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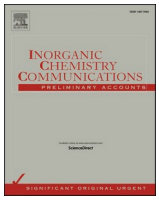

Recent development for biomedical applications of magnetic nanoparticles

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ABSTRACT

In recent decades, the use of engineered nanoparticles has been increasing in various sectors, including biomedicine, diagnosis, water treatment, and environmental remediation leading to significant public concerns. Among these nanoparticles, magnetic nanoparticles (MNPs) have gained many attentions in medicine, pharmacology, drug delivery system, molecular imaging, and bio-sensing due to their various properties. In addition, various studies have reviewed MNPs main applications in the biomedical engineering area with intense progress and recent achievements. Nanoparticles, especially the magnetic nanoparticles, have recently been confirmed with excellent antiviral activity against different viruses, including SARS-CoV-2(Covid-19) and their recent development against Covid-19 also has also been discussed. This review aims to highlight the recent development of the magnetic nanoparticles and their biomedical applications such as diagnosis of diseases, molecular imaging, hyperthermia, bio-sensing, gene therapy, drug delivery and the diagnosis of Covid-19.

1. Introduction

Nanotechnology has been one of the fastest developing branches of science and technology in recent years [1,2]. Nanotechnology focuses on the design and synthesis of nano-sized materials. This technology has a huge number of applications in various fields of science including biological and synthetic chemistry [3]. At nanoscale, the materials have diameter of nanometers, and typically a few molecules [4]. Nanomaterials are smaller particles that have shown very promising chemical, biological, and physical properties, depending on the nanomaterials' size, morphology, and shape [5–7]. These materials show a wide range of applications in various areas, such as biomaterials, nanomedicines, the environment, imaging, nano-electronics, industry, and agriculture, as well as the use of nanotechnology for diagnosis, treatment of various diseases, novel drug formulation, cell tracking, tissue repair and drug delivery in the healthcare sector [8–10]. Magnetic nanoparticles (MNPs) are materials widely used in nanomedicine, analytical chemistry, and bio-sensing [11,12]. However, there are many types of different nanoparticles, including MNPs as a class of new materials that provide interfaces among physics, biology, and chemistry. MNPs are also used in clinical practices as contrast enhancing agents in magnetic resonance imaging. In addition, various methods have been developed for these materials in hydrophobic comprising interactions and electrostatic interactions [13]. These materials currently draw many interests for fabrication and design, such as nano-bio composites that include MNPs and nucleic acid molecules. These have a wide range of applications, including nanoelectronics, biomedical diagnosis, therapy, magnetic separation, and MRI [14–17]. The involvement of MNPs is important to prepare available systems for *in-vivo* applications. MNPs combinations with polymers attracts the researcher's interest to participate in stable composite or colloidal systems because the polymer shell works as a compatibilizer that interacts with the environment, by which polymers provide catalytically- or biologically-active functional sites, and MNPs properties allow manipulation of the systems [18]. MNPs holds several unique properties which provide wide applications such as biomedical separation, hyperthermia, catalysis, magnetic resonance imaging, magnetic target drug delivery, nucleic acid and cell separation, COVID-19 diagnosis, biosensing, and various applications as shown in Fig. 1. There are different types of MNPs, for instance, oxides, ferrites, and ferrites with a shell, metallic with a shell coating, fluorescence, and data storage. Thus, the current review focuses on the recent decade developments in MNPs for biomedical applications.

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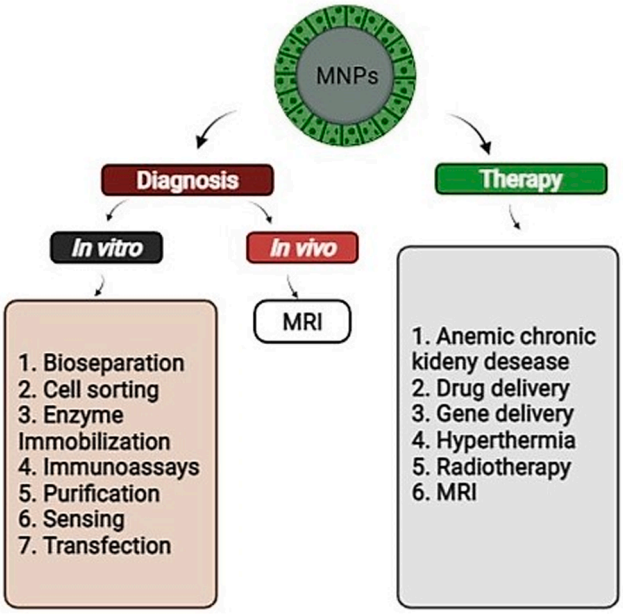

Fig. 1. Various Biomedical uses of MNPs for diagnosis and therapy.

2. Recent development in magnetic nanoparticles for biomedical applications

2.1. Gene delivery

Magnetic nanoparticle (MNP) used in gene delivery were attached to the delivery system and promoted cellular uptake via their gene encapsulation [13]. Nemours methods for the delivery were using with MNPs such as polymeric, viral and non-viral delivery systems as shown in Fig. 2. Non-viral transfection agents showed a significant developmental role for gene delivery with new methods based on chemistry and physics, which are helpful for energetic processes and charge interactions. This method is better for *in vivo* and *in vitro* gene transfections, which consist of biocompatible MNPs. Attachment of MNPs to the reporter gene through high field magnets for cells or tissues of the targeted site with rapid and excellent transfection present future potential uses [19]. Technology-related NPs are used in many diverse areas regarding biomedical and molecular sciences due to the easy entry of nanomaterials to any part of the body. Hence, NP technology is the best method for targeting gene delivery of DNA into cells and tissues with controlled behavior of these assemblies. DNA binding of NPs with polyethyleneimine coated with MNPs have been reported for gene delivery [20]. These MNPs have currently attracted attention from researchers due to novel magnetic properties that have been studied in magnetoception, gene binding, endosomal escape, cellular uptake *in vivo*, and *in vitro* targeting and intracellular trafficking for gene delivery [21]. In the magnetofection process, the modification on the surface of iron oxide-based MNPs increases the efficiency of transfection and decreases cytotoxicity. Besides, the selected agents such as non-ionic water-soluble surfactant such as pluronic F-127, anionic surfactants such as lauroyl, oleic acid, and sarcosinate, fluorinated surfactants such as, ethyl-thiopropionate, polymers such as poly-L-lysine, polyethylene, poly dendrimers, poly propyleneimine, carbohydrates such as heparin sulfate and chitosan, silica particles, proteins, cationic cell-penetrating peptides, transfection reagents, non-activated viruses envelope, and viruses such as retrovirus, and adenovirus are used as a coating agent in term of conjunctions with polyethyleneimine since the polyethyleneimine-coated MNPs provide suspension stability in water, and are able to control the behavior of MNPs by magnetic force and bind to nucleic acid [20].

Gene therapy using a magnetic field provides the best way to treat brain tumors by permitting penetration of the blood-brain barrier by these particles to transport therapeutic genes with low toxicity to cancerous brain tissues. Developed with magnetosome and polyamidoamine dendrimers and the peptides of Tat due to the magnetic field externally, and the peptides of Tat observed in better efficiency for the transfections. Where the magnetosomes were extracted from *M magnetospirillum gryphiswaldense* MSR-1, Human glioblastoma U251, cells cultured in Dulbecco's modified eagle's medium which supplemented with heat-inactivated 10 % fetal calf serum, glutamine 4 Mm, penicillin 50 u/mL, streptomycin 50 lg/mL, EDC, and luciferase plasmid pGL-3 4818 base pairs as a reporter gene used, and the conjugation of Tat peptides onto MS-PAMAM were done by heterobifunctional coupling reagents [22]. Furthermore, nanoparticle technologies (MNPs) better treat cancer cells when used with gene transfections [23]. For corneal endothelial cells, the anti-apoptotic p35 gene therapy has been reported to use lipofection with MNPs in humans and corneas explanted from humans. In combination with X-treme GENE-HP, silica iron oxide is observed to provide high-efficiency transfection with no harm to function and viability. Silica iron oxide was synthesized in 60 co gamma-irradiation, sterilizing at 25 kGy doses. The concentration was

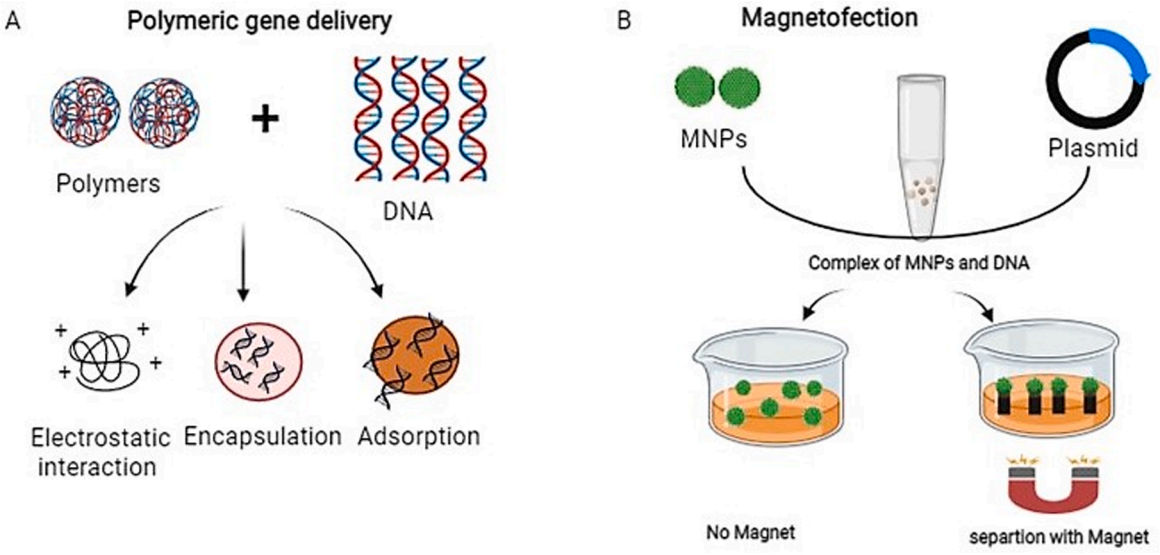

Fig. 2. a) polymeric gene delivery system and b) process of Magnetofection.

determined by the iron content in the suspension, which was observed at 6–9 nm with negative surface charge and core materials. The higher saturation magnetization enabled the assembly of the concentration to PDNA and reagents for the conversion of liposomal transfection into magnetic lipoplexes. The magnetic lipoplexes were then prepared in a 48-well cell culture plate for a single transfection in 16.4 μl of MNP suspension, 19.7 Fe/ml in water mixed with 5.2 μl of transfection reagent, and 108 μl of pDNA solution, which resulted in the complex assembly of a final 10 μg/ml of pDNA concentration. Moreover, MNPs could be considered an enhanced tool for the treatment of and the targeted-site delivery system for corneal endothelial cells [24]. MNPs with the properties of cell-penetrating peptides and oligonucleotides enhance the transfection into cells for plasmid transfections, splice corrections, and the silencing of gene efficacies. MNPs incorporated into complexes of these peptides have been observed to provide higher biocompatibility and the correct transfection to the desired cells. However, the attachment of these peptides to inorganic MNPs such as Fe_3O_4 is considered to offer an efficient and selective platform for gene

Table 1
MNPs with different synthesis method, size, shape, stability and applications.

MNPs Composition	Synthesis method	Size & Shape	Stability	Application	Ref
Silica-iron oxide MNPs coated with polyethylenimine	Hydroxide precipitation	6.8 nmCrystallite	stable	Gene deliveryLabeled cell detection by MRI	[84]
PSCFO	Solvent diffusion	34–12 nmHighlyMonodispersed	stable	Therapeutic agentsGene delivery	[85]
Fe_3O_4 coated with chitosan and gallic acid	Epichlorohydrin crosslinking	11–13 nmSpherical	Highly Stable	Drug deliveryControl release	[86]
CPPs-CTS@MNPs	Hydrothermal co-precipitation	2–10 nm	stable	Gene delivery	[87]
PEG/PEI/Tween 80-SPIONs	Thermal Decomposition	9–13 nmSpherical	Stable	MRI Contrast Agent	[66]
CM-dextran coated MNPs	Co-precipitation	15.1 ± 2.5 nm	Stable	MRI contrast agents	[88]
Ce6-MNPs	Co-precipitation	15–25 nmquasi-spherical	Stable	MRI and NIR Fluorescence imaging	[89]
Lipo[MNP@m-SiO_2]Trastuzumab-conjugated (Lipo[MNP@m-SiO_2]-Her_2Ab)	Not specified	16-nmMonodispersed	Highly Stable	Fluorescence MR imaging for breast cancer	[90]
Fe_3O_4@AuNanoroses	Co-precipitation	70 nmFlower-like cluster	Stable	Integrating aptamer based targeting,MRI,Optical imaging, Photothermal therapy, Chemotherapy	[91]
PC-Fe_3O_4	Sonication	6–14 nmSpherical	Stable	Targeted Drug Delivery	[92]
Fe_3O_4-CMCH	Co-precipitation	10 nmSpherical	Stable	Drug Release and Hyperthermia Treatment	[93]
CS-CDpoly-MNPs	Co-precipitation	19–24 nmSpherical	Stable	Targeted Drug Delivery	[94]
Chitosan coated SPIO-NPs	Co-precipitation	69 nmSpherical	Stable	Targeted Drug Delivery	[95]
Chitosan and prindopril erbumine coated Fe3O4	Sonochemical	15 nmCubic inverse spinal	HighlyStable	Drug delivery	[96]
Fe_3O_4-PLGA:PEG4000	Co-precipitation	25–75 nmCrystalline	HighlyStable	Lung cancer treatment	[97]
Asp@IONPs	One pot synthesis	17.80 ± 3.09 nm	Stable	Biomedical application	[98]
Ag@MGO NCs	Green synthesis	5.5 nmSpherical	Stable	Anti-microbial	[99]
Apt@MGO	N/A	11 nm	N/A	Photothermal therapy,	[100]
(OA)-coated Fe_3O_4	Co-precipitation	7.8 ± 1.9 nmDispersed	Stable	Biomedical application	[101]
Protein A modified Fe_3O_4	Co-precipitation	10 nmCrystalline	Stable	Drug deliveryCancer treatment	[102]
Pluronic F127-coated Mg1-xCaxFe_2O_4 ferrites	N/A	10 nmquasi-spherical	Stable	HyperthermiaTreatment	[103]
MNP-NP-He	Self-assembled-monolayer deposition	6–8 nmRoughly spherical	Stable	Biomedical application	[104]
Gd^3 + MNPs	MW-assisted polyol synthesis	6–24 nmCrystalline	Stable	Biomedicine	[105]
DMSA-coated MNPs	Co-precipitation	9.2 nmUniform monodisperse	Stable	Biotransformation *in vivo* and drug delivery	[106]
Fe_3O_4@SiO_2	Co-precipitation	10–20 nmSpherical	Stable	Chloroauric Adsorption	[107]
PSS-Fe_3O_4	Co-precipitation	50–200 nmSpherical	Highly Stable	N/A	[108]
PEG- Fe_3O_4	Co-precipitation	25 nmSpherical	Stable	BPA degradation Catalytic Activity	[109]
Fe_3O_4/PB/GOD	Co-precipitation	30–60 nmSpherical	Stable	Glucose Biosensor	[110]
Fe_3O_4/r-GO	Massart's method	20 nmSpherical	Stable	Electrocatalytic Activity	[111]
Tyr-modified MNP/CNTs	Not Specified	100 nmSpherical	Stable	Electrocatalytic Magneto-switchable Biosensor	[112]
NaOl/ MPEG-Modified SPION	Co-precipitation	6–12 nmSpherical	Stable	Protective Coating	[113]
Na-citrate/CTAB/TMAH conjugated IONPs	Co-precipitation/ Thermal Decomposition	17–21 nmSpherical	Stable	DNA Tracer	[114]
Ag-MNPs@PCL	Co-precipitation	14–22 nmSpherical	Stable	Wound Healing	[115]
Fe_3O_4-hydrochar	Hydrothermal Carbonization	40.16 nm(Pores)	Less Stable	Removal of Cd	[116]
Fe_3O_4	Temperature pyrolysis	84 nmSpherical	Stable	Immunotherapy	[117]
Fe@PDA-PEG	Sonication	162 nmSpherical	Highly Stable	M2-to-M1 TAMs repolarization Photothermal Therapy	[118]
Pa-M/Ti-NCs	One-pot Hydrothermal	80 nmSpherical	Stable	FerroptosisImmunomodulation	[119]
ETP-PtFeNPs	Modular Conjugation	24 nmSpherical	Stable	Immunogenic Chemotherapy	[120]
Den − DOX − Fe3 + − TA	Not specified	33–60 nmSpherical	Less Stable	ApoptosisFerroptosis	[121]
Fe3O4@TiO2@Lys MIPs	Sonication	380 nmSpherical	Stable	Phosphoprotein Biomarker Separation	[122]
Col-L-MBC	Pyrolysis	Honey-Comb	Stable	Heavy Metal Removal	[123]
SAPEG-MPDA@SPIO/$Fe3^+$NPs	Dual-Soft Template Method	155 nmSpherical	Stable	Chemo-Photothermal treatment	[124]
Fe_3O_4@C/Ag Nps	Solvothermal	360–733 nmSpherical	Stable	Degradation and Reduction of Methylene blue and 4-nitropheno	[125]
Fe3O4@SiO2	Solvothermal	250–400 nmSpherical	Stable	Detection of*P. aeruginosa*	[126]

N/A = not avilable

therapy. The Fe_3O_4 was prepared by hydrothermal co-precipitation with an average diameter of 6.4 nm. A SYRO II peptide synthesizer was used for the synthesis of peptides (PF220, PF221, PF222, PF223, PF224, and PF14). Peptide–plasmid complexes modified with MNPs bypGL3 plasmid were used for the transfection [25]. The MNPs used in gene delivery were listed in Table 1.

2.2. Drug delivery

MNPs are attracting the interest of researchers with their enormous inherent properties and novel features such as biodegradability, biocompatibility, heat therapy potential, and magnetic characteristics. In addition, MNP applications are provided in biomedical areas that use drug-targeted delivery and therapy-based hyperthermia, as shown in Fig. 3. For various diseases such as pulmonary disorders, hyperthermia is the best approach due to the therapy of thermal activation. However, with a higher capacity of loading and releasing into controlled sites, MNPs are the best option for drug delivery systems such as those used to treat lung cancer and cystic fibrosis [26]. The surface coating and magnetic core of MNPs are usually crucial to the drug delivery system. Under physiological conditions, the coating may remove or minimize the accumulation and bio-conjugation of functional groups for targeted ligands and anticancer drugs. Chitosan nanoparticles have better antimicrobial and biological properties due to their high surface-to-volume ratio, and their ability to provide a better drug delivery system was observed in their applications [27]. Chitosan iron oxide MNPs coated with phytic acid lead to the formation of nanocomposites of phytic acid chitosan iron oxide, which are thermally stable as anticancer nanocomposites with the properties of super-paramagnetic.

The phytic acid-chitosan-iron oxide nanocomposite PTA-CS-MNP obtain by mixing of PTA sodium solution 2 g in 100 ml of deionized water with a certain amount of CS-MNPs, and the solution was kept under vigorously stirring for 24 h and the slurry was centrifuged and washed, and dried at 60 °C ovens. Nanosized were prepared by co-precipitation process where PTA-CS-MNP nanocomposite and MNPs, CS-MNPs are roughly spherical in morphology the average size were 8 ± 3 nm, 15 ± 6 nm, and 12 ± 4 nm, respectively. The cytotoxicity of the system observes on HT-29 cancer cells of the colon and is not cytotoxic over normal cells [28]. To reduce the toxicity of MNPs, various inorganic and organic materials utilize in coating for the functionalization of their surface. However, with external magnetic files, the MNPs can be directed in controls manners to the pathological regions drug loading and targeted release with their temperature sensitivity and pH properties, which reduce the dosage and enhance the efficiencies as a drug delivery vehicle [29]. The Fe_3O_4 MNPs @ copolymer PEGylated PLGA particles were used *in vitro* to release doxorubicin as an anticancer agent, where the MNPs were synthesized by improved chemical co-precipitation method and PLGA-PEG_{1000} copolymer as initiator were synthesized through melt polymerization method under the vacuum system. Doxorubicin-encapsulated Fe_3O_4 MNPs modified with PLGA-PEG copolymer were prepared by double emulsion process with minor modifications. Doxorubicin-encapsulated Fe_3O_4 MNPs with average crystalline shape and 10 nm in size were reported [30]. The nano-scale metal–organic frameworks observed efficient drug delivery carriers with large surface area, tunable functionality, and high porosity. However, chitosan surface-modified MNPs encapsulated with folic acid targeted molecules have better ability for drug delivery as doxorubicin attached to magnetic metal–organic framework observed with higher drug loading with optical image demonstration. Where the Fe_3O_4@OCMC were physically immobilized on the surface of OCMC on MNP, and the folic acid socked into Fe_3O_4@OCMC in one pot synthesized and then attached with carbon dots respectively and doxorubicin-loaded on the surface. The morphology showed that these nanomaterials are spherical with 200 ± 10 nm in size [31]. Although nano-carriers for drug delivery, the magnetic iron oxide nanoparticles provide better nano-platforms with high loading carrier ability. However, these nanoparticles have great importance in targeted drug delivery for cancer treatment [32]. MNPs coated with bovine serum albumin were used to deliver curcumin in different buffer solutions against MCF-7 breast cancer cells, which observed significant cytotoxicity against these cells line. The bovine serum albumin-coated magnetic nanoparticles F@BSA NPs were synthesized through curcumin carriers by desolvation and co-precipitation method. F@BSA@CUR NPs loaded MNPs have an average spherical shape and 56 ± 11.43 nm average size reported [33]. The MNPs uses in a drug delivery were listed in Table 1.

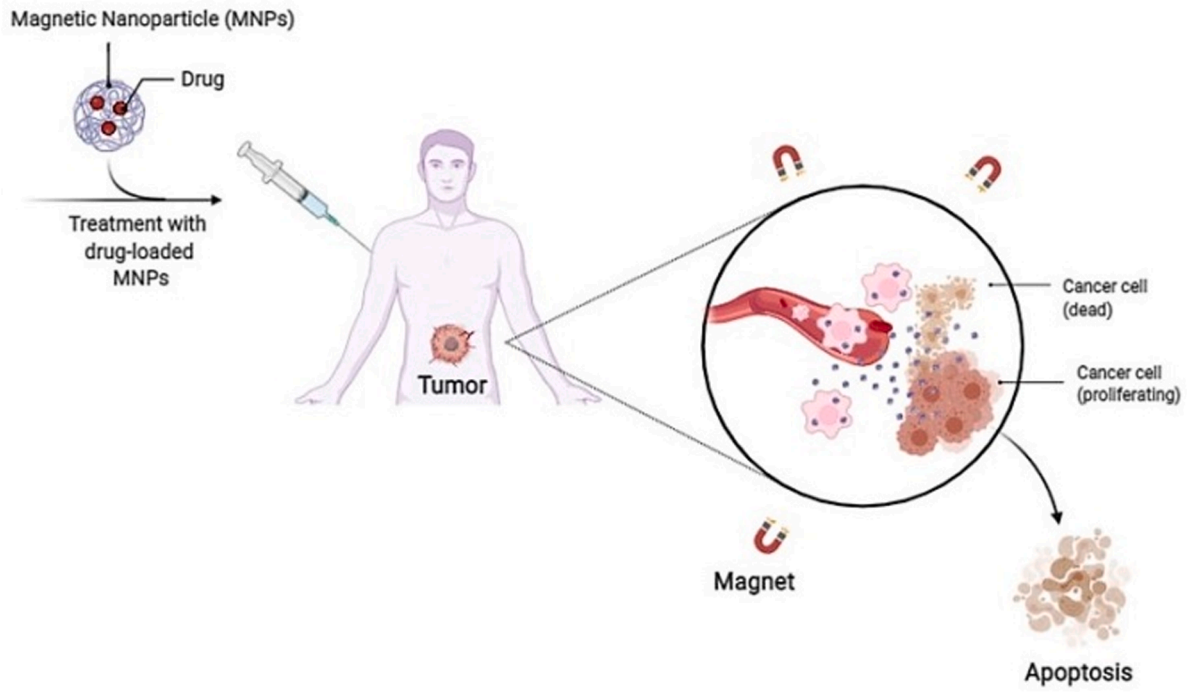

Fig. 3. Drug targeted delivery with MNPs mechanism with external magnetic field for cancer treatment.

2.3. Hyperthermia

Magnetic hyperthermia and drug delivery–based biomedical applications have emerged with MNPs because of their bioavailability, solubility, metabolism, permeability, excretion, identification of various medicines, and cell internalization enhanced by their surface properties. However, these parameters highly require increasing the efficiency of several therapeutic therapies. Magnetic hyperthermia has synergistic effects, which improve the drug delivery systems with engineered MNPs [34] as shown in Fig. 4. Recent developments in microdevices and nanodevices have led to better therapeutic and diagnostic tools in oncology. Superparamagnetic nanoparticles in magnetic hyperthermia have a success ratio with cancer treatment, but heating efficiency is required for cancer cells to be killed [35]. In the treatment of cancer, the tissue is exposed to higher temperatures up to 41 °C–47 °C, which can kill the cancer cell by damaging its DNA [36]. Deep-seated or small tumors can be treated in the presence of small magnetic fields in localized magnetic hyperthermia with minimized amounts of MNPs. However, the heating efficiency must be enhanced [37]. Hence, the use of MNPs can enhance hyperthermia treatment with their functionalities [38]. In magnetic fluid hyperthermia, MNPs were used to treat cancer, enhancing the efficacy of radiation and chemotherapy in clinical trials, where they used 31 different commercially available MNPs for magnetic fluid hyperthermia, in which the efficacy of heat was measured by a specific absorption rate. [39]. The sugar alcohol mannitol introduces to the iron oxide MNPs surface MNPs, which substantially affect colloidal stabilization and surface potential with superparamagnetism at room temperature. The MMNPs were prepared through coprecipitation of Fe^{2+} and Fe^{3+} ions in a medium under N_2 atmosphere, followed by in-situ D-mannitol coating.

These mannitol magnetic nanoparticles employ as carriers for doxorubicin hydrochloride delivery as an anticancer drug attached to the surface of these magnetic nanoparticles with negatively charged and doxorubicin positively charged in the delivery system by electrostatic interaction. The efficiency of loading was 60 % observed with sustained release and pH-dependent with self-healing abilities used in the therapy for hyperthermia [40]. However, the biocompatible MNPs in magnetic fluid hyperthermia used as mediators of heat in cancer therapy observe lower side effects and higher efficiencies [41]. The attachment of gold nanoparticles to the core of iron oxide nanoparticles observe with properties as a nano-heater. Au nanoparticles in size of 3.9 ± 0.2 nm attached to Fe_3O_4 cores with a size of 49.2 ± 3.5 nm in the aqueous medium. This does not affect the efficiency of heating and provides a flexible background for the multifunctional functionalization properties. The MNPs showed high viability *in vitro* cytotoxicity > 97.5 % on microglial BV2 cells over the control groups under magnetic field [42]. Hyperthermia in clinical and theoretical fields is the most promising approach to treating cancer, and magnetic hyperthermia has positive advantages with other hyperthermia treatments. However, the MNPs used require proper dosage, proper location, and injection locations [43]. In hyperthermia treatment, the superparamagnetic nanoparticles work as agents for heating to treat cancer. Although the superparamagnetic nanoparticles obtain magnetic hyperthermia, excellent capabilities generate heat and effectively inactivate the inaccessible tumor cells. MNPs and magnetic fields are the backbones for the variations of hyperthermia properties, which enhance the avoid unwanted heating up in healthy cells in magnetic hyperthermia [44]. However, in magnetic fluid hyperthermia, the MNPs target the tumor magnetically and heated in an altered magnetic field, leading to tumor cell deaths by binding to the cells' membrane and forming agglomerates before entering inside the cell. Hence, the agglomerates and intercellular immobilization influence the MNPs properties of heating, leading to uncontrolled local heating inside the cell, but the attachment of larger size MNPs agglomerates reduces the heating efficiency in tumors [45]. The MRSA Apt@Au NRs and MRSA Apt@Au NPs are functionalized by MRSA aptamer with Au NRs and Au NPs for MRSA bacteria destruction through targeted photothermal therapy. Although both of them binding to the MRSA bacterial cells. only the Apt@Au NRs can kill the cells effectively by hyperthermia due to the strong photothermal conversion, and NIR light absorption. Besides, this immobilization provided a multivalent effect, and increase the strength of binding with affinity to reach the targeted cells was reported [46].The MNPs uses in hyperthermia were listed in Table 1.

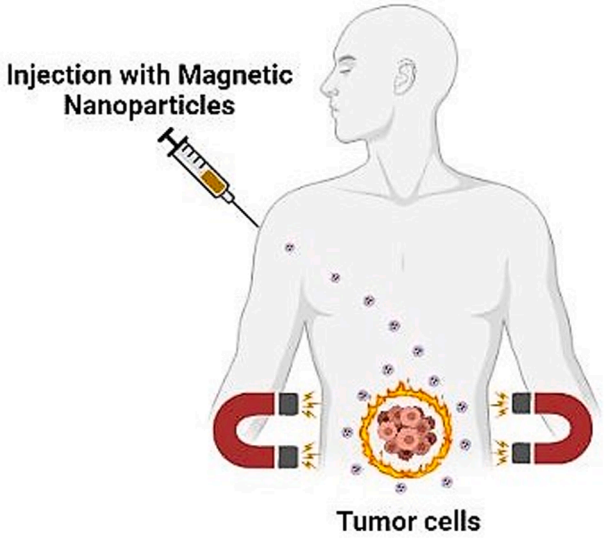

Fig. 4. Hyperthermia therapy mechanisms with external magnetic field for cancer treatment.

2.4. Biosensing

The biosensing growing demands are leading approach to develop ultrasensitive signal amplification approaches for detection based on novel characteristics such as biocompatibility, electro-conductivity, and ease with synthesis to capture targeted cells and pathogen as shown in Fig. 5. The iron magnetic nanoparticles are best with the applications in electrochemical biosensing, which leads to the development of electrochemical nano-biosensors, which include various types such as enzyme, immune, aptamer, and DNA [47]. Magnetic nanoparticles coated with gold increase the interest of researchers due to their multifunctional properties in nano-medicine and analytical chemistry. The iron oxide nanocrystals were modified with the surface functional groups with gold. Hence, surface functionalization provides applications in biomedicine and analytical sensing [48]. However, MNPs in sensing play a role with their high significance to create viable solutions for lower limits detection and non-specific effects [49]. The rapid detection of *Salmonella enteritidis* on sandwich immunoassay the surface Plasmon resonance immunosensor attached with functionalized iron oxide magnetic nanoparticles with antibody reported. The immune-MNPs measured the refractive index changes linking with analyte binding in low concentrations and analyte delivery to sensor surface rapidly. However, the surface Plasmon resonance developed immunosensor provides a low cost, simple, and sensitive foodborne pathogens detection *in situ* [50]. The yolk-shell Fe_3O_4@C nanoparticles retained the properties of magnets used for concentration and separation due to their multifunctional biosensing for glucose and H_2O_2 label-free colorimetric detections. The yolk-shell Fe_3O_4@C YSNs obtained by selective etching process of SiO_2 with spherical shape and 220 nm in size were reported [51]. MNPs have been extensively investigated for their ability to mimic enzymes such as catalase, peroxidase, superoxide dismutase, and oxidase [52]. Although the effectiveness in cost, numerous uses, and resistance to harsh conditions such as a wide variety of pH, temperatures, denaturation, and storage impact, these nanoparticles, often

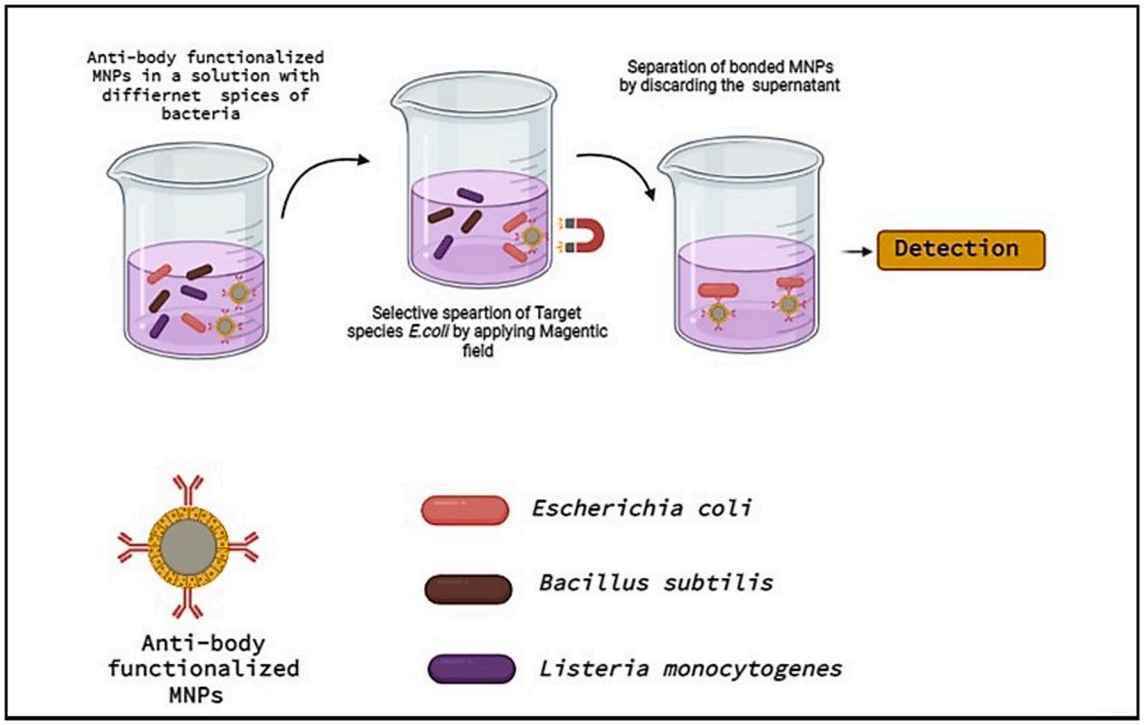

Fig. 5. Schematic illustration of MNPs based detection method for capturing and concentrating target cells of *E.coli.*

known as nanozymes, have surpassed natural enzymes in terms of interest [53]. Nanozymes, which have artificial enzyme-like activity, have been used to detect biomolecules such as glucose, H_2O_2, glutathione, nucleic acids, urea, serotonin, and creatinine. Electrodes modified MNPs to detect various biomolecules with minimal inference, high sensitivity, and rapid response. The Ag@MWCNT-IL-Fe_3O_4 nanocomposite modified with magnetic glassy carbon electrode promotes the electrons transfer reactions of glucose oxide and the morphology of 3D pores structure, uniformly distributed, and 10–15 nm in size is observed [54]. As a biomolecule, glucose use to demonstrate the use of MNPs in biosensors. Compared to colourimetric assays, a modified electrode with nanocomposites develops to facilitate direct electron transfer from GOx for glucose detection [55]. To detect tumor markers such as α-fetoprotein, an immunosensor based on electro-chemiluminescence is used [56]. The majority of glucose sensing techniques depend on reactive oxygen species by MNPs with oxidase/peroxidase activity [54]. The MNPs uses in hyperthermia were listed in Table 1.

2.5. Molecular imaging

The recent development in MNPs arises the era of personalized approaches for therapeutic in clinically controlling the patients of cancer. MNPs with novel physicochemical properties observed with multifunctional capabilities for imaging, with improving stability, biocompatibility, safety, thermal and photodynamic responses, and signal of imaging [57]. However, for magnetic resonance imaging, the MNPs are explored extensively with a versatile platform. MNPs can use as imaging tools for MRI-optical, MRI-radioisotopes, and T1–T2 MRI. Currently, the researcher focused on the emerging imaging through magnetic such as magneto-motive ultrasound imaging, magnetic particle imaging, and magneto-photoacoustic imaging [58]. Cellular and molecular imaging denote to the visualization of the targeted cells and molecules in an intact animal. MRI provides various advantages in safety, high-resolution imaging which is functionally relevant to be identified among various types of tissues [59]. The stimuli-responsive ligands design to interact with numerous physicochemical aspects, which lead to improvement of MNPs in cancer targeted imaging, its therapy, and diagnosis [60]. Although the role of MNPs explores extensively, the probing in magnetic resonance imaging depends on the structural features of MNPs in atomic and molecular scales.

The relationships among structures depend on the shape, size, structure of a crystal, assembled structure, and surface modifications [61]. Early cancer can identify through magnetic resonance imaging and magnetic hyperthermia, so the MNPs can be attached to the system to diagnose cancer with proper drug delivery and treatments [62]. The superparamagnetic iron oxide nanoparticles curcumin binds to amyloid plaques, and then these MNPs were coated with polyethylene glycol-polylactic acid block copolymer and polyvinylpyrrolidone through antisolvent precipitation. The stable, spherical, 10 nm sized and biocompatible curcumin MNPs were produced in a multi-inlet vortex mixer. However, these MNPs diagnose Alzheimer's disease in transgenic mice with magnetic resonance imaging, which was observed with great potential to diagnose Alzheimer's disease with MRI [63]. However, every imaging system has its own set of benefits and drawbacks. Not only may a single system provide complete information in biological systems. While Iron oxide NPs initially designed to be used as Magnetic resonance imaging difference agents, advancements in coating technologies have permitted the attachments of additional practical moieties for imaging, such as those for optical and nuclear imaging. Complementary imaging modalities that work together to provide more detailed information *in vivo* may integrate into these multifunctional Iron oxide NPs as shown in Fig. 6. The use of polymers on the iron oxide nanoparticles surface, such as chitosan, has aided these developments by providing many reactive sites for the addition of imaging moieties using simple amine-reactive chemistries [64]. The evolved magnetic nanosensor technology's unique detection method allows for rapid detection of a target without the need for extensive sample purification or signal amplification. Since light is not used in the assay (as in fluorescence, absorbance, chemiluminescence, and so on), the results are unaffected, and tests can perform in turbid, light-impermeable media like blood, culture media, cell suspensions, lipid emulsions, and tissue. Since the assay does not involve the sample immobilized on a flat surface (such as microarray glass slides), hybridization and binding kinetics are faster [65]. Iron oxide nanoparticles are synthesized with PEG and PEG/PEI by

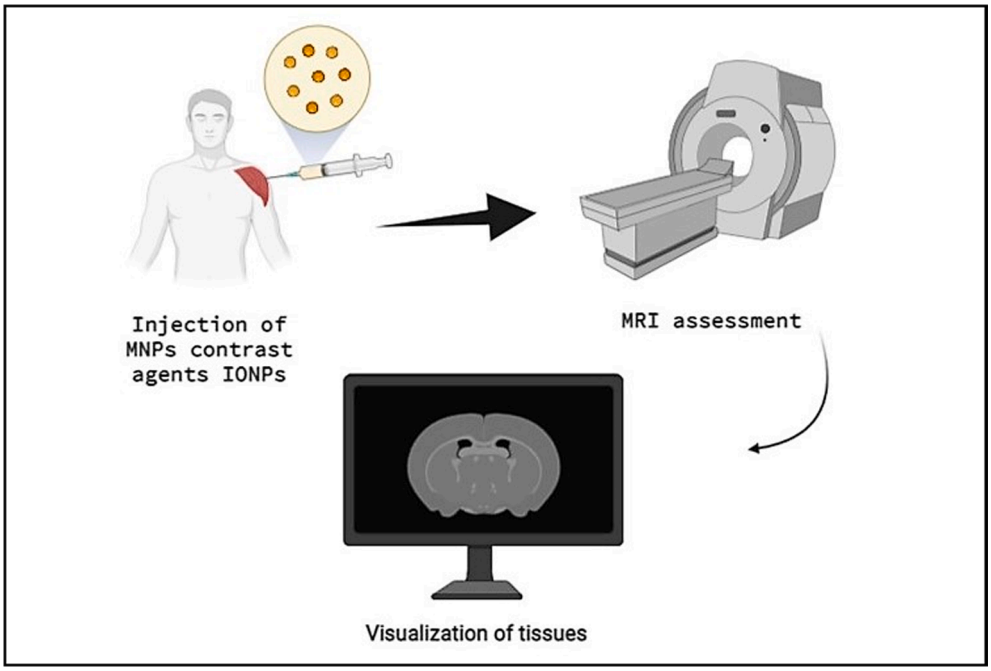

Fig. 6. Schematic illustration of IONPs contrast agent for the diagnosis of cancer with MRI.

the thermal decomposition process having excellent colloidal stability in phosphate buffer saline, with 19.5, 21, and 24 nm in hydrodynamic size which can be observed with low cytotoxicity by MTT assay. These modified MNPs show great potentials for mouse brains as MRI contrast agents [66]. The MNPs uses in MRI were listed in Table 1.

2.6. Disease diagnostic

The ability to characterize uncommon biomarkers in easily accessible bodily sources (e.g., fine needle aspirates, biopsies, and whole blood) quickly and sensitively would profoundly affect life sciences and clinical practice [67]. Magnetic nanoparticles (MNPs) possess several physical and chemical properties that make them promising synthetic platforms for creating novel chemical, biological and analytical detection systems [68]. Besides, nanomaterials characteristics and properties allow a potential for theragnostic to detect and treat various diseases. The personalized theragnostic nanomedical therapy by conjunction with MRI with iron oxide MNPs therapy is a newly arise concept [69]. These MNPs can be found everywhere as imaging modalities agents for therapeutic, theragnostics, and bio-sensing agents [54]. Multifunctional magnetic nanoparticles proposed as a new DNA preparation technique that saves time and money and is a way to detect DNA point mutations. Exogenous material identification, protein immobilization, and bacteria capture by nanoparticles are all methods of high sensitivity. As MRI contrast agents, several generations of nanoparticles are commercially viable. The use of magnetic nanoparticles in medical diagnosis is a novel method [68].

The detection and separation of various strains of bacteria with magnets gain much importance with the use of MNPs recently [70] as shown in Fig. 7. Although, with MNPs and multimodal imaging fused with MRI and other imaging tools widely used in detecting and diagnosing diseases [71]. Platelet-derived vesicles with proteins membrane obtained from the blood of mice coated on the iron oxide MNPs. The platelet-mimicking PLT-MNs were synthesized through PLT vesicles, clustered with MNs and coated with PLT vesicles, where the PLTs isolated from the fresh mice blood with pores 200 nm in size. However, the platelet-derived MNPs could inherit long-term circulation and target cancer, observing MRI and photothermal therapy. These biomimetic can

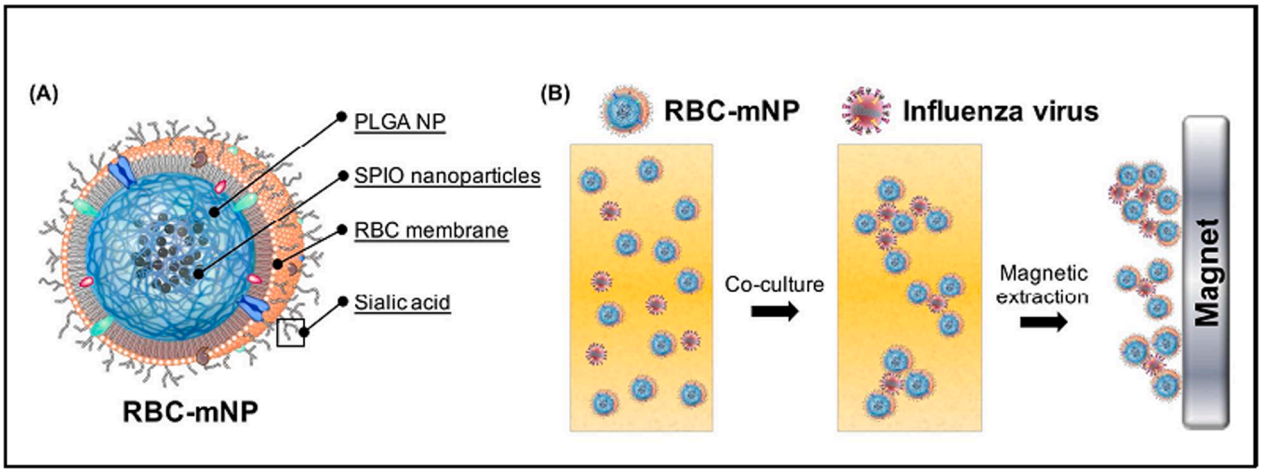

Fig. 7. Schematic illustration of erythrocyte membrane cloaked MNPs [73]. Copyright 2017, American Chemical Society.

use in the therapy and diagnosis of various diseases [72]. The erythrocyte membrane masked nanoparticles were modified with magnetic functionalities used against the isolation and target the influenza model virus with mimicking characteristics. These cell membrane cloaked nanoparticles were formed by the coupling of the nanoparticles similarly in size and the cell membrane vesicles with PLGA cores of 227.0 ± 7.0 nm as shown in Fig. 5 [73]. Iron oxide MNPs provided good platforms for bacterial pathogen therapy and diagnoses due to their magnetic properties due to these MNPs in bioimaging agents, magnetic hyperthermia, and drug delivery to treat infections caused by bacteria [74]. The antibodies derived MNPs were observed as a biomarker for Parkinson's and Parkinson's dementia disease, with ultra-sensitive IMR to assay the plasma α-synuclei, where the hydrodynamic antibody is functionalized with MNP Fe_3O_4 of 40 nm[75]. Although MNPs had the magnetic susceptibility biocompatibility to cross the blood-brain barrier, overcoming the hurdles and MNPs can be the best option to treat and diagnose the diseases of the central nervous system [76]. The MNPs uses in disease diagnostic were listed in Table 1.

2.7. Magnetic nanoparticles in the diagnosis of COVID-19

Coronavirus infection COVID-19 is caused by a virus strain that causes a respiratory infection known as severe acute respiratory syndrome coronavirus-2 [77]. Furthermore, the rapid spread and mortality rate makes it too dangerous for immune-compromised patients. Nanotechnology is the advanced technology that provides a better platform for diagnosing and treating COVID-19 [78,79]. The use of MNPs to capture the biomolecule, allows the simple, fast, and efficient methods to extract and purify biomolecules [80]. However, for the diagnosis, RT-PCR molecular-based techniques are widely used to diagnose accurately and timely but are time-consuming and labor-intensive. Hence, the poly amino ester and carboxyl group coated MNPs synthesize to extract viral RNA to detect the COVID-19 causing virus with great potential, based on the lysis and the binding mechanism may be used for *in vitro* diagnosis such as virus extraction. Therefore, then the isolated RNA was introduced to RT-PCR reactions with a simple way to purify the viral RNA within 20 min, to identify two regions of (N gene, and ORFlab) of the viral RNA. Although this method is excellent and straightforward, reducing a long time to early diagnosis of COVID-19 [81] as shown in Fig. 8. The zinc ferrite nanoparticles were reported, which are surface-functionalized with silica and carboxyl modified with polyvinyl alcohol, which observes the isolation from a specimen of viral RNA with an automation process as shown in Fig. 6. The zinc ferrite NPs was obtained by the synthesis through combustion, and the surface was functionalized with carboxyl modified polyvinyl alcohol and silica. The morphology was nanocrystalline and spherical. Moreover, this protocol is needed to diagnose the COVID-19 at a molecular level early [82]. Homogeneous biosensing which is based on MNPs is the most promising process for highly sensitive and rapid detection of biomolecules. Functionalized MNPs (BNF-80 NPs with protein A) with SARS-CoV-2 by the magnetic response in AC magnetic field for rapid and sensitive detections were achieved. The mimic SARS-CoV-2 includes spike proteins and polystyrene beads used for detection, which provides a rapid and sensitive diagnosis process for SARS-CoV-2. Hence, the functionalized MNPs work as a sensor to detect the mimic virus which includes the 100 nm PS beads in conjugation with SARS-CoV-2 spike proteins [83]. Furthermore, the diagnosis and treatments of SARS-CoV-2 are challenging and need more research to obtain valuable solutions to overcome these situations.

