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Journal of Composites and Compounds

Theranostic Nanocomposites for Multiple Sclerosis: Advances in Theranostic Nanoplateforms, Multimodal Imaging, and Targeted Immunomodulation

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ABSTRACT

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) where immune-mediated processes lead to demyelination and neurodegeneration, followed by the progressive loss of axonal functions. Current immunotherapy approaches suffer from several limitations, while repeated use of gadolinium-based contrast agents in selected magnetic resonance imaging (MRI) examinations has raised concerns regarding tissue retention, motivating the development of alternative imaging approaches.

During the last decade, the concept of theranostics has been actively developed and realized via the design of nanocomposite materials that possess both diagnostic and therapeutic functions. The current mini-review highlights recent advances in various theranostic nano-platforms for the treatment of MS. It includes SPION-based systems allowing MRI visualization of the focal inflammation and targeted drug delivery, (polymeric) nanoparticles for antigen-specific immunomodulation, and carbohydrate-based nanomaterials for their ability to harness intrinsic immunomodulatory properties.

Recent studies showed the potential of these approaches to specifically deliver therapeutic cargo to the lesion site, enhance the visibility of plaques on MRI, and modulate the local immune response. Being used in combination with advanced hybrid imaging modalities such as MRI/PET, MRI/CT, or MRI/optical imaging, and augmented by AI-powered image analysis, theranostic nanoparticles may enable longitudinal monitoring of the nanoparticle biodistribution and provide important mechanistic insights for each stage of the treatment. Overall, theranostic nanocomposites represent a promising strategy for integrating diagnosis and targeted therapy in multiple sclerosis, providing a foundation for future precision medicine approaches.

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Peer review under responsibility of UGPH.

ARTICLE INFORMATION

Article History:

Received 10 October 2025

Received in revised form 23 March 2026

Accepted 30 March 2026

Keywords:

Multiple sclerosis

Theranostics

SPIONs

Targeted immunomodulation

Multimodal imaging

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<https://doi.org/10.61882/jcc.8.1.3> This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>)

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1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by a combination of inflammatory, autoimmune, and neurodegenerative processes that lead to immune-mediated demyelination, axonal degeneration, gliosis, and consequent neurological disabilities [1-4]. This disease is considered to be one of the leading causes of non-traumatic disability in young adults, with more than 2.8 million people worldwide affected by it [2]. While the etiology of MS is not fully understood, the contribution of genetic, environmental, and immunological factors is evident [3, 4].

There is a complex pathophysiology of immune-mediated damage to the CNS in MS. In particular, autoreactive T-helper lymphocytes, particularly Th1 and Th17, B-cells, microglial cells, macrophages, and other inflammatory mediators play a key role [3, 4]. Current MS therapy includes a wide range of immunomodulatory, immunosuppressive monoclonal antibodies and other biologics that have been developed and approved over the last two decades. However, most of them are only partially effective in reducing relapses and slowing down the progression of disability [5, 6]. Moreover, these traditional immunomodulatory therapies have limited ability to repair the damaged CNS. At the

same time, the long-term use of conventional immunosuppressants is associated with the development of a large number of side effects, ranging from increased risk of infections to malignancies [7]. In addition, most biotherapeutics have low ability to penetrate the blood-brain barrier (BBB), which restricts their access to the target tissue [8]. The use of nanotechnology-based therapeutic platforms is being advanced to address these critical challenges in MS care [9].

Magnetic resonance imaging (MRI) is the cornerstone of MS diagnosis, monitoring, and treatment response evaluation. MRI typically uses extracellular contrast agents, such as gadolinium compounds. Gadolinium-based contrast agents (GBCAs) are generally considered safe, whereas prolonged exposure may result in retention in peripheral tissues and the brain, prompting researchers to develop alternative contrast-free methods [10]. Notably, artificial intelligence (AI)-enabled methods have proven valuable in detecting active lesions using routine MRI scans [11, 12].

Nanotechnology in combination with molecular and cellular MRI has opened new horizons for developing next-generation theranostic (therapeutic and diagnostic) devices capable of delivering therapeutics across the BBB and visualizing disease sites at the same time [13]. Theranostic nanocomposites integrate

therapeutic payloads with diagnostic imaging components within a single multifunctional platform, enabling simultaneous disease visualization, targeted drug delivery, and treatment monitoring. Theranostic nanocomposites, as well as therapeutic nanoplateforms with theranostic potential, are particularly attractive in the context of MS due to their potential to deliver various cargos, including drugs, to specific areas within the CNS, thereby supporting the concept of image-guided therapy [14, 15]. Besides, developing therapeutic approaches utilizing MRI-compatible positron emission tomography (PET), computed tomography (CT), optical, and magnetic particle imaging (MPI) is also gaining increasing attention [16, 17].

Among various nanomaterials, superparamagnetic iron oxide nanoparticles (SPIONs) were extensively explored as theranostic constructs due to their attractive physicochemical properties and biocompatibility [18, 19]. At the same time, smart polymers, such as poly (lactic-co-glycolic acid) (PLGA), represent another class of polymeric materials that can be utilized in combination with various types of molecular imaging to harness endogenous cell machinery for targeted MS therapy [20, 21]. Another attractive option is represented by natural polymers that can be used to deliver therapeutics with reduced toxicity and enhanced biocompatibility [22]. Aptamers represent another class of molecular recognition elements that can be utilized to develop targeted therapies and diagnostics of various CNS diseases, including MS [23].

The recent advances in the field of nanotechnology, molecular imaging, and targeted drug delivery offer great potential for the development of various theranostic nanocomposites for multiple sclerosis. The present review aims to highlight the progress in this area, as well as the challenges and opportunities for future research and the successful translation of these multifunctional theranostic nanocomposites into the clinic.

Several recent reviews have focused on specific aspects of nanotechnology for multiple sclerosis, such as the use of nanocarriers for drug delivery, nanomedicine, or specific imaging approaches [24-26]. Unlike previous reviews, the present one focuses on recent advances in SPION-based theranostics, polymeric and polysaccharide nanocomposites, multimodal molecular imaging and artificial intelligence theranostic platforms for multiple sclerosis. This mini-review aims to summarize recent progress in the development of theranostic nanocomposites to monitor and treat MS, focusing on SPION-based imaging and therapy, polymeric and polysaccharide theranostics, and multimodal molecular imaging of MS pathology. Finally, we discuss the challenges and future perspectives for the clinical translation of AI-assisted theranostic platforms. A conceptual overview of theranostic strategies discussed in this review is presented in Figure 1.

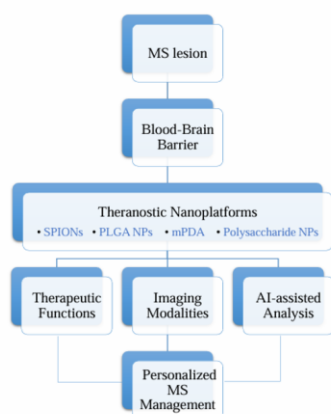


Fig. 1. Conceptual framework of theranostic nanocomposites for multiple sclerosis. Theranostic nanoplateforms are designed to overcome blood-brain barrier limitations and integrate therapeutic functions, multimodal imaging, and artificial intelligence-assisted analysis within a unified framework. The convergence of these components supports personalized diagnosis, treatment, and longitudinal monitoring of multiple sclerosis.

2. SPION-Based Theranostic Platforms: From Molecular Imaging to Targeted Therapy

SPIONs are among the most experimentally validated nanomaterials utilized in therapeutic and diagnostic applications [18, 19, 27]. Their versatility and attractive physicochemical properties allow the development of a wide range of MRI contrast agents and therapeutics that can simultaneously carry imaging reporters and biotherapeutics to the site of action. In this section, we will focus on the unique characteristics of SPIONs, their applications for molecular imaging of MS pathology, and therapeutic interventions targeting various aspects of the disease.

2.1. Physicochemical Properties and MRI Contrast Mechanisms

SPIONs typically consist of an iron oxide core (either magnetite or maghemite) surrounded by a shell of dextran, PEG, silica, carboxymethyl dextran, or other protective molecules [18, 28]. Particles of less than 5-20 nm do not retain their magnetization upon removal of the external magnetic field, allowing their use as superparamagnetic nanoconstructs. Being superparamagnetic, SPIONs allow obtaining high-resolution images of the lesion site in the CNS [18, 19]. Specifically, SPIONs affect the relaxation times of protons, particularly T2 and T2*, thus reducing the signal intensity relative to the surrounding healthy tissue [28]. On T2-weighted MRI, SPIONs appear as dark spots, thus allowing the determination of the location of cellular infiltrates in MS lesions. Compared to linear GBCAs, SPIONs are biodegradable and therefore may be a safer option, although their chronic use may lead to iron overload that should be monitored [18, 19]. However, unlike GBCAs, SPIONs primarily generate negative (T2/T2*) contrast, which may complicate image interpretation in regions affected by susceptibility artifacts, although this limitation can be mitigated using advanced susceptibility-sensitive MRI techniques.

Besides serving as contrast agents, SPIONs allow visualizing the immune cell infiltration in MS lesions [29, 30]. In preclinical studies, SPION-enhanced MRI may be combined with ex vivo single-cell RNA sequencing or spatial transcriptomic analyses to correlate imaging findings with the cellular composition of inflammatory lesions [31, 32]. In particular, SPIONs can be used to visualize inflammatory cell activity, especially macrophages and microglia, within MS lesions using T2- and T2*-weighted MRI [33, 34].

