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Superparamagnetic iron oxide nanoparticles use in the temporal lobe epilepsy model

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ABSTRACT

Epilepsy is one of the oldest and most important diseases in the world, affecting the lives of many people. Although the basis of its treatment is anti-seizure drugs, only 70% of patients respond to drug therapy. Temporal lobe epilepsy (TLE), which means drug-resistant epilepsy, is the most common condition of focal epilepsy. In the case of TLE, new methods are needed, considering the possible situations that may occur during surgical intervention. In recent years, it is thought that superparamagnetic iron oxide nanoparticles, which have attracted attention with their wide range of use, biocompatibility, and unique properties, may contribute to magnetic targeted drug therapy. This review aimed to evaluate the effect of superparamagnetic iron oxide nanoparticles on TLE.

Keywords: Epilepsy, magnetic nanoparticles, superparamagnetic iron oxide nanoparticles, temporal lobe epilepsy.

Epilepsy is one of the most common chronic brain disorders affecting approximately 70 million people in the world, characterized by seizures caused by paroxysmal and self-limiting hypersynchronization of neurons.[1-3] Conversely, the World Health Organization (WHO) refers to epilepsy as "a chronic, non-contagious brain disease that affects approximately 50 million people worldwide."[4] The WHO reported that epilepsy is one of the oldest diseases in the world, dating back to 4000 years before the Common Era (BCE). It also noted that it is characterized by recurrent seizures, which can involve a part of the body or the whole body, and are sometimes accompanied by loss of consciousness and control of bowel or bladder function, with short periods of involuntary movement.[4]

In epilepsy, epileptogenesis, known as the process involving a chronic structural and morphological change process, and the mechanism by which the normal brain develops epilepsy are not fully understood.[3] Epilepsy may develop due to acute brain damage caused by stroke, brain tumors, gene mutations, metabolic disorders, and autoimmune conditions.[5] Epilepsy is a common abnormal neurological syndrome.[6] In addition, epilepsy is often associated with cognitive deficits, neurological comorbidities, such as schizophrenia, anxiety, and depression, and psychiatric disorders, such as autism spectrum disorders that severely affect the quality of life for patients.[1] These comorbidities are varied in incidence and severity depending on the etiology of epilepsy and the age at which the condition develops.[5]

Advances in genetics, biochemistry, neurophysiology, and imaging have led to the development of diagnostic biomarkers for epilepsy and redefining the etiology of some epileptic

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syndromes. In the last decade, the etiology of epilepsy has been detected earlier in the course of the disease than ever before. At the same time, advances in the study of experimental models of epilepsy have provided a better understanding of the underlying mechanisms of the disease and contributed to the identification of treatments targeting specific etiologies.[7]

Anti-seizure medication is the mainstay of epilepsy treatment. Today, there are more than 30 anti-seizure medications.[8] Conventional medications appear to have little effect on symptoms of approximately 25% of epilepsy patients, and 75% of these patients develop refractory epilepsy causing temporal lobe epilepsy (TLE).[9]

Temporal lobe epilepsy was first described by Hughlings Jackson in 1898.[10] Temporal lobe epilepsy is a common drug-resistant epilepsy of unknown etiology in adults.[11] It is the most common focal epilepsy syndrome in adults, characterized by seizures originating from or involving the hippocampus.[12,13] It is difficult to treat therapeutically due to its frequent resistance to antiepileptic drugs.[14] Seizures are resistant to drug therapy in about 30% of patients.[15]

Patients with refractory TLE constitute the majority of patients referred to surgery in the treatment of epilepsy, and at least one-third of these patients are seen to be drug-resistant. In this case, it is thought that removing some or all of the temporal structures such as the hippocampus (i.e., resection) may be the solution. However, bleeding, high blood pressure, and significant infection risk are among the possibilities.[12] Reliable preoperative localization is crucial for the success of surgery in drug-resistant epilepsy. Computer-aided calculations and quantitative approaches are needed for neuroimