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ABSTRACT

The ability to manipulate magnetic nanoparticles with external magnetic fields and their compatibility with biological systems make them versatile tools in the field of nanomedicine. Recently, the integration of various nanotechnologies with biomedical science, pharmacology, and clinical practice has led to the emergence of the discipline of nanomedicine. Owing to the special qualities of nanoparticles and related nanostructures, their uses in controlled drug and gene delivery, imaging, medical diagnostics, monitoring therapeutic outcomes, and supporting medical interventions offer a fresh approach to difficult problems in difficult areas like the treatment of cancer or crippling neurological diseases. The potential for multi-functionality and advanced targeting tactics in nanoparticle products exists. It may maximize the effectiveness of current anticancer drugs by enhancing the pharmacodynamic and pharmacokinetic characteristics of conventional therapies. These nanometer-sized substances' distinctive electrical, magnetic, and optical characteristics have opened up a wide range of biological uses. As they may be used in healthcare situations due to their bioactivity, iron-oxide-based magnetic nanoparticles, in particular, have been shown to be incredibly useful deep-tissue scanning tools. In addition to having a broader operating temperature range, smaller size, reduced toxicity, easier processing, and less cost of production, newer nanoparticles (MNPs) also offer other benefits. MNPs offer a lot of promise for use in clinical settings because of a variety of exceptional and distinctive chemical and biological features. Modern targeting techniques and nanoparticles studied in clinical trials are included in this review. It highlights the difficulties in applying nanomedicine items and transferring them from the laboratory to the clinical environment. It also addresses topics of nanoparticle design that might create new clinical applications for nanomedicine items. Magnetic nanoparticles used in nanomedicine offer several novel and promising features that make them valuable tools for various applications. When utilized in nanomedicine, magnetic nanoparticles have a number of exciting new properties that make them useful instruments for a range of uses. Drug delivery, hyperthermia therapy, magnetic resonance imaging contrast agents, diagnostic imaging and monitoring, theranostic applications, biocompatibility and biodegradability, remote control and manipulation, and responsive nanoparticles are the main factors that add to their novelty. In general, the amalgamation of nanoscale characteristics and magnetic properties presents a multitude of opportunities for inventive medical applications, offering focused, effective, and least intrusive approaches to diagnosis and treatment. The sector is still investigating novel ways to increase the safety and efficacy of magnetic nanoparticles in nanomedicine. The purpose of this article is to provide basic details about magnetic nanoparticles and the characteristics of these particles in biomedical applications. The features of these nanoparticles in medication delivery and their numerous uses have received extra focus in the study. It seeks to summarize current advancements in MNPs for medical applications and examine the possibilities of MNPs in tumor therapeutic applications, in addition to future study opportunities.

I. INTRODUCTION

Magnetic nanoparticles are being actively researched and utilized in the field of nanomedicine for a variety of applications. These nanoparticles are typically made of magnetic materials like iron oxide or iron–platinum and are often coated with biocompatible materials to enhance their stability and biocompatibility. Using an external magnetic field, therapeutic medications or molecules may be loaded onto magnetic nanoparticles and directed to precise target areas within the body. Treatment effectiveness can be increased and negative effects can be decreased with this tailored medication administration. In addition, when placed in an alternating magnetic field, magnetic nanoparticles may produce heat. This characteristic is used in magnetic hyperthermia treatment, which involves heating these nanoparticles selectively in the presence of an outside magnetic field in order to cure or kill cancer cells. Furthermore, magnetic nanoparticles can be employed in several imaging modalities, including magnetic resonance imaging (MRI), as contrast agents. They improve the visibility of particular tissues or structures, which helps with illness monitoring and early detection. Better imaging of tissues and organs is possible with the use of magnetic nanoparticles, which can increase the sensitivity and resolution of MRI images. Magnetic nanoparticles are a promising treatment option for blood purification in diseases such as sepsis since they may be used to extract toxins, infections, or certain biomolecules from the circulation. In cancer treatment, magnetic nanoparticles can be used for both drug delivery and hyperthermia therapy, making it possible to specifically target and treat cancer cells while minimizing damage to healthy tissues. Target cells can receive therapeutic genes through the use of magnetic nanoparticles as gene therapy carriers. To identify certain proteins, infections, or environmental contaminants, magnetic nanoparticles are employed in biosensors and diagnostic equipment. Magnetic nanoparticles have been explored for applications in the nervous system, such as crossing the blood–brain barrier and delivering drugs to specific regions of the brain. Although indications only arise at aggressive cancer levels, initial-stage cancer detection is of significant interest and difficult to prevent its spread. Very precise, quick, durable, non-invasive, or minimally invasive techniques are crucial. In this context, nanoparticles have already demonstrated their utility in medicine by applying imaging technology to the targeting and visibility of tumors, enabling early cancer detection. Targeted drug distribution is another biomedical use of nanoparticles. Intelligence nanocarriers might enhance treatment efficiency by transporting anticancer medications to a predetermined location where their release occurs without damaging healthy tissue.[1,2] Nanomedicine uses nanoparticles for diagnosing, detecting, monitoring, treating, and curing illnesses beginning at the molecular level using designed nanocarriers, which is the word for using gy for medical needs.[3] Using products and substances between 1 and 1000 nm in size characterizes nanoparticles as a complete research field.[4]

To handle lipid problems, inflammation and angiogenesis inside atherosclerotic plaques, and the protection of thrombosis, among other ailments, nanoparticles may offer a secure and efficient foundation for regulated medication delivery for various active components.[5] Nanocarriers are special because of their small dimensions, high specific surface area ratios, and advantageous physicochemical characteristics. They may alter medications' pharmacodynamic and pharmacokinetic characteristics, improving their treatment efficacy. Drug content on nanocarriers can improve *in vivo* behavior, prolong the duration a molecule spends in the bloodstream, and enable codrug-controlled release by enabling medications to accumulate, ideally near the tumor site. Nanomedicine substances can change how pharmaceuticals are distributed throughout the body.[6] At the heart of magnetic delivery methods are magnetic nanoparticles (MNPs), designed to target site-specific malignancies while potentially providing a controlled-release pattern appropriate for treating diseases. MNPs can be employed in nanomedicine as optional possibilities for medication-targeted treatment when employing an external load magnetic field because of their multi-functional dimension. MNPs could be created into drug delivery platforms with dimensions that are equivalent to the organism's antibody Levor molecules for enhanced bioactivity while integrating therapeutic agents that might be challenging to distribute to cancerous cells because of their adjustable physicochemical characteristics as well as the large ratio of surface to volume standard for nanomaterials.[7] To upgrade existing systems for *in-vivo* usage, MNPs must be involved. Since the polymer shell functions as a compatibilizer that communicates with its surroundings, providing functional places that are catalytically or biologically effective, and since MNPs have unique characteristics that allow manipulation of the processes, combos of MNPs and polymers are appealing to investigators interested in creating stable composite or colloidal processes. Figure 1 illustrates the many applications of MNPs, including biological separation, hyperthermia, catalysis, MRI, magnetic drug target delivery, nucleic acid and cell separation, COVID-19 detection, and biosensors.

Nanoparticles have been discovered to help gather data at all phases of clinical procedures due to their application in several innovative tests to cure and diagnose procedures. The major advantages of these nanomaterials are linked to their surface characteristics because different proteins could attach to the surfaces. For example, nanoparticles are utilized as tumor tags and indicators in various

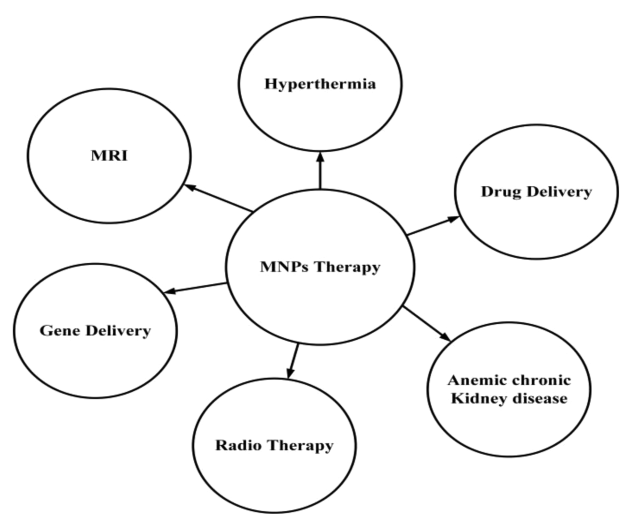

FIG. 1. Various biomedical uses of MNPs for therapy.

biomolecule identification procedures. When using nanoparticles for the delivery of drugs, the physical properties of the medication are taken into consideration when choosing the nanoparticles. Using bioactive natural chemicals with nanoelectronics is highly appealing and has grown significantly in recent years. When it comes to the distribution of natural remedies for treating cancer and numerous other disorders, it offers several benefits. A wide range of unique properties of natural products, including their ability to induce tumor-suppressing autophagy and their ability to act as antibiotics, have led to extensive research into their potential as therapies for many disorders.[8]

Such procedures involve highly sensitive magnetic nanoparticles and feasible magnetic application devices to be fully clinically effective. Nanoparticles flow along a magnetic field's gradient, and frequently, magnetic values are decreased to zero just a few millimeters away from a permanent magnet. This makes it difficult to create magnetic properties that sufficiently affect particle movement inside organisms. Higher force gradients may be achievable with novel magnetic field deployment techniques, enabling the material's movement far deeper inside the body.[9] Moreover, as such information is necessary for any therapeutic application, systems that can successfully predict magnetized particle mobility in complicated *in vivo* environments will be needed. Finally, the therapeutic effectiveness of these novel models and systems will depend on using extremely sensitive, less harmful magnetic nanoparticles. When a tumor is discovered, it has only a 50% chance of spreading locally. In these circumstances, it may be addressed using tried-and-true techniques like radiotherapy, systematic chemo, or even tumor antibodies. For the remaining 50% of cases, potential surgery treatments are not accessible. A combination regimen of systematic radiation therapy and chemotherapy treatment treats tumors with significant local dissemination.

Nanoparticles (NPs) have drawn the interest of investigators from various fields, including physics, chemistry, engineering, and biology, to synthesize, comprehend, and develop new potential applications. MNPs have been used for scanning, diagnostics, biocatalysis, immobilization, regulated medication administration, prolonged and directed hyperthermia, and the treatment of cancer.[10] Magnetic nanocomposites, metal oxides, and pure metallics are the typical classifications for magnetic NP. MNPs must possess an adequate degree of bioactivity and should not cause inflammation or cytotoxic responses in the body to be used as a nanocarrier for therapeutic purposes. Just iron nanoparticles, especially its two oxidations, including magnetite and maghemite, can satisfy these restrictions given the diverse magnetic nanoparticles.[11] Because iron is present in so many bodily organs, including the heart, spleen, and liver, and because it serves as the structural basis for important biological molecules like hemoglobin, myoglobin, and ferritin, they are biocompatible.[12]

At pH 7, MNP ought to have high solubility in water. They must also demonstrate an elevated magnetization level to regulate their circulatory transit using magnetism and immobilize them within specific sick tissues. MNPs may enter cells by endocytic means and have several desirable characteristics, including a large surface area, a high specific surface area ratio, the flexibility of separating using outside magnetic fields, rapid mass flow, and the potential to be functionalized for stimuli-responsive impacts.[13] A significant estimation of the homogeneity level in NP dispersion is the polydispersity index (PdI). Its value normally ranges from 0 to 1, with a rise in PdI values indicating a larger size dispersion in the NP collection. Monodisperse NP samples are those with PdI values less than 0.1. Changes in the PDI can be utilized to detect aggregating or physical instabilities.[14] The efficient treatment uses the mono-dispersibility of NP since it allows for precise estimation of their pharmacokinetic behavior after delivery.[15]

With an emphasis on the methods of focused and imaging-assisted drug administration, this review gives an overview of current developments in the creation and use of MNPs for the delivery of drugs. MNP kinds, characteristics, drug delivery systems, active targeting strategies, and therapeutic application are only a few subjects covered in this domain.

The anticipated contributions of this review paper are as follows:

- This paper presents a comprehensive analysis of the most recent advancements in the area of magnetic nanoparticles and gives a wide-ranging summary of their uses in nanomedicine.
- The incorporation of magnetic nanoparticles into biomedical applications, particularly in the administration of medications, is a major topic of discussion in this study. With the increasing interest in using nanotechnology to improve medication distribution methods and healthcare, this concern is essential.
- The work addresses novel uses for magnetic nanoparticles within nanomedicine, including hyperthermia treatment and the specific delivery of drugs.
- In the framework of innovative therapeutic alternatives, this study highlights the clinical application of magnetic nanoparticles.
- It offers a basis for knowing the present state of the practice and acts as a basis for more study and advancement in this exciting field of nanomedicine.

The following portions of this paper are arranged as follows: In Sec. II, they give a summary of the many varieties of magnetic nanoparticles. The therapeutic properties of MNP are discussed in Sec. III. A detailed presentation of nanomedicine-based cancer therapy is provided in Sec. IV. An overview of inorganic nanomedicine-based cancer therapy is provided in Sec. V. In Sec. VI, a magnetic particle characteristic is reviewed. Section VII provides an explanation of the magnetic nanoparticles' properties. A detailed presentation of nanoparticles in medicine is provided in Sec. VIII. Section IX presents the use of nanotechnology. Food and Drug Administration-approved nanomedicines are included in Sec. X. The conclusion is finally provided in Sec. XI.

II. COMPREHENSIVE EXPLORATION OF MAGNETIC NANOPARTICLES IN NANOMEDICINE

The review deals with many different things related to using tiny particles in medicine, especially magnetic ones. This explores the different kinds of tiny particles that have magnetism and their special qualities, like being able to help with healing. The article talks more about how nanomedicine can be used to treat cancer, and it shows how it has the potential to be very effective. In addition, it shows how small particles not made from living things can be used to treat cancer and gives a detailed look at the characteristics of magnetic nanoparticles. This text is about how nanotechnology is used in different ways in medicine. It also talks about the rules and regulations that govern these medical technologies.

The article deals with using tiny particles called nanoparticles in medicine, specifically focusing on magnetic nanoparticles. This text talks about different kinds of small magnetic particles and what makes each of them special, especially their ability to help with healing. The article discusses how nanomedicine can be used in cancer treatment and highlights the exciting possibilities it offers. Moreover, it talks about using tiny particles in cancer treatment and thoroughly examines the traits of magnetic particles. This text talks about how nanotechnology is used in medicine. It also mentions that there are some medical treatments that have been approved by the FDA. It explains how these treatments are regulated.

III. NANOPARTICLE IN THE MEDICAL FIELD

A. Material

Ferrites with the basic chemical formula M (Fe_2O_4), where M may represent a divalent action like nickel, cobalt, magnesium, or zinc, magnetite (Fe_3O_4), and magnetite are the three most popular types of magnetic nanoparticles (Fe_2O_3). Nickel, cobalt, and iron are a few examples of novel nuclei.[16]

B. Types of nanoparticles in medicine

The preparation techniques used, such as the emulsified polymerization process, mini-emulsion polymerization, microemulsion polymerizations, and emulsion-solvent evaporative cooling procedures, all have a significant impact on the morphological features of polymeric NPs (such as spheroid, bolts, and diskettes), size and shape distribution, and physiochemical properties. Nanospheres, or microcapsules, are two different types of polymeric nanoparticles. The active chemicals can be deposited on the material surface or retained in the NP matrices by either physical encapsulation or chemical coupling. Nanostructures are large colloidal NPs (whose shape does not always remain round). The application of chitosan in biosensing is a particularly intriguing field of study. Chitosan was able to be conjugated into a variety of nanomaterials because it contains amino and hydroxyl sites. This sparked research and the creation of chitosan-nanocomposite-based biosensing, which monitored glucose, DNA, and proteins. These sensors also use nanotechnology and several other polymers. Excellent research observed encouraging outcomes when everolimus was delivered to lungs mesenchymal cells specifically and specifically utilizing chitosan-based particles covered with hyaluronic acid. Chitosan and gelatin were used to create a nanocomposite scaffold that contained bovine serum albumin and basic fibroblast growth factor (bFGF)-loaded chitosan nanoparticles (BSA). The findings showed continuous production of a protein, together with a notable increase in fibroblast cellular proliferation. Moreover, Cai *et al.*[17] created auto-fluorescent gelatin nanomaterials that were MMP-responsive probes for imaging cancerous cells. The work established a straightforward synthesis method, demonstrated the bioactivity of polymers, and gave a clever method to watch the behavior of cancer cells. Cai *et al.*[17] revealed intriguing outcomes for oral subcutaneous insulin delivery using chitosan- and sodium tripolyphosphate-based nanoparticles loaded with adrenaline.

C. Core shell structure

Metallic cores covered with biomaterials, which are increasingly used for simpler processing and superior management, are

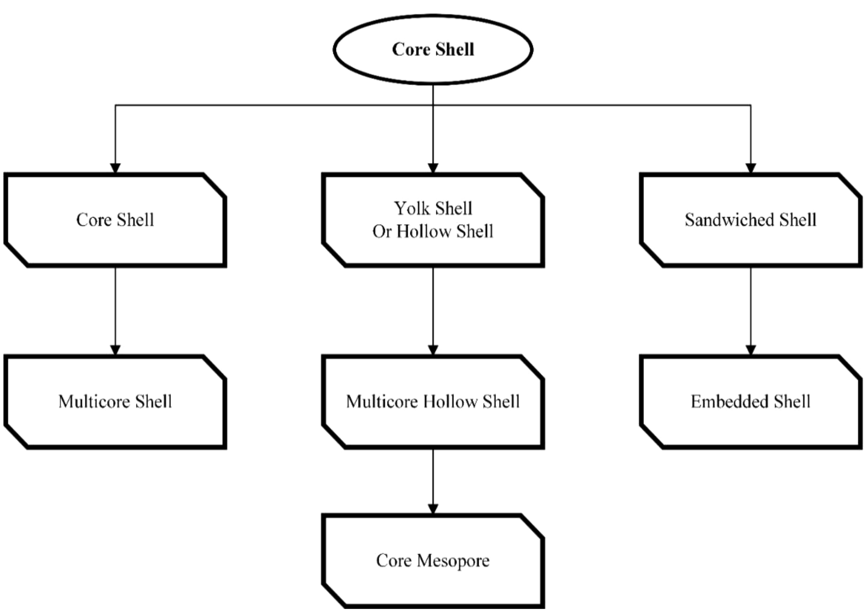

FIG. 2. Types of core shell.

mentioned in Fig. 2. Magnetite nanoparticles that have structural properties and magnetic iron oxide that is either in the form of magnetite (Fe_3O_4) or magnetite (Fe_2O_3). Substances like silica, dextran, polyvinyl alcohol (PVA), or gold and other metals that may be packed together are used to create the structure model; such particles are created by ionic and non-ionic surfactants or by encapsulating inside of peptides or carbon cages such as ferric. The analytical numerical methods investigated in the literature[18–30] are used to investigate the structure model of these particles. Carboxylic, amino group adsorption, biotin, streptavidin, or antibodies then functionalize these particles.

It takes the form of biocompatible porosity resins that contain magnetic nanoparticles. This approach's benefits include generating particles with spherical shapes and a comparatively small size variation.