While GBCAs are primarily used to visualize BBB disruption, USPIO accumulation has also been observed in some inflammatory lesions without conventional gadolinium enhancement, potentially reflecting phagocyte-mediated transport or subtle inflammatory changes not detected by standard GBCA imaging rather than universal passive passage across an intact BBB [19, 34]. This property is particularly valuable because macrophage and microglial activity represents an important component of MS pathology [34]. Therefore, SPION-enhanced MRI provides complementary information to conventional gadolinium-enhanced MRI by reflecting inflammatory cell activity rather than BBB permeability alone. [34].

2.2. Biological Rationale for SPION-Based Theranostics in MS

Active MS plaques have been shown to accumulate macrophages and microglia that demonstrate increased phagocytosis and ultrasmall superparamagnetic iron oxide (USPIO) uptake [30-32]. This phenomenon can be utilized for

targeting inflamed sites via enhanced delivery of theranostic nanoparticles and for their specific and sensitive detection by MRI.

SPION-enhanced MRI has been successfully applied for the noninvasive visualization of spinal cord inflammation in the most common animal model of MS, experimental autoimmune encephalomyelitis (EAE) [33, 34]. Additionally, SPIONs can be used as multifunctional nanoplateforms for simultaneous diagnosis and therapy by conjugating targeting moieties, imaging reporters, and therapeutics on their surface. Collectively, these findings highlight the potential of SPION-based theranostic platforms for simultaneous imaging and targeted therapy, although further clinical studies are required to confirm their efficacy and long-term safety in patients with MS.

2.3. Therapeutic Modalities Enabled by SPION Platforms

Besides optical imaging, SPION-based theranostics can be utilized for various treatment modalities (Table 1). Here, we focus on the most promising therapeutic concept currently under investigation for the treatment of MS, which is targeted drug delivery via the enhanced permeability and retention effect.

Table 1.

Representative therapeutic modalities enabled by SPION-based platforms for multiple sclerosis and their potential clinical relevance [35-38].

Therapeutic Modality	Mechanism	Potential Relevance to MS
Magnetic hyperthermia	Localized heat generation under alternating magnetic fields	Experimental concept with no established MS-specific therapeutic efficacy
Targeted drug delivery	Delivery of immunomodulatory or neuroprotective agents to inflammatory lesions	Improved therapeutic specificity and reduced systemic toxicity
Reactive oxygen species (ROS) modulation	Platform-dependent ROS modulation through engineered surface chemistry or antioxidant cargo delivery	Potential neuroprotection and mitigation of tissue injury
Immunomodulation	Regulation of macrophage, dendritic-cell, and T-cell responses	Promotion of immune tolerance and suppression of neuroinflammation

One of the most promising therapeutic strategies for MS is the use of SPIONs for targeted drug delivery. Various drugs and biologics can be attached to the surface of SPIONs or encapsulated within their core and subsequently visualized by MRI [35].

Besides conventional chemically synthesized small molecule drugs and peptides, oligonucleotide therapies and antibody fragments are also considered as potential cargos for SPIONs. Another attractive concept is to use SPION-based theranostics in combination with tolerogenic immunotherapy or other promising nanoparticle-based therapeutic approaches for the synergistic downmodulation of autoreactive T cells, which is currently under investigation [21, 36].

2.4. Multimodal Imaging and Theranostic Integration

An especially attractive feature of SPIONs is their potential application in multimodal settings in combination with other imaging techniques, such as positron emission tomography (PET),

single-photon emission computed tomography (SPECT), optical imaging, or magnetic particle imaging (MPI). While MRI has excellent anatomical resolution in preclinical and clinical settings, its main drawback is the limited amount of quantitative and functional information available about the target tissue. However, simultaneous or sequential application of different imaging methods allows obtaining more information about the target lesion or cell population than any single method alone [37].

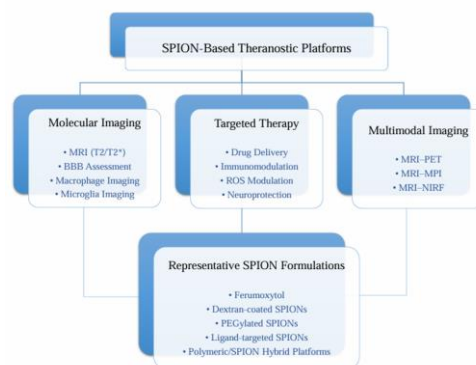


Fig. 2. Representative SPION-Based Theranostic Platforms for Multiple Sclerosis.

As summarized in Figure 2, SPION-based theranostic platforms integrate molecular imaging, targeted therapeutic delivery, and multimodal imaging approaches, highlighting their versatility for the diagnosis and treatment of multiple sclerosis. Such combined approaches can be extremely useful for SPION-based theranostics, as they allow visualization and quantification of the amount of delivered SPIONs, assessment of their targeting efficiency, and detailed analysis of the therapeutic effects at different levels [38]. In particular, optical imaging in the near-infrared region (NIRF) has been successfully utilized to visualize the biodistribution of SPIONs across the BBB [37].

Another promising method is MPI, which directly detects SPIONs and has already shown extraordinary sensitivity and quantitative potential in several preclinical studies [37, 38]. Together, there is a growing need and opportunity to combine different SPION-based theranostic platforms to visualize and control the processes of nanoparticle delivery across the BBB, lesion targeting, and subsequent treatment.

2.5. Translational Challenges and Opportunities

Although many SPION-based theranostic platforms have been described in the literature, the majority of them are still at early stages of development and have not undergone serious clinical evaluations. One of the most widely studied clinical iron oxide nanoparticles is ferumoxytol – an ultrasmall superparamagnetic iron oxide that has been approved by the FDA for clinical use.

Ferumoxytol was initially designed and utilized for iron supplementation; however, several clinical and translational studies have shown its potential as a contrast agent for MR lymphangiography and imaging of inflammation in the central nervous system (CNS) [39]. Thus, ferumoxytol can potentially serve as an important clinical platform for developing new theranostic agents based on SPIONs.

At the same time, there are several translational roadblocks that need to be addressed for SPION-based theranostics to reach their full potential in the clinic. First, additional preclinical studies are needed to optimize the biokinetics and surface chemistry of

SPIONs to achieve reproducible BBB crossing and lesion targeting and to confirm their long-term safety in vivo [18, 39, 40].

Second, there is an urgent need for better standardization of production and characterization of SPIONs to ensure lot-to-lot consistency. Third, the development of theranostic platforms requires regulatory approval of both diagnostic and therapeutic components, which may be challenging in some jurisdictions. Nevertheless, rapid progress in the field of SPION-based theranostics will lead to the appearance of new multifunctional nanocomposites that will allow the combined treatment and control of MS pathology.

3. Polymeric and Polysaccharide-Based Nanocomposites for Targeted Immunomodulation

Despite the advantages described, SPION-based systems possess certain limitations for image-guided therapy. Unlike SPION-based systems, most polymeric nanoplateforms discussed in this section have primarily been investigated as therapeutic platforms. Nevertheless, they provide a versatile foundation for future integration with imaging agents, making them promising candidates for next-generation theranostic applications. However, polymeric nanocomposites offer biocompatibility, flexible drug-release rate profiles, and high drug-loading capacity, as well as the ability to induce antigen-specific tolerance [27, 40]. These properties are of particular interest in the context of MS because they enable designer cell reprogramming and antigen-specific immunomodulation. The concept and opportunities for developing tolerogenic nanostructures have attracted increasing attention in recent years due to their ability to restore peripheral tolerance and prevent allogeneic rejection while minimizing immunosuppressive side effects [41]. The most promising polymeric nanomedicines include PLGA nanoparticles, mPDA nanovaccines, and polysaccharide-based nanocomposites, many of which possess future theranostic potential through integration with imaging functionalities.

3.1. PLGA Nanoparticles for Induction of Antigen-Specific Immune Tolerance in MS

Overall, this section highlights the potential of PLGA-based systems as multifunctional tools for cell reprogramming, immune modulation, and targeted delivery of therapeutic compounds. PLGA nanoparticles have garnered significant attention due to their biodegradable and biocompatible nature, as well as their established safety profile in various biomedical applications [20]. Their high physicochemical versatility allows encapsulating diverse cargo molecules, ranging from peptides and proteins to nucleic acids and small-molecule drugs, and to precisely control the release rate.

Din et al. designed an aqueous remote-loading strategy to encapsulate myelin oligodendrocyte glycoprotein (MOG) peptides within PLGA nanoparticles, resulting in improved antigen retention and prolonged dendritic cell (DC) exposure. The in vivo administration of MOG-loaded PLGA nanoparticles to EAE mice significantly reduced disease severity by inducing antigen-specific immune tolerance. Specifically, the treatment skews DC differentiation toward a toleragenic phenotype, enhances the frequency of Tregs, and promotes anergic T-cell responses [20].

Furthermore, PLGA nanoparticles serve as excellent vehicles for delivering gene-regulatory therapeutics. Li et al. developed cationic lipid-assisted PEG-PLGA nanoparticles (CLANs) capable of delivering small interfering RNAs (siRNAs) that target critical immune regulators, CD40 and LKB1, in DCs [36]. Such siRNA cargo modulates tolerogenic DC differentiation and skews

pathogenic Th1/Th17 responses toward suppressive Treg differentiation. In the EAE model, the treatment with CLANs suppressed CNS infiltration by pathogenic T-cells and ameliorated clinical symptoms, highlighting the therapeutic potential of immunomodulatory nucleic acid-based therapeutics [36]. Overall, the studies discussed demonstrate the versatility of PLGA-based nanomedicines in programming antigen-specific immune tolerance in EAE.

