic fields. All SPIONs were superparamagnetic in behavior, but SPIONs coated  
430 with 14DAB- 4ABA-, 4ABA-TA-, and 34DABA- displayed greater magnetization ( $M_s = 55$  to  
431  $71$  emu/g) with good dispersibility in water. 34DABA-coated SPIONs exposed rapid thermal  
432 reaction on applying magnetic field and extended therapy temperature to low concentration  
433 equals to  $0.5$  mg (mL)<sup>-1</sup> in comparison to 4ABA-, 14DAB-, and 4ABA-TA-coated SPIONs.  
434 Furthermore, 34DABA-coated SPIONs showed great heating efficiencies with SAR of 432.1  
435 W/g and killing efficacy of about 61 to 88% in liver HepG2 cancer cells in comparison to  
436 water/magnetic field based thermotherapy. Thus, 34DABA-coated SPIONs are favorable heating  
437 mediators for hyperthermia and could be utilized as operative nanomedicines aimed at treatments  
438 of cancer [94]. The thermal reaction of tumor tissue to hyperthermia depends on the MNPs  
439 configuration setup along with its different parameters. Injection approach effects mass transfer  
440 during treatment, which is related to the success of hyperthermia cancer treatment. In one of the  
441 study mechanical response of tumor tissue to single and three site injections was compared. The  
442 results indicated that increasing injection sites enhances heat and mass transfer fluxes slightly;  
443 but more expressively influenced by rate of injection. The three-point injection improved  
444 distribution of nanoparticles and heat uniformly, which increased tissue damage and reduced the  
445 risk of tissue necrosis [95].

446

### 447 **3.4. Radiotherapy**

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

451 cells by generating ionic radiation or free radicals [96]. They propose distinctive benefits over  
452 existing radiotherapy practices via decreasing damage to off-target tissues because of non-  
453 particular treatment nature via active and passive targeting [97]. Additionally, MNPs holds high  
454 atomic number ( $Z$ ) as well as display significant absorption of X-ray photons, resulting in  
455 increase in production of secondary electrons for DNA destruction on increasing dose of  
456 radiations. SPIONs enhance radiotherapy effectiveness and specificity regarding DNA  
457 destruction via catalyzing production of ROS through ionizing rays causing considerably strong  
458 oxidative pressure, particularly hydroxyl radicals which destroy DNA of cells [98,99].  
459 Currently, MNPs coated with gold (Au@IONPs) gained significant consideration towards cancer  
460 therapeutics. *In vitro* studies were carried out to find out anti-cancerous impact regarding  
461 Au@IONPs nanoparticles with core-shell morphology in thermo-radiotherapy. Furthermore,  
462 apoptosis level stimulated in glioma U87-MG human cells was examined after getting combined  
463 therapy (hyperthermia + Au@IONPs + radiotherapy). After incubating nanoparticles with cells,  
464 hyperthermia was done for one hour (43 °C) and after that they were instantaneously exposed to  
465 6 megavolts of X-ray. The MTT results showed no substantial cytotoxicity regarding  
466 nanoparticles at below concentration of 10 µg/mL and also enhanced cytotoxic effect concerning  
467 radiation and hyperthermia was observed. Reason of cell death had been apoptosis due to  
468 combined effect of nanoparticles, radiation, and hyperthermia on cancerous cells. Thus, prepared  
469 nanoparticles are good radio-thermo-sensitizer that activates noteworthy apoptosis levels for  
470 cancer treatment [100]. A novel platform based on MNPs modified with cationic polymer for  
471 promoting radiotherapy to treat glioma. Modified MNPs induced cytotoxicity to in glioma cells  
472 on radiations besides encouraging substantial survival advantages in athymic and  
473 immunocompetent mice having glioma. Taking advantage of magnetic features of MNPs, it was  
474 discovered that nanoparticles were taken up by MDSC (myeloid derived suppressor cells) inside  
475 tumor of brain. Efficiency of nanoparticles was estimated by glioma cells destructions in addition  
476 to repolarization of MDSCs from immuno-suppressive to pro-inflammatory phenotype that  
477 helped antitumor impact as well as radio-therapeutic impacts synergistically (Figure 4). These  
478 nanoparticles offers fast targeting dual platform aimed at radiotherapy of glioma through  
479 immediate tumor abolition and management of myeloid phenotypes in central nervous system  
480 [101].