IV. MAGNETIC NANOPARTICLE TYPES

In addition to having unique relevance in physical theory, magnetic nanoparticles (MNPs) are a novel form of nano-magnetic substance with several uses in the biomedical industry. MNPs are typically magnetized composite materials made of metals and their oxidation, such as iron, nickel, cobalt, etc. Typically, X-ray distribution (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and other techniques are used to characterize the structural features of MNPs.[31] MNPs are typically superparamagnetic and mostly composed of superparamagnetic nanoparticles of iron oxide when their dimension is smaller than 50 nm (SPIONs).[32] Such MNPs are currently mostly utilized to research the functioning of MNPs *in vivo* since they display non-permanent magnetization or the ability to become magnetized in the presence of an external magnetic force. The tracking techniques apply to magnetized nanoparticles. They may transport a range of tiny molecules, proteins, RNA, etc., because of their enormous specific surface areas. Nanometal particles' magnet characteristics make it simpler to enhance, segregate, transport, and identify them in different directions. Under high-frequency magnetism, MNPs have a magnetocaloric action that can inadvertently kill tumor cells.[33] Nowadays, MNPs are often employed in medicine for therapy, medication administration, supplemental evaluation, and identification.

A. Magnetic nanoparticles with a silica coating

Magnetic nanoparticles coated with nanosilica are silica-coated magnetic particles ($nSiO_2$). Because of their outstanding thermal properties, magnetic characteristics, chemical stability, and non-toxicity, compounds have received greater attention.[34] Interaction with organosilane molecules is a typical technique for modifying silica-based substances to provide the possibility for an organic synthesis process. Recently, it has become a growing sector, and most applications use SPIONs.[34] Nanomaterials with spherical shapes are called $nSiO_2$ microspheres. They have received much study and use in medication transporters and controlled drug release in recent days. By injection, percutaneous infiltration, or inhalation, $nSiO_2$ microspheres can enter living things. Among these, inhaling through the lungs allows the $nSiO_2$ microparticle drug-carrying device to immediately pass the "blood–lung barrier" and enter the bloodstream, attaining systemic administration.[35] A novel class of magnetized silica nanoparticles may be created by wrapping iron oxide nanoparticles in $nSiO_2$ microparticles. The silicon surfaces can then be functionalized using –COOH, –NH2, or –OH to continue to respond.

B. Magnetic nanomaterials with a lipid coating

Magnetic liposomes are colloid structures created whenever phospholipid bilayers encircle magnetic nanoparticles. A nano-scale iron oxide-phospholipid combination was the subject of the initial theory and description of magnetized liposomes. It is common practice to manufacture lipid-coated magnetic particles utilizing microemulsion and various emulsified processes.[36] Emulsions are bioreactors for creating iron oxide bodies with lipid coatings on magnetic particles. The base of a traditional magnetic liposome is an iron oxide substance with a dimension of around 14 nm, and the outside is covered with a phospholipid bilayer. This particuliposome's interior cavity is filled with i particles. This magnetized liposome exhibits elevated iron oxide body concentrations to ensure maximum cytotoxicity. This arrangement can enhance the absorption of iron by cells at low temperatures. It is among the most important cell magnetic indicators because of its excellent biocompatibility, targeted selectivity, and other benefits, notably magnetism liposomes formed on SPIONs as a T2 contrast material broadly employed in nuclear magnetic resonance.[37] The phospholipid bilayer serves as the skeleton of the vesicle-type magnetic nanoparticle, a unique structure of the MNP scattered throughout. Vesicle-type nanoparticles are a subclass of liposomal particles that have recently drawn attention from researchers because of their superior drug-holding ability. By utilizing dimensions excluding chromatography to incorporate superparamagnetic maghemite particles in lipid unilamellar vesicles, it is easy to create vesicle-type magnetic particles.[38] Vesicular magnetized liposomes can be categorized into one of three groups based on where the magnetic nanoparticles are located within the liposomes: Liposomes containing hydrophobic MNPs in the internal aqueous cores, hydrophobic nanocomposite liposomes that are enclosed in a phospholipid bilayer, and MNPs that are implanted on the exterior of the phospholipid membrane all include hydrophobic MNPs in the aqueous solution.[39] The MNPs comprised of vesicle-type magnetized liposomes are typically 1–10 nm in size. Therefore, there will not be any issues with blood capillary obstruction or aggregation. It may be easily expelled from the body because of this property. It is utilized in biomedicine as a medication transporter, hyperthermia intermediate, and magnetic resonance contrasting agent due to its excellent biocompatibility and low toxicology.

C. Magnetized nanoparticles with a polymer coating

Polymer nanocomposites were created at the point where the areas of polymeric material and inorganic nanoparticles met. Owing to MNPs' high energy content and substantial surface area, which make it challenging to distribute them evenly in polymers, their study and use are severely constrained. Therefore, improving these phenomena through polymer modification is a good option. Presently, two processes—chemical covalent bond alteration and self-assembly—are used to create magnetized polymeric drug carriers.[40] As the study has progressed, several scientists have altered the active groups on the surfaces of MNP transports and packed biomolecules with functionalities that respond to stimuli on the carriers dependent on MNPs. This has been built upon to create a responding magnetized polymeric drug-carrying platform consisting of several smart nano-drug-controlled-release devices.[41]

D. Superparamagnetic iron oxide nanoparticles (SPIONs)

The most significant component of magnetic nanoparticles is oxidized iron, primarily Fe_3O_4 and Fe_2O_3. Significant paramagnetic energy may be produced because of the sequences of delocalized electrons outside of the nucleus of the iron, which create a net magnetism vector. Iron oxide nanoparticles will display superparamagnetic behavior whenever their dimension is below a certain cutoff at the legal limit. Aggressive pressure and magnetization will both decrease concurrently. When a nanoparticle is exposed to a magnetic field, it can become magnetized very fast, and when the magnetic field is eliminated, the magnetization rapidly dissipates. A nanoparticle called SPION, which has a crystalline core made of Fe_3O_4 or $-Fe_2O_3$, with a dimension of 10–100 nm, can create high magnetization in an exterior magnetic field but loses that magnetization when the exterior magnetic field is removed.[42] Microemulsions, laser pyrolysis, and sol–gel procedures are a few techniques for creating nanoscale metal cores. Nonetheless, co-precipitation and thermal degradation are the two primary processes for their formation. Due to its superparamagnetic characteristics, SPION has seen extensive usage in the biomedical realm. Several SPION formulations are being tested in medical studies, and it is becoming increasingly clear that they are effective.[43] SPION is biocompatible in a positive way. For those with impaired liver and renal functioning, this could bind to hemoglobin through the body's natural physiologic and metabolic processes to prevent buildup. SPION can also increase T2WI and decrease T2WI signal intensity. It has significant application value in detecting, identifying, and treating tumors.[44]

V. HEALING CHARACTERISTICS

Despite significant advances over the 21st century, the average lifespan is still short in several places, and malignancy is a frequent and growing primary cause of severe medical problems and increased mortality. In the European Union exclusively, it is projected that 1.3×10^6 people will die from cancer in 2022.[45] MNP compositions induce a range of tumors and malignancies. The shift of MNPs from basic research to practical alternatives in oncologic therapy, theranostic usage, and drug delivery methods represented a milestone. MNPs immobilized with antibodies can produce potent sensing platforms. Numerous biological uses, such as the therapy of cancer and malignant cells, have been identified.[46]

A. Delivery of drugs

A wide range of MNPs and targeted drug loadings are now covered by systems for drug delivery, incorporating intraocular distribution using intelligent microrobot technologies or the distribution of erythropoietin-hybridized MNPs for the therapy of nervous system injuries.[47] The toxicity of magnetized nanosystems for the distribution of conventional platinum-based anticancer drugs was studied *in vitro*.[48] It has been demonstrated that form has a significant role in cytotoxicity, with spherical-shaped NPs being much less harmful than analogous cylindrical or elliptical shapes, particularly when the quantity of reactive oxygen species (ROS) is elevated.

TABLE I. The summary of current drug distribution criteria for drug-delivery treatments.

References	Nanoparticles types	Creation of MNPs and coatings	Medication or molecular type	Particular illness/application
52	$NiFe_2O_4$	Trichloroacetic acid (BTC) serves as the organic binder for MOF in the core-shell method	Adsorption of curcumin in a mesoporous hosting	Delivery of drugs
53	MMS using Fe_3O_4	Co-precipitation and the W1/O/W2 technique for evaporating solvents from ternary emulsions	5-fluorouracil	5-fluorouracil
54	$ZnFe_2O_4$ using NHSs	Solvothermal technique	Doxorubicin	Therapy for cancer
55	Fe_3O_4 and SPIONs	Co-precipitation; stabilization of dextran (DEX)	Camptothecin (CPT) effect on AT3B-1 cancer cells	Prostate cancer
56	Fe_3O_4	PEG, hyaluronic acid, dextran, and conjugated human plasma albumin	Erlotinib, gallic acid, doxorubicin, cetuximab, quercetin, and actein	Lungs cancer
57	Using Fe_3O_4 NPs, the magnetic hydrogel	The technique of co-precipitation; production of hydrogel	Doxorubicin (DOX)	Hyperthermia and breast cancer

Effective drug distribution using MNP-coated nanomaterials necessitates a complete understanding of the drug molecule's proteic activity.[49] Pharmacokinetic behavior is of the highest significance as it can result in improved medication delivery and, as a result, more effective illness therapy and control. For efficient performance at the intended place, medicines, genes, and other physiologically significant compounds can be coupled with NPs. There have been several publications on uses for drug delivery that handle a range of difficult-to-target cancers or diseases.[50] Table I depicts the current drug distribution criteria for drug-delivery treatments.

B. Cellular medication absorption

Paclitaxel (PTX), also known by its brand name Taxol, is a chemotherapeutic drug used to treat a variety of cancers. The porous structure of MNPs that contains mesopores (Dp = 2–50 nm) significantly improves their ability to ingest various physiologically active chemicals. A thin line separates cellular uptake and aggregation, and MNPs must only assemble at the targeted area if malignancy or tumor cells are present.[51] The absorption of NPs by cancerous cells has been seen using other *in situ*/operando characterization techniques. Moreover, Raman spectroscopy was used for this goal whenever tumor cells were exposed to Co-NPs. When utilizing biomimetic MNPs, enhancements in cellular uptake were seen, confirming once more that the secret to getting beyond biological obstacles is to leverage other bio-inspired processes.[52]

C. Hyperthermia

Recent studies have examined magnetic nanoparticles studied for biological and thermal applications.[58] Uses for hyperthermia are of special interest because they could open up new avenues for diagnosing and treating illnesses and identifying, administering, and preventing cancer.[59] Several difficulties involving using a ferrofluid medium and crucial heat transfer problems have been researched. For applications involving therapeutic hyperthermia or the modeling of magnetic gel behavior under magnetic direction, discrete Fourier transform (DFT) modeling utilizing the Monte Carlo approach is also accessible.[60] The influence of Ti ions on MNPs' Néel relaxing, the release of drug modeling using the zeroth ordering, first order, Korsmeyer–Peppas or Higuchi model kinetic parameters, the magnetism decreases necessary for sustained hyperthermia, and other processes have all been the subject of detailed mechanistic investigations. Important characteristics of MNPs that correlate with how well they function in hyperthermia studies have been uncovered through theoretical models. A few of these studies have identified the ideal aspect ratio for the greatest warming impact. The temperature reduction process was revealed to be highly dependent on the heating rate of a core–shell magnetic NP structure, closing the loop in the heat treatment.[61]

D. Hypoxia

Hypoxia, when the body's tissues have inadequate oxygen supply, is a turning moment in the fight against cancer resistant to conventional or focused therapy. The hemoglobin molecules oxyhemoglobin and deoxyhemoglobin are created when oxygen attaches to hemoglobin. These two aspects undergo concentration changes that may be seen using the functioning MRI (fMRI) method: BOLD MRI.[62] Whenever H–MnFe$(OH)_x$ hydroxide nanocapsules were created with significant loading, for instance, employing a chemotherapy medication, doxorubicin (DOX), within both *in vitro* and *in vivo* actual evidence of antitumor synergies, degradable Fe-based nanohybrids were employed for hypoxia-modulated tumor therapy.[63]

E. Drug targeting utilizing magnets

At the forefront of biomedicine and diagnostics is finding an efficient therapeutic strategy for targeting cancer and tumors.[64] This is an outcome of conventional chemotherapy becoming nonspecific, allowing the potent anticancer medications to injure normal tissue. MNPs react to an outside magnetic field, providing a way to direct the distribution of magnetized nanocarriers carrying lethal drugs to the intended organ or tissue. This procedure is complicated by several factors, such as the speed of blood circulation, the way drugs are immobilized on MNP carriers, the poor diffusing controls after intravenous infusion, the shape of the afflicted organs, and their depths. Furthermore, accurate diagnosis is crucial for the survival of afflicted individuals to improve their chances of survival, particularly when the therapeutic formulations must target certain organs or tissues.[65]

Many organizations investigated the flow behavior of multidisciplinary team (MDT) as well as their capacity to enter various tissues, including ocular tissue. The regulation of NP aggregating is crucial and is handled by numerically solving the vorticity stream-function formulations when the targeting illness is located at the arterial segment.[66] Numerous research teams looked into the possibility of presenting multiple core MNPs of less than 50 nm via tissue of the cornea utilizing a magnetic field gradient of 20 T m^{-1} or the prospective disposal of MNP-tagged cytokines during cardiopulmonary bypass utilizing simulation studies depending on Navier–Stokes calculations.[67] The depth element of the tumor appears to be common since many study groups concluded that the greatest outcomes in MDT can only be reached when damaged tissues are near the body surface. In addition, understanding and improving the drug-delivery nanovehicles requires a thorough understanding of MNP activity in the coronary circulation system.[68]

F. Delivery of drugs on demand

Hybrid compositions with nanotechnology can discharge the loading molecules when needed, but they can also leak divalent cations from ferrous composites.[69] Theoretically, the magnetic core must maintain its integrity during its journey through the biological process; however, the leaching test described is crucial proof of its integrity.

G. Apoptosis

Another significant accomplishment of using SPIONs is the procedure of programmable cell death (apoptosis); HT-29 cells have demonstrated apoptosis by SPIONs.[70]

VI. CLINICAL CANCER TREATMENT USING NANOMEDICINE

Drug conjugates, viral vectors, polymer-based nanocarriers, lipid-based nanocarriers, and inorganic nanoparticles are only a few examples of the several kinds of nanomedicine substances that have been employed in therapeutic cancer treatment.

A. Cancer treatment with viral nanoparticles

Combining tumor-homing virus with medicinal protein expression is a sophisticated method of creating nanoparticles for cancer treatment. Myxoma and vaccinia strains of the pox virus tend to proliferate in tumor cells. Effective pox virus replication also benefits from unique traits of cancerous cells, such as blockage of apoptotic pathways, dysregulation of cell reproduction, and immune evasion.

B. Cancer treatment with organic nanocarriers

Several synthetic or natural substances intended for focused or non-targeted medication delivery compensate for organic nanocarriers. Pharmaceutical conjugates, lipid transporters, protein carriers, glycan carriers, and synthetic polymer carriers are the broad categories into which they may be separated. Although drug conjugates have successfully entered the clinical setting, there have been only hesitant attempts to do the same with nanocarriers consisting of lipids, proteins, or polymers.

VII. CONJUGATED DRUGS

Pharmaceutical conjugates have become the most effective nanomedicine therapies in the treatment of cancer patients. The small scale in the smaller nanometric range and subsequent conjugation to active pharmacological substances. The targeting peptide, antibody, and polymer are covalently attached to the active ingredients. The conjugation, which is often mono- or oligomeric, is designed to increase the drug's focused distribution while having little to no effect on the drug's solubility and stability. The medicine is often enclosed by nanocarriers made of lipids, enzymes, and glycans, eliminating the requirement to attach the medication to the carriers.

A. Nanocarriers with a lipid basis

Several lipid-based nanocarrier structures, liposomes, and micelles are among the most often studied. In comparison to ADCs, which generally contain 1–6 active ingredients per monoclonal antibody, lipid nanocarriers have a maximum capacity that is three to four times greater. Non-PEGylated liposomal doxorubicin, vincristine sulfate liposomes, non-PEGylated liposomal daunorubicin, liposomal mifamurtide, and non-PEGylated liposomal cytarabine are five further lipid nanocarriers that have been given the green light for therapeutic application.

B. Synthetic polymer-based nanocarriers

BIND-014 is the initial target of polymer nanoparticles in medical tests. It comprises PLGA-PEG nanoparticles targeting prostate-specific membrane antigen coated with docetaxel (PSMA). BIND-014 contains up to ten times more docetaxel administered to tumors than free docetaxel in several model organisms.

VIII. Cancer treatment with inorganic nanoparticles

Applications of inorganic nanoparticles range from drug administration to radiation enhancement to tumor imaging. The nanoparticles of iron oxide are mostly employed for diagnostics reasons, while they have also been evaluated in human clinical trials for tumor imaging using magnetic resonance. An aqueous colloidal distribution of nanoparticles of iron oxide is called NanoTherm®. An alternate magnetic field application is used to accomplish thermos-ablation after injecting the tumor.

IX. MAGNETIC PARTICLE CHARACTERISTIC

Several initiatives have been undertaken in recent times to manufacture and synthesize magnetic nanoparticles for use in various industries, including biotechnology, therapeutic agents, and computers. Generally speaking, these NPs' implementation outcomes are predicated on their practical structure and synthesis. Several different MNP kinds are currently being created. Several different MNP kinds have so far been created. Metal oxides (Fe_2O_3, Fe_3O_4), ferrites (MFe_2O_4, M = Cu, Ni, Mn, Mg, etc.), pure metal nanoparticles (Fe, Ni, Co), and base metals constitute the most prevalent of these (FePt, CoPt). The manufacture of these nanoparticles should take into account several important factors, including their intrinsic magnetic characteristics, structure, size, protective coatings, charge density, persistence in aquatic media, and nontoxicity. The dimensions, structure, protective coatings, and chemical stability of magnetic nanoparticles could be best regulated by selecting an appropriate synthesis technique. Iron oxides typically have a significant impact on the selection of a magnetization. Compared to other magnetic nanoparticles, these compounds have good magnetic characteristics on one side and strong resilience over deterioration. The following points present the main characteristics of magnetic nanoparticles:

The crystalline phase of MNPs is required, and there can be only one area per particle.

- Nanoparticles should have a consistent size and shape and a restricted diameter. A sample should contain only identically shaped nanoparticles throughout.
- Spherical nanomaterials are what they typically employ. Naturally, they also use additional advanced structures like nanorods and nanotubes.
- Stability and biocompatibility: These are two requirements for biomedical field systems that could be addressed by core architectures, which have a metallic or metal oxide base and a covering of polymeric or inorganic compounds on top. It has been discovered to bond to biomolecules or impart biocompatibility to nanomaterials.
- Tiny size and hemodynamic length: a size of less than 50 nm is yet another character in this subject as a result of the fact that it promotes diffusion and prevents particulates from being eliminated by the body's reticuloendothelial system (RES).