3.2. Mesoporous Polydopamine Nanovaccines

Mesoporous polydopamine (mPDA) nanoparticles represent another promising class of functional nanomaterials that may serve as building blocks for future theranostic systems because of their unique physicochemical properties. mPDA nanoparticles are characterized by a highly porous structure, allowing for substantial loading of various therapeutic agents, and exhibit excellent antioxidant properties due to the abundance of catechol groups on their surface [21]. Phan et al. developed a novel tolerogenic nanovaccine based on mPDA nanoparticles that shows impressive results in the EAE model [21]. Systemic administration of autoantigen-loaded mPDA nanoparticles resulted in the formation of tolerogenic DCs, which in turn promoted the expansion of Tregs and suppressed pathogenic T-cell infiltration into the CNS. Another advantage of mPDA-based systems is their ability to scavenge reactive oxygen species (ROS), making them a promising strategy for reducing oxidative stress in preclinical EAE models, with potential future applications in MS. Although this platform primarily demonstrated therapeutic efficacy, its high loading capacity and surface functionalization capability make it suitable for future theranostic development.

3.3. Natural Polysaccharides-Based Nanocomposites

Natural polysaccharides are considered promising biomaterials for designing nanomedicines due to their biodegradable and biocompatible nature, low toxicity, and unique biochemical features [22]. Both plant and microbial polysaccharides have been extensively studied for their beneficial properties against MS. The biological activity of natural polysaccharides mainly depends on their monosaccharide composition, molecular weight, and structure, namely, the presence of glycosidic linkages and branching [22]. They can be used as immunomodulatory agents, antioxidant means, and neuroprotective drugs. For instance, β -glucans are known to regulate macrophage activity and cytokine response, while fucoidan, a sulfated polysaccharide extracted from brown algae, exhibits anti-inflammatory and antioxidant properties. Thus, these polymers can be used as building blocks for multifunctional nanomedicines with enhanced bioavailability, stability, and target-specific properties.

3.4. Aptamer Functionalized Nanoconjugates

Aptamer-based nanoconjugates represent a new class of targeted therapeutic systems that utilize the specific binding properties of aptamers to deliver cargo molecules into target cells. These nanoconjugates are characterized by their small size, high stability, and reduced immunogenicity compared to traditional antibodies [23]. Moreover, Aptamer-functionalized nanoconjugates have considerable potential for future theranostic applications for dual theranostic applications, enabling simultaneous molecular imaging and targeted therapy. This feature is of particular importance for treating challenging diseases such as MS, where the development of effective theranostic platforms is a critical unmet need.

Although there are few studies directly targeting MS, the general therapeutic potential of aptamer-based nanoconjugates has been demonstrated in the context of neuro-oncology. Although the described polymeric and polysaccharide-based nanoplatfroms demonstrate promising therapeutic potential, the majority of them are at the pre-clinical stage, and their clinical use is hindered by various challenges, including scalability, safety, reproducibility, and regulatory approval. Moreover, the differences in cargo loading, targeting ability, and mechanisms of action should be taken into account while choosing the optimal nanomedicine platform for the further clinical translation in the context of MS theranostics. Table 2 summarizes the key characteristics, mechanisms of action, advantages, and challenges of the discussed polymeric and polysaccharide-based nanoplatfroms, as well as their potential for clinical translation and current stage of development Multimodal Imaging Strategies for Theranostic Monitoring

4. Multimodal Imaging Strategies for Theranostic Monitoring

The efficacy of theranostic nanocomposites relies not only on the ability to affect the disease state but also on the possibility to monitor the biodistribution of administered nanoparticles and their ability to achieve the desired targeting effect. Thus, multimodal imaging, which allows assessing both anatomical and physiological changes as well as molecular mechanisms occurring in the organism, has become a research priority in theranostics [16, 37].

4.1. MRI-Based Monitoring

MRI is the method of choice for MS diagnostics and monitoring due to its superior soft-tissue contrast and superb anatomical detail [4, 10]. SPION-based MRI enables visualization of both lesion sites enriched with SPION nanoparticles and the anatomical details of these lesions [28]. Furthermore, serial MRI scans allow noninvasive follow-up on the biodistribution of the nanoparticles, evaluating the efficacy of treatment, and monitoring disease progression. This makes MRI a routine method in image-guided nanomedicine.

4.2. PET and SPECT Imaging

Meanwhile, PET and SPECT are considered a valuable source of functional and molecular information complementary to anatomical imaging. Both modalities enable quantitative assessment of relevant biological processes in the body after the administration of radiolabeled compounds, thus providing information on nanoparticle biodistribution and pharmacodynamics [37].