2.8. Future prospects and challenges

Magnetic nanoparticles have been used in diverse fields such as agriculture, biomedical, environmental, catalysis and biosensing. In this review, we summarize recent developments in the field of biomedical applications of MNPs. Various synthetic methods have been used to produce MNPs with many promising properties. MNPs conjugated with various biomolecules such as chemicals, nucleic acids, and enzymes have been used in research with a wide range of applications. In addition to gene delivery and genes expression, host cells can be efficiently used with good results. Nano-based cancer therapies and nanomedicines provide a safe and effective platform. However, various types of MNP

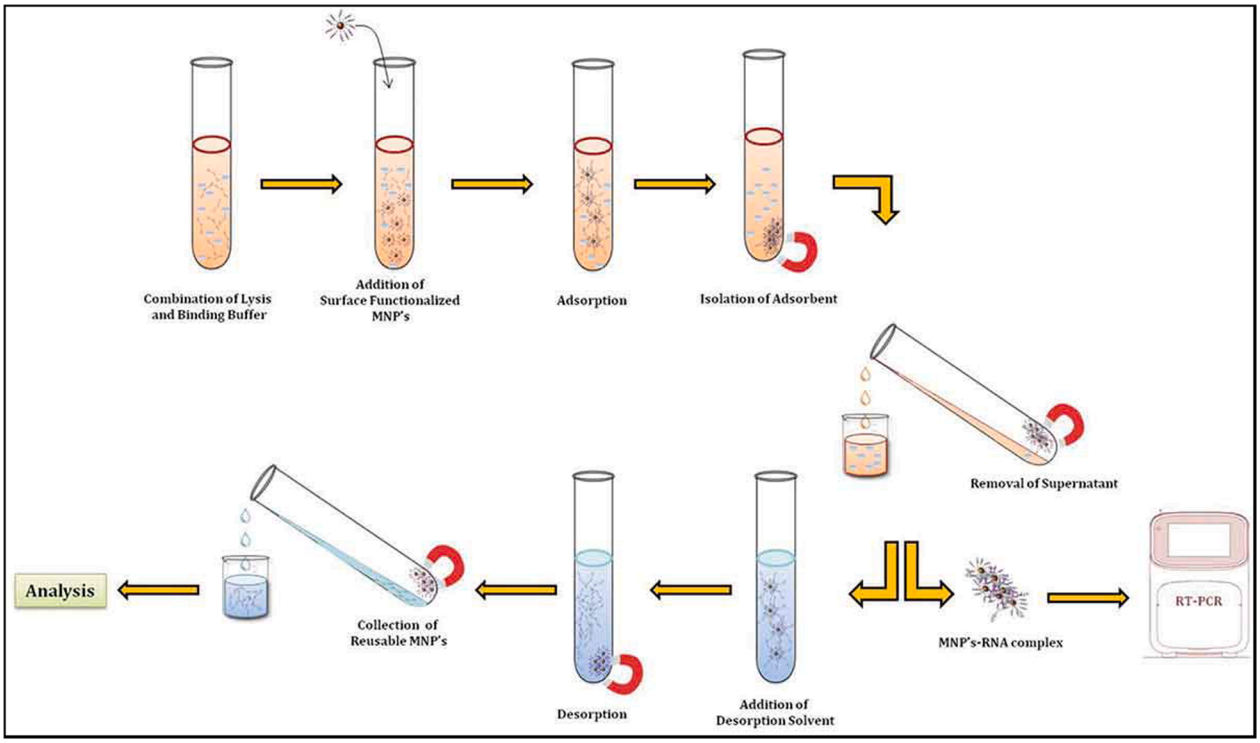

Fig. 8. Schematic procedure for surface functionalized MNP's assisted RNA-extraction [81]. Copyright 2020 Taylor & Francis.

modalities are have been clinically investigated for cancer therapies and cell imaging. In addition, MNPs for magnetic hyperthermia and drug delivery–based biomedical applications have emerged because of their bioavailability, solubility, metabolism, permeability, excretion, identification of various medicines, and cell internalization. In drug delivery, MNPs play a greater role then conventional drug delivery due to the drug dose and reduce their side effects. In addition, magnetic hyperthermia has synergistic effects that improve drug delivery systems with engineered MNPs. In recent decades developments in microdevices and nanodevices have led to better therapeutic and diagnostic tools in oncology. The recent development of MNPs has led to an era of personalized therapeutic approaches for the in clinical control of patients with cancer. MNPs with novel physicochemical properties observed have multifunctional capabilities for imaging, with improved stability, biocompatibility, safety, thermal and photodynamic responses, biosensing, and signal of imaging. MNPs face critical biological barriers in synthesis and formulations, such as effective drug delivery, localization to the target sites, and technical obstacles specifically to cancer. Bacterial resistance to widespread antibiotics is also a concern to serious health issues due to numerous multidrug-resistant strains, and the unavailability of new antibiotics will lead to a serious threat. In the recent decade the MNPs based procedures are developed for the treatment of infections that are caused by pathogenic microbes and to eradicate the biofilms with minimum resistance. COVID-19 infection is caused by a virus strain that causes a respiratory infection known as severe acute respiratory syndrome coronavirus-2. Furthermore, the rapid spread and mortality rate makes it too dangerous for immune-compromised patients. Nanotechnology is the advanced technology that provides a better platform for diagnosing and treating COVID-19. MNPs play a crucial role in the diagnosis of COVID-19. Although, the diagnosis and treatments of SARS-CoV-2 are challenging and need more research to obtain valuable solutions to overcome these situations

To overcome these challenges, constructive and critical research is demand for the fabrication and designing of MNPs in biomedical fields. In addition, a regular connection and mechanism are required for conducting between the researchers and institutions to develop specific and standard platforms *in-vivo* to perform the pre-clinical and clinical trials. For the practical implementation for cancer treatment and other biomedical application, MNPs faces an enormous number of challenges due to their biocompatibility and toxicity for long term. The scientific community requires addressing enormous kind of challenges and performing hassle-free clinical trials for the construction and development of MNPs for a better future.

3. Conclusion

Magnetic nanoparticles possess diverse properties, making them unique for applications in various sectors such as medicine, sensing, imaging, and environmental remediation, etc. As known, the average diameter of these nanoparticles is ranging from 1 to 100 nm and suitable for the applications in gene delivery to a specific cell or organ. Besides gene delivery, magnetic nanoparticle in the form of liposomes, and polysomic are used as carriers for drug delivery. Therefore, these nanoparticles are widely used in the field of biomedical applications, as discussed above. Similarly, it is widely used in molecular imaging, sensing, and diagnosis of various bacterial, fungal, and viral diseases. These nanoparticles could also be considered as promising agents for the diagnosis and treatment of coronavirus disease (Covid-19), which cause global havoc in the last two years.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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