X. PROPERTIES OF MAGNETIC NANOPARTICLES

MNPs must be robust, nontoxic, and biodegradable to be used *in vivo*. These characteristics could be controlled by altering the nanoparticles' diameter and the coating's characteristics. Fe, nickel, and cobalt are metallic materials that have been demonstrated to be harmful due to corrosion and acid erosion. These factors make shielding magnetic particles necessary to safeguard them against deterioration. Magnetic nanoparticles must penetrate past the reticuloendothelial system (RES) for biomedical applications. The opsonization process starts when nanoparticles are injected into the bloodstream. In this procedure, plasma-coated nanoparticles are later destroyed by phagocytic cells and prevented from reaching target cells. To prevent this from happening, nanoparticles are coated with either an organic layer made of surfactants and polysaccharides or an inorganic layer called silicon and charcoal. The MNPs' cycling time and colloidal stability may be increased by this extra layer.

A. Size

- The ideal choice for *in vivo* models is tiny nanoparticles between 10 and 50 nm in size since they have several advantages.
- By lowering the magnetic contact of nanoparticles, colloidal stability can be increased, and aggregating can be avoided. The size of NPs must possess superparamagnetic characteristics to achieve this. As a result, size reduction is required to attain superparamagnetic characteristics.
- The dipole–dipole interaction is related to the particle size of the sixth power. Because of this, decreasing size results in smaller dipolar interactions and a lessening of particle agglomeration.
- The precipitation could be avoided by small NPs.
- At a fixed quantity, small nanoparticles have a greater area on the surface. This could increase the covering and targeting processes' effectiveness.
- At a pH = 7, small NPs may be stable in water.

B. Control capability

The feedback control of magnetic nanoparticles is guaranteed by the gradients of the external magnetic field coupled with the intrinsic permeability of the magnetic fields within human cells. This function and remote control are used for the transfer and deposition of MNPs, the targeted transfer of anticancer medications to the tumor location, the labeling of specific biological components, and other related activities. The power could be transmitted from the stimulated fields to the nanoparticle via these atoms, which could also react in resonance to field-time-dependent alterations. Chemotherapy and radiation therapy both use it as a tonic.[71]

XI. APPLICATION OF NANOTECHNOLOGY

A. Biomedical application

In essence, every medicine molecule is a creation of natural or artificial nanoengineering. As an illustration, the typical aspirin, the most popular and efficient medication, is only 0.6 nm in size. Therapy immunotherapies, measuring around 30 nm in width, are on the large side. Hemoglobin is one of many polypeptide chains with a diameter of 5 nm, and natural molecules of a similar size may also be employed therapeutically. The mammalian cell's double-stranded DNA is packed tightly into its 2- to 5-Am-diameter nucleus, with a width of ~2.5 nm and a length of about 2 m. The next generation of cancer therapies created by nanotechnology applications will completely depend on monoclonal antibodies. They serve as imaging tools, drug targets, drug transporters, and even drug molecules. At least nine FDA-approved antigens are now being tested in clinical studies to be employed for cancer treatment. The ability to logically create and synthesize efficient small-molecule inhibitors of protein activity constitutes one of the greatest discoveries in therapeutic discovery. The use of applications of nanotechnology, which have been around for a while, would eventually result in the creation of various medications. For instance, targeted proteins and their ligands or intermediates are employed as a blueprint for the logical design of novel medications using nuclear magnetic resonance and x-ray crystalline structure. Using cancer therapy or vaccinations is an intriguing strategy for eliminating tumors. Small tumors are

TABLE II. Evolution of nanodrug delivery system.

Year	Nano-drug
1989	Polymeric particles • Lupron • Endometriosis
1990	PEGylation • Adagen
1995	Liposomes • Doxil
1995	Lipid disk • Amphotec
1995	Nano/microemulsion • Neoral
1996	Iron oxide • Feridex
2002	Polymer micelles • Estrasorb
2003	Nanocrystal • Emend
2005	Albumin NPs • Abraxane
2010	Virus-like particle • Human papillomavirus vaccine
2013	Hydrogels • TraceIT
2015	Oncolytic viruses • Imlygic
2018	Lipid and nucleic acid • Onpattro
2020	Lipid and nucleic acid • COVID-19 vaccine
2021	Nanocrystals • Cabenuva

believed to be eliminated by the body through an effective immune reaction, but aggressive cancers could eventually evolve defense systems that prevent the host from detecting their presence. The system ought to be capable of eliminating the tumor if techniques to stimulate the immune function against such tumors could be developed, and this kind of chemotherapy may be effective against every kind of cancer. To increase the autoimmune reaction against the illness, the tumor antigen is not particularly immunogenic. The antigens have been coupled to solid-core nanobeads in a novel vaccination formulation.[19]

B. Industrial applications

Magnetic iron oxides are frequently employed as synthetic pigments in porcelain, paints, and ceramics. Magnetics might be quite useful in many facets of life and in several industrial sectors. Both from the perspective of the fundamental study of materials science and their applications, such materials are fascinating.[20] Many significant processes, including the production of NH_3, the high-temperature water–gas shift reaction, and the desulfurization of natural gas, have used hematite and magnetite as catalysts. Additional reactions include the Fischer–Tropsch synthesis of hydrocarbons, the large-scale production of butadiene, the oxidation of alcohols, and the dehydrogenation of ethylbenzene to styrene.[21]

C. Environmental applications

The enormous adaptability of nanoscale iron particles for *in situ* applications is a similarly significant characteristic. To further increase the speed and effectiveness of iron nanoparticle remediation, improved iron nanoparticles such as catalyzed and supporting nanoparticles have been created.[22] Iron nanoparticles are being acknowledged as a flexible technique for the remediation of many types of pollutants in groundwater, soil, and air on both the experimental and field scales, despite certain remaining unresolved issues related to their utilization.[23] Several MNPs have been researched recently for the elimination of organic and inorganic contaminants.

XII. FDA-APPROVED NANOMEDICINE

The international demand for nanoparticle drugs is predicted to surpass US$200 billion by 2024 at a CAGR of 10%, according to the most recent study. For the next seven years, the nanocarriers industry is projected to rise at a compound annual growth rate of 21.9%, according to a preliminary study of the economy. The U.S. is home to the biggest global market for medicine delivery using nanostructures. The market is projected to be worth $12.8 billion by 2020. With a predicted market size of US$38.8 billion and a

TABLE III. Nanomedicine and its carrier.