In the context of neuroinflammatory disorders, PET/SPECT imaging might be used to assess microglial activation as well as the overall inflammatory state of the brain and the efficiency of immunomodulatory treatment. Therefore, PET and SPECT, when

Table 2.

Comparison of polymeric and polysaccharide-based nanoplatfroms for multiple sclerosis [20-23, 36, 41].

Platform	Primary Mechanism	Major Advantages	Major Limitations	Clinical Translation Potential	Development Stage
PLGA nanoparticles	Autoantigen delivery and induction of antigen specific immune tolerance	Excellent biocompatibility; controlled drug release; versatile cargo loading; FDA approved polymer	Limited BBB penetration; manufacturing complexity; limited clinical validation in MS	High	Preclinical

read in combination with MRI data, might provide crucial mechanistic insights into the disease states visualized at a higher anatomical level.

4.3. Optical Imaging Approaches

Optical imaging techniques, particularly NIRF imaging, are widely used in preclinical theranostic studies because of their high sensitivity and relative simplicity. NIRF imaging facilitates visualization of nanoparticle transport across the BBB and enables real-time monitoring of tissue-level biodistribution [42].

Although limited by tissue penetration depth, optical imaging provides valuable molecular information that complements MRI and nuclear imaging modalities [43]. Hybrid MRI–NIRF platforms have therefore become increasingly common in nanoparticle development studies [42, 43].

4.4. Magnetic Particle Imaging

MPI is a rapidly emerging imaging modality that directly detects magnetic nanoparticles without background tissue signal [42]. Unlike MRI, which visualizes secondary effects induced by SPIONs, MPI directly measures nanoparticle concentration, enabling highly sensitive and quantitative tracking of magnetic nanomaterials [38, 42].

These characteristics make MPI particularly attractive for monitoring nanoparticle delivery, cell-tracking applications, and image-guided therapeutic interventions. Although clinical implementation remains limited, MPI is increasingly recognized as a promising companion technology for SPION-based theranostics [42].

4.5. Integrated Multimodal Theranostic Platforms

The ultimate objective of multimodal imaging is the development of integrated platforms capable of simultaneously providing anatomical, molecular, and functional information. Such systems may combine MRI, PET, CT, MPI, optical imaging, or photoacoustic imaging within a single nanoparticle construct [37, 38].

Integrated multimodal platforms offer several important advantages, including comprehensive characterization of disease activity, quantitative monitoring of therapeutic delivery, assessment of target engagement and biological response, improved patient stratification, and facilitation of longitudinal precision-medicine approaches. By combining complementary imaging modalities within a single nanoscale construct, these systems may provide a more complete understanding of disease progression and therapeutic efficacy than any individual imaging technique alone. Nevertheless, differences in imaging sensitivity, spatial resolution, cost, availability, and regulatory approval remain important barriers to the widespread clinical implementation of integrated multimodal theranostic systems [37, 38]. Table 3 provides a comparative overview of the current clinical translation status of the major theranostic nanoplatfroms investigated for multiple sclerosis.

Table 2.
Continue.

Platform	Primary Mechanism	Major Advantages	Major Limitations	Clinical Translation Potential	Development Stage
mPDA nanovaccines	Tolerogenic immune modulation and ROS scavenging	High antigen loading capacity; antioxidant activity; dual immunomodulatory and neuroprotective effects	Limited long term biosafety data; early stage validation	Moderate–High	Preclinical
CLAN nanoparticles	siRNA mediated dendritic cell reprogramming	Efficient nucleic acid delivery; targeted immune engineering; multiplex gene silencing	Complex formulation; delivery efficiency and regulatory challenges	Moderate	Preclinical
Polysaccharide nanocomposites	Intrinsic immunomodulation and targeted drug delivery	Natural origin; biodegradability; low toxicity; antioxidant properties	Batch to batch variability; limited targeting specificity	Moderate	Preclinical
Aptamer functionalized nanoconjugates	Target specific therapeutic delivery and molecular recognition	High binding specificity; low immunogenicity; potential theranostic capability	Limited MS specific evidence; susceptibility to nuclease degradation; no clinical validation	Emerging	Early preclinical

Table 3.
Clinical translation status of major theranostic platforms for multiple sclerosis [20–23, 38, 44].

Platform	Imaging Capability	Therapeutic Capability	Major Limitation	Clinical Translation Status
SPIONs	MRI, MPI	Drug delivery, ROS modulation	Long term safety and regulatory challenges	Early clinical imaging studies
Ferumoxytol	MRI	Limited therapeutic use	Off label imaging; limited theranostic capability	Clinical use (off-label MRI imaging)
PLGA nanoparticles	Optional imaging	Antigen specific immune tolerance	No clinical MS studies	Preclinical
mPDA nanovaccines	Optional imaging	Tolerogenic vaccination	Limited long term validation	Preclinical
Polysaccharide nanocomposites	Limited imaging	Immunomodulation	Limited targeting specificity	Preclinical
Aptamer nanoconjugates	Molecular imaging	Targeted delivery	Very limited MS evidence	Early preclinical

5. Challenges, Limitations, and Future Perspectives

Although numerous breakthroughs in theranostic nanocomposites for the treatment of MS have been made, their transition from proof-of-concept studies to routine clinical practice is not straightforward [45]. Indeed, biological, production-related, safety, regulatory, and economic limitations hinder the widespread implementation of the discussed platforms, and these challenges should be addressed to unleash their true clinical potential. Below, we highlight the most pressing limitations, as well as the prospects for the development of theranostic nanomedicine to manage MS.