481  
 482 Figure 4. MNPs resulting in extreme cytotoxicity specific to cancer. MDSCs, incompletely  
 483 exposed in addition to repolarized in M1-like phenotype producing anti-cancerous impact after  
 484 radiation therapy along with MNPs. The combined influence showed positive efficacy. Reprinted  
 485 with permission from the reference [101].

486  
 487 Magnetite nanoparticles coated with PEG are favorable candidate as radiation sensitizer for  
 488 radiotherapy. They improved cancer therapy and decreases adverse impacts regarding radiations.  
 489 On exposition to radiations surface coating of PEG possibly be fully or partially destroyed. This  
 490 makes iron ions more accessible and perform as a catalyst to produce ROS species that improves  
 491 the cancer radiation therapy. Cytotoxicity studies revealed percentage killing of cells employing  
 492  $\text{Fe}_3\text{O}_4$  coated with PEG is greater for MCF-7 in comparison with L929. However, percentage  
 493 with bare MNPs is greater for both when compared with PEG coated MNPs. Thus, PEG coating  
 494 enhanced biocompatibility of MNPs that makes them appropriate for radiotherapy and also  
 495 upholds innovative opportunities in field of cancer radiotherapy for improving clinical  
 496 effectiveness in dissimilar cancer types [102]. MNPs conjugated with quercetin (QMNPs) were  
 497 prepared to investigate their sensitivity towards breast cancer in radiotherapy treatment. *In vitro*  
 498 results presented that HePG-2, MCF-7, and A459 cancerous cells incubation along these  
 499 nanoparticles effectively for twenty-four hours prevented cancerous cell growth depending on  
 500 concentration with values of  $\text{IC}_{50}$  equal to 77.5, 11, and  $104 \text{ nmol}(\text{mL})^{-1}$ , correspondingly.  
 501 Irradiation (IR) coupling with QMNPs powerfully blocked proliferation of MCF-7 cancerous  
 502 cells. QMNPs had no toxicity assessed by renal, hepatic, and hematological markers. In addition,  
 503 in white albino female rats, they prevented cancer growth and persuasively improved adjacent  
 504 radiotherapy inside MNU (N-methyl-N-nitrosourea) prompted breast cancer. Such radio-  
 505 sensitizing along anti-cancerous happenings had been because of immunomodulation, cell cycle  
 506 detention, cytotoxicity, in addition to effectiveness by apoptosis generation. Conclusively, MNPs  
 507 with radiotherapy possess prospective targeted therapy for treating breast cancer [103].  
 508 SPIONs have demonstrated fascinating characteristics beneficial for diagnostic and therapeutic  
 509 application. Radio-sensitizing properties regarding SPIONs in brachytherapy and electron beam



510 radiotherapy had been investigated. *In vitro* investigations were performed consuming HeLa  
511 cells with SPIONs. Irradiations doses ranged from 0 to 10 Gy were done by 0.38 MeV <sup>192</sup>Ir  
512 brachytherapy as well as electron beams of 6 and 12 MeV energy. Radio-sensitization  
513 classification was done through evaluating improvement in ratio of sensitization (SER), gained  
514 from survival loops. Results showed SPIONs encourage radio-sensitization in electron beams  
515 particularly at low energy having value of SER of 1.5. It is further noticeable in brachytherapy  
516 having SER of 2. High concentration of SPIONs is increases radio-sensitization impacts more. In  
517 summary, radio-sensitization is influenced by energy of radiation as well as SPIONs  
518 concentration. Additional categorization concerning radio-sensitization persuaded by SPIONs  
519 might permit medical translation regarding SPIONs as per radio-sensitizer for radiotherapy  
520 [104].

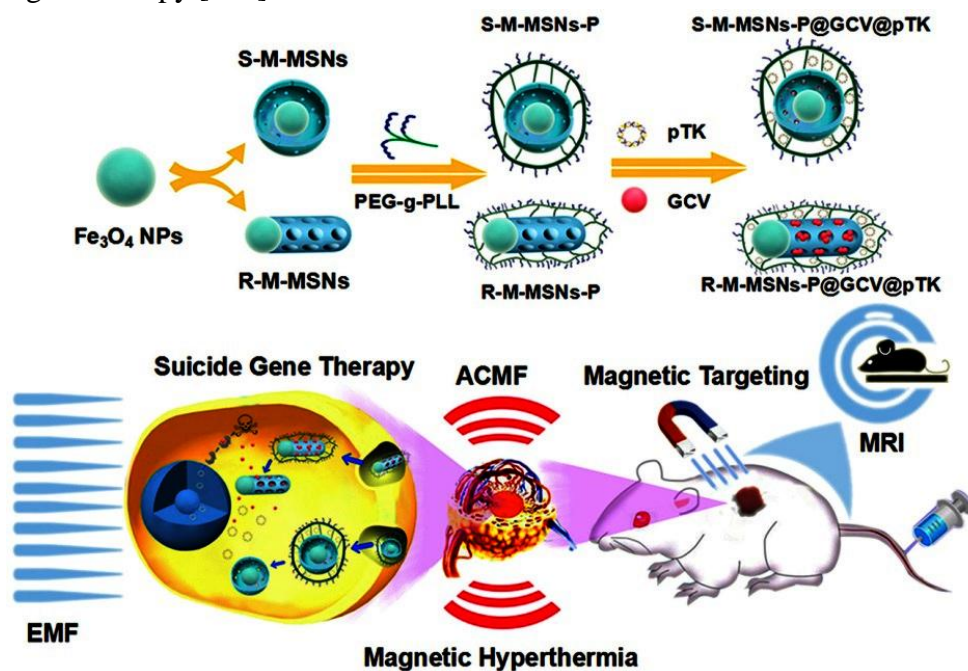
521

### 522 **3.5. Gene therapy**

523 Gene therapy signifies a different substitute to manage diseases with no adequate cure. Gene  
524 therapy to treat cancer made good progress in the last three decades. Comparatively gene therapy  
525 has better safety with tolerable adverse effects than chemotherapy for the treatment of cancer  
526 [105]. The major dissimilarity between gene therapy and chemotherapy is that in chemotherapy  
527 drugs are being delivered, whereas in gene therapy targeted biological moieties for instance  
528 RNA, DNA, or else siRNA, peptides, and proteins are been delivered to cancer site, and by this  
529 manner death of the cells possibly is induced. When one part of the body has cancer, human  
530 damaged DNA is categorized by presence of atypical proteins. This could be treated by replacing  
531 defected gene in cancer cells [106]. On the other hand, siRNA suppressed protein activities,  
532 occurring because of cancer cells. siRNA integrated with nanoparticles could be carried and  
533 delivered to cells, since medicinal RNA are very degradable when injected directly in  
534 bloodstream. siRNA-MNP complex becomes practically unidentifiable for human body. Their  
535 cellular uptake gets improved with longer circulation time. Because of vascular nature of tumor,  
536 MNPs enter and accumulates in tumor [107].