Drug	Nanocarrier	Indicator	Benefits	Year
Doxorubicin		Ovarian	• Boost delivery to particular locations (tumor) • Reduction of systemic toxicity	• 1995; 2005 • 2008
Amphotericin B		Fungal infection	• Reduction of toxicities	• 1995
Daunorubicin		Kaposi sarcoma	• Boost delivery to particular locations (tumor) • Reduction of systemic toxicity	• 1996
Cytarabine	Liposomes	Lymphomatous meningitis	• Boost delivery to particular locations (tumor) • Reduction of systemic toxicity	• 1997
Amphotericin B		Protozoal pathogens or fungus Stress stimulator for the lungs	• Diminished nephrotoxic • Toxicity reduction • Enhanced administration for a lower volume	• 1997 • 1999
Verteporfin		Decreased vision Ocular histoplasmosis Myopia	• Site-specific distribution is enhanced (lesion vessels) • Responsive to the light release	• 2000
Morphine sulfate		Pain loss	• Prolonged-release	• 2004
Vincristine		Acute lymphoblastic leukemia	• Boost delivery to particular locations (tumor) • Reduce toxicity	• 2012
Irinotecan		Pancreatic cancer	• Boost delivery to particular locations (tumor) • Reduce toxicity	• 2015
Pegademase bovine	PEGylated adenosine Deaminase enzyme	Immunodeficiency disorder	• Lengthen the body's time spent in the circulatory and reduce immunogenicity	• 1990
Sevelamer HCL	Poly	Chronic renal disease	• Boost delivery to particular locations (tumor)	• 2000

CAGR of 24.5% from 2020 to 2027, China, the second-largest worldwide economy, is expected to have a marketplace of US$38.8 billion. Unquestionably highlighting the market's capabilities and potential, the projected enormous growth of the NP market and particularly targeted drug delivery raises the need for novel therapeutics to enter the clinical stage to meet the rising demand for efficient treatment options for the growing patient population.[24–29]

Table II lists FDA-approved, classified nano-pharmaceutical compositions over time (polymeric nano-medicines, micelles, liposomes, antibody-drug conjugates, protein nanoparticles, inorganic nanoparticles, and nanocrystals). Table III presents an official version of FDA-approved nanomedicines organized by the kind of nanomaterials used in them. This table was taken and altered from the publication by Yaylaci *et al.*[30]

Table III shows the nanomedicine and its carrier with its nanocarrier, benefits, and year. Figure 3 shows the number of drugs published in different years.

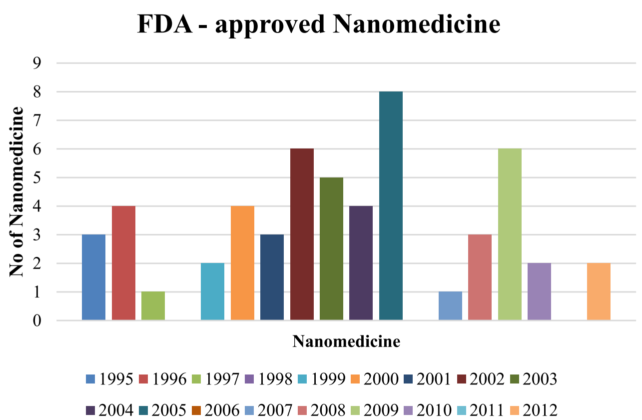

FIG. 3. FDA-approved nanomedicine.

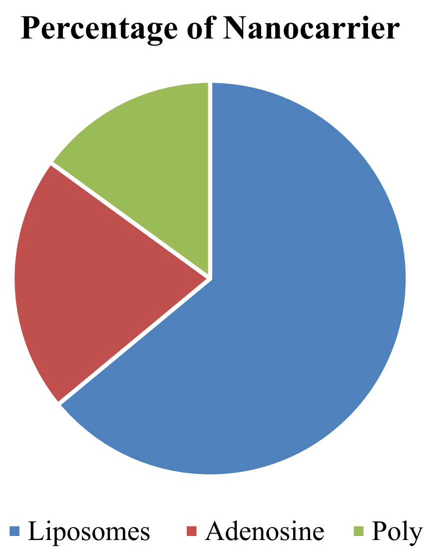

FIG. 4. Percentage of nanocarrier.

Same as that, Fig. 4 presents the pie chart of mostly used nanocarriers. The figure shows that liposomes are the most widely used, poly is used in at least one place, and adenosine stays in between at the mid-level.[72–84]

XIII. CONCLUSION

Among the scientific fields with the most rapid growth is nanomedicine, which is also one of the most potential cancer therapy options at present. Several nanomedicine frameworks have been created, and numerous of them are employed in the treatment of cancer patients. MNP systems come in many forms and are now undergoing rapid development. The MNPs may be customized for illness diagnosis and therapy, including for both early-stage and late-stage cancers. The major objectives are obtaining improved biocompatibility, precision-targeting, and a higher accumulation of target cells for appropriate biological reactions. Healthcare professionals can choose from a variety of therapy approaches using multi-functional MNPs. Due to their particular uses in fields including medical, sensors, the presence of body and environmental clean-up, magnetic nanoparticles have various unique features. In addition to delivering genes, magnetic nanoparticles in the form of liposomes and polysomics are utilized to transport drugs. As a result, the use of these nanoparticles in biological applications is widespread. Similarly, it is frequently employed in molecular sensors for the visualization and detection of several bacteria, fungi, and viral illnesses. When utilized in nanomedicine, magnetic nanoparticles have a number of exciting new properties that make them useful instruments for a range of uses. Drug delivery, hyperthermia therapy, MRI contrast agents, diagnostic imaging and monitoring, theranostic applications, biocompatibility and biodegradability, remote control and manipulation, and responsive nanoparticles are the main factors that add to their novelty. In general, the amalgamation of nanoscale characteristics and magnetic properties presents a multitude of opportunities for inventive medical applications, offering focused, effective, and least intrusive approaches to diagnosis and treatment. The sector is still investigating novel ways to increase the safety and efficacy of magnetic nanoparticles in nanomedicine. Moreover, it should be noted that the creation of novel nanomedicines continues to be a significant issue for academics, policymakers, and business. Collaboration among academics, industry, and regulatory bodies is required to guarantee the security and efficacy of nanomedicine products. In the end, nanoparticles are predicted to be the futuristic substance that will allow for excellence in every aspect of nanomedicine. The main target of this article is to provide basic details about magnetic nanoparticles and the characteristics of these particles in biomedical applications. The features of these nanoparticles in medication delivery and their numerous uses have received extra focus in the study. It seeks to summarize current advancements in MNPs for medical applications and examine the possibilities of MNPs in tumor therapeutic applications in addition.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

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Author Contributions

Mahmoud M Selim: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (equal); Resources (lead); Writing – original draft (equal); Writing – review & editing (equal). **Sherif El-Safty**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Validation (equal); Writing – original draft (equal); Writing – review & editing (equal). **Abdelouahed Tounsi**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal); Validation (equal); Writing – original draft (equal); Writing – review & editing (equal). **Mohamed Shenashen**: Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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