5.1. Biological and Physiological Barriers

One of the main challenges in CNS drug delivery is the ability to deliver sufficient amounts of therapeutic agents through the BBB. While many nanoparticle formulations have been reported to possess the ability to penetrate the BBB via receptor-mediated endocytosis, adsorptive transcytosis, or an inflamed BBB, the efficiency of BBB crossing is often insufficient for effective treatment.

Moreover, MS lesions are characterized by remarkable inter-individual and intra-individual heterogeneity. From this perspective, the concept of the personalized medicine paradigm is highly relevant to MS because different lesion subtypes (active,

chronic active, and inactive) require specific considerations regarding BBB infiltration, cellularity, vascularity, and metabolism. Therefore, future theranostic nanomedicine may offer an unprecedented opportunity to personalize treatment by designing smart nanoparticles that respond to particular biochemical or immunological triggers prevailing in certain lesion subtypes [4].

In addition, it should be noted that the inflammatory milieu associated with MS can profoundly impact the performance of nanoparticle-based therapeutics, which is another challenge for the design of efficient MS-targeting nanoparticles. Thus, the understanding of interactions between nanoparticles and the MS microenvironment should be further explored [41].

5.2. Safety and Toxicological Considerations

Despite the encouraging preclinical data regarding the brain targeting ability of iron oxide nanoparticles, the long-term impact of their repeated administration on the body still requires thorough evaluation. Specifically, iron oxide nanoparticles possess inherent toxicological risks, such as iron overload, oxidative stress, immunomodulation, hypersensitivity, and others.

For polymeric nanoparticles, safety concerns are primarily related to the physicochemical properties of the polymer shell, biodegradation byproducts, and potential immunogenicity. However, despite the overall good biocompatibility profile of

PLGA, its hydrolysis products can cause local acidification of the tumor microenvironment [46].

Meanwhile, natural polysaccharide-based systems are generally considered safe, although the heterogeneity of their physicochemical properties can be a limiting factor for their clinical translation. Therefore, establishing standardized protocols for physicochemical and biological characterization of polysaccharide-based nanoparticles is essential for their successful clinical implementation.

5.3. Manufacturing and Scale-up Perspectives

A theranostic nanoparticle platform typically requires a cascade of production steps that should all be optimized to achieve consistently high-quality products. Therefore, the manufacturing process is rather complicated and requires special attention at every stage, from nanoparticle formation to surface functionalization and drug encapsulation. A critical point in the development of any nanoparticle platform is the optimization of the fabrication process to achieve the desired nanoparticle size, surface charge, hydrophobicity, and drug/payload content.

For scale-up, nanoparticle manufacturing is further challenged by the need to optimize the process of lyophilization, which is often a time- and resource-consuming process that requires product-specific fine-tuning of process parameters. Thus, in the nanoparticle manufacturing field, achieving consistent and high product quality is paramount, which can only be accomplished by optimizing each step of the production cascade under strictly controlled conditions [47].

5.4. Regulatory and Clinical Translation Considerations

Due to their combined diagnostic and therapeutic functions, theranostic nanoparticles can be considered as either drugs, medical devices, diagnostic imaging devices, or a combination thereof, which complicates the regulatory approval process compared to conventional therapeutics and diagnostics [48]. Another challenge is the need for standard operating procedures for theranostic nanoparticle characterization, as well as harmonized definitions of clinically meaningful endpoints for their evaluation. Moreover, there is limited regulatory expertise regarding the evaluation of multifunctional nanomedicine products [47].

Therefore, academia, clinicians, industry, and regulatory authorities must work collaboratively to establish standardized regulatory pathways for theranostic nanomedicine.

5.5. Future Directions and Opportunities

5.5.1. The Role of Artificial Intelligence

With the advent of artificial intelligence (AI) and radiomics, a new paradigm of precision theranostics is unfolding that will profoundly reshape conventional treatment approaches [11, 12, 49]. Specifically, using AI to mine routine magnetic MRI scans for predictive biomarkers can enable the conversion of standard-of-care diagnostic imaging into powerful decision-making tools that guide the choice of treatment for individual MS patients.