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

550 attached electrostatically to MNPs aimed at targeted delivery of DNA to UL cells. MNPs  
 551 addition caused decrease in required time for fruitful transfection by immediate escalation in  
 552 efficacy. After plasmid delivery, therapeutic impact onto prime UL cells was evaluated. It  
 553 encodes simple herpes virus 1 (HSV-1) thymidine kinase gene. Treating by ganciclovir,  
 554 increases efficiency to twenty percent in suicide-gene treatment inside UL cells introduced by  
 555 pPTK-1 plasmid. Finally, consumption of MNPs with cationic peptides are promising carriers to  
 556 develop non-viral modular carriers aimed at suicide-gene delivery in UL cells [109].  
 557 Magnetically mediated suicide-gene therapy is favorable for suicide gene therapy. M-MSNs  
 558 comprising MNPs with nanoparticles of mesoporous silica were synthesized. Then carboxyl-  
 559 modified M-MSNs had been loaded with PEG-g-PLL and GCV. After that they were attached to  
 560 M-MSNs surface that offered positively charged surface for absorption of TK plasmid (Figure  
 561 5). They were evaluated for their role in MRI, magnetically targeted as well as hyperthermia-  
 562 assisted suicide gene therapy of hepatocellular carcinoma (HCC). Rod-shaped MSNs showed  
 563 greater capacity for loading, rapid release of pro-drug, improved magnetic gene delivery, in  
 564 addition to enhanced hyperthermia in comparison with spherical MSNs. M-MSNs showed  
 565 extremely active double magnetic improved *in vivo* suicide-gene therapy along reduced  
 566 methodical toxicity. It also has capability for monitoring therapy outcome via MRI. Attributed to  
 567 magnetic targeting and hyperthermia, developed M-MSNs are possibly better candidate aimed at  
 568 HCC suicide gene therapy [110].



569  
 570 Figure 5. M-MSNs aimed at suicide-gene therapy regarding hepatocellular carcinoma cells  
 571 mediated magnetically. Reprinted with permission from the reference [110].  
 572

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

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

598

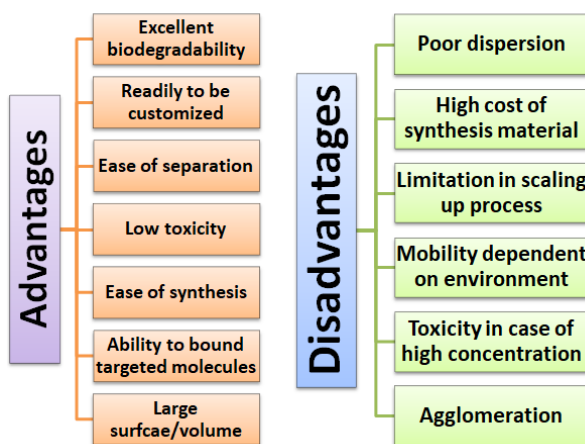
#### 599 **4. Advantages and limitations of magnetic nanoparticles for cancer therapy**

600 MNPs are amongst widely investigated nanostructured material, by reason of their possible  
601 usages in different research fields wavering from data storing to catalyzing applications,  
602 including cancer detection and therapy [114,115]. MNPs have many benefits, particularly high  
603 ratio to surface area to volume, size of pores, modified surfaces, more than one interaction or  
604 binding sites, making them greatly appropriate to be utilized for treatments of diverse diseases  
605 [116].

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

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

616 MNPs organizes in 2-D (two-dimensional) space [118]. Furthermore, to retain MNPs in the  
 617 targeted region is difficult after the removal of magnetic field. Another problem is related is time  
 618 of exposure to applied magnetic field, it is not possible to expose patients for unlimitedly  
 619 external magnetic field. This all reduced therapeutic effectiveness and limits it to intensity,  
 620 frequency, as well as exposure time of applied field [24]. Toxicity of MNPs depends mainly on  
 621 administration method, surface chemistry, biodegradability, etc. Normally shape, composition,  
 622 surface area, coating, and dimensions MNPs are considered to determine cytotoxicity. MNPs  
 623 functionalization is vital for confirming minimum toxic impacts [119]. In some cases, controlled  
 624 release of ions for instance, cobalt ions from MNPs surface is helpful and can be consumed as  
 625 toxic agents for cells, like chemotherapeutic drugs [120]. Therefore a comprehensive valuation  
 626 regarding therapeutic and safety efficiency concerning MNPs must be executed before any  
 627 treatment for clinical usage [121]. Another issue is lasting effects of MNPs inside the body.  
 628 Commercially available MNPs are not biodegradable and their prolonged accumulation in tissues  
 629 can be dangerous for healthy cells. It is important to know how MNPs interacts with cancerous  
 630 and healthy cells in human body as well as their excretion [115,122].  
 631 SPIONs (superparamagnetic iron oxide nanoparticles) accumulation becomes unstable inside  
 632 biological medium or solutions that are same as body fluids [123]. They possess diverse adverse  
 633 effects, for instance deterioration in functioning of brain, liver, skin, stomach that might persist  
 634 for ten years [124]. MNPs faced different physiological barriers lessening therapeutics  
 635 localization at targeted site, which limit their use in cancer theranostics. Another limitation is  
 636 particular targeting to cancer bearing site that reduces dosage and effectiveness regarding MNPs  
 637 [125]. Few of the advantages along with disadvantages are illustrated in Figure 6.



638  
 639 Figure 6. Some of the advantages and disadvantages regarding MNPs.  
 640

## 641 5. Conclusions

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

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

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

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

678

## 679 **6. Experts opinion**

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

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

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

703 **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]

704 MNPs toxicity is one of the serious causes regarding their biomedical applications. It reduces  
 705 therapeutic efficiency along with immunity or inflammatory activation because of their  
 706 agglomeration in organs. On entrance in cells, the toxicity can upset nuclear activities, leakage of  
 707 cell membranes that results in adversative metabolic action, proliferation of cells, and viability  
 708 consequences. Even though MNPs and SPIONs are FDA approved, but their usage in treating  
 709 cancer should be wisely directed and organized, since their large amount might be  
 710 unsafe. Excessive use of MNPs can cause changes in living cells because of ROS production  
 711 cytoskeletal destruction, mitochondrial impairment, as well as DNA configuration alteration.  
 712 One challenge is scaling up of the magnetic system. Prototypes devices for small-sized animals  
 713 could be built exploiting stable magnets with benchtop amplifiers, whereas establishing large  
 714

715 systems need high-powered electromagnets.  
 716 MNPs display substantial promise for theranostic applications as contrast enhancers and  
 717 therapeutic agents for cancers. MNPs indicate the potential to be engaged in treating  
 718 cancer treatments because of their specific characteristics that deliver acute data to physicians  
 719 offering ultimate care. MNPs have been investigated extensively attributed to their ease of  
 720 synthesis and functionalization; still, inadequate formulations get permitted for clinical uses.  
 721 However, there is room to translate MNPs from lab to clinic that requires complete  
 722 understanding concerning MNPs effects on human physiological reactions. Research showed  
 723 numerous formulations consisting MNPs have unsuccessful results to produce satisfactory  
 724 treatment levels in large animals and humans; similar to results that were perceived in small  
 725 animals. For MNPs translation to clinics, ability to load drug, improving their specificity and  
 726 affinity to target cells, in addition to obtain required release of drug depending on tumor  
 727 microenvironment must be considered with the help of superior animal theoretical models. Table  
 728 3 summarizes some features of the reported magnetic nanoparticles intended for cancer therapy.  
 729 Taking account of countless advantages, we are confident that combine diagnostic and  
 730 multimodal therapy consuming MNPs would propel forward their clinical employment and  
 731 considerably influence cancer therapy in near future.

732 **Table 3.** Some features regarding the reported magnetic nanoparticles intended for cancer  
 733 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	MCF-7	-	Radiotherapy (X-ray irradiation)	Additional oxidative stress	[141]
SPIONs	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]

734

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

747

#### 748 **Disclosure statement**

749 Authors have no competing interest to disclose.

750

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