While AI will complement rather than replace theranostic nanomedicine, its integration with nanotechnology will create synergies by enabling an unprecedented level of precision in patient stratification [49, 50]. Therefore, future theranostic platforms should be designed with end-use in clinical practice in

mind. Specifically, developing multimodal nanoplatforms capable of simultaneously delivering therapeutics and imaging agents is essential for implementing precision medicine in clinical practice.

5.5.2. Multimodal Therapeutics

We foresee that future MS therapeutics will combine multiple mechanisms of action to address the multi-faceted nature of MS pathology. In other words, nanoparticle-based platforms will be used to deliver a cocktail of immunomodulatory, genetic, antioxidant, and regenerative therapeutic agents to promote a broad spectrum of anti-inflammatory and neuroprotective effects. The simultaneous incorporation of extracellular vesicle-mediated delivery, gene editing, and RNA therapeutics into nanoparticle-based systems holds promise for multimodal MS treatment [51, 52]. However, increasing therapeutic complexity may also increase manufacturing costs, regulatory requirements, and translational barriers, emphasizing the need for clinically practical platform designs.

5.5.3. Biomarker-Guided Theranostics

A promising direction in biomarker-guided MS management is the identification of predictive biomarkers that can guide the selection of the most beneficial theranostic platform for individual MS patients. In this context, theranostic nanomedicine will employ a combination of MRI-based (e.g., T2-weighted lesion load) and immunological biomarkers to optimize the choice of nanoparticle platform to maximize therapeutic benefit. Prospective clinical validation of such biomarkers remains essential before routine implementation in precision medicine [53].

5.5.4. Toward Clinically Translatable Theranostic Platforms

As we move toward the next phases of theranostic nanomedicine development, it is critical to keep in mind that more intricate designs, while appealing, are often associated with reduced clinical feasibility due to manufacturing and regulatory constraints [47]. Thus, future studies should focus on the development of clinically viable multifunctional theranostic nanomedicine. Specifically, we argue that the next generation of theranostic nanomedicine should be designed with the principles of clinical translation in mind, not the other way around.

Overall, future perspectives in theranostic nanomedicine for multiple sclerosis lie in the combination of innovations in nanomaterial design and clinical translation through the implementation of multimodal preclinical research, artificial intelligence, and biomarker-guided patient stratification. These aspects are anticipated to promote the rapid transition of various theranostic platforms into clinical practice and contribute to enhanced diagnostics, treatment, and management of the disease [47, 50].

6. Conclusion and Future Outlook

Theranostic nanocomposites can simultaneously address multiple unmet clinical needs in MS management by integrating diagnostic imaging, drug targeting, and immunomodulation into one nanoscale device. Thanks to the rapid advancement of materials science, molecular imaging, and neuroimmunology, the field of theranostic nanomedicine has witnessed an explosion of research activity to develop smart nanoparticles that can simultaneously detect and treat MS.

Among the reported nanoparticle platforms, SPION-based composites appear to be the most advanced theranostic option, offering unparalleled opportunities for combined imaging and drug targeting [18, 38]. At the same time, polymeric nanoparticle platforms, such as PLGA and mPDA-based systems, have demonstrated encouraging results in terms of antigen-specific immunomodulation and reprogramming of immune cell function [21, 36]. Natural polysaccharide-based systems can also be used to develop multifunctional theranostic nanoparticles by combining molecular imaging, drug targeting, and immunomodulatory payload to create a synergistic therapeutic effect.

Multimodal imaging has emerged as an important component of theranostic nanoparticle development by integrating complementary imaging modalities, including MRI, PET, optical imaging, and MPL. This integrated approach enables comprehensive assessment of nanoparticle biodistribution, molecular interactions, and therapeutic response, thereby supporting more effective image-guided management of multiple sclerosis.

Despite encouraging progress, most theranostic nanoplatforms remain at the preclinical stage, and successful clinical translation will require further validation, standardized manufacturing, and well-designed clinical studies. Important knowledge gaps remain regarding long-term safety, reproducible blood–brain barrier penetration, optimal nanoparticle design, and comparative clinical effectiveness across different theranostic platforms. Future research should prioritize standardized preclinical evaluation, biomarker-guided patient stratification, and multicenter clinical trials to facilitate successful translation into routine clinical practice. Nevertheless, the convergence of advanced nanomaterials with molecular imaging and targeted immunomodulation provides a promising foundation for the development of next-generation theranostic strategies for multiple sclerosis.

Acknowledgments

The authors would like to extend their gratitude to ChatGPT (OpenAI) and Grammarly Premium for providing language editing and proofreading services. The authors take full responsibility for the final content of this manuscript.

Author contributions

AmirAbbas Amini: Investigation, Writing – original draft, Writing – review & editing; **Vahid Sadeghi:** Writing – original draft, Writing – review & editing; **Meysam Mansouri:** Writing – original draft, Writing – review & editing.

Funding

No funding was received for this study.

Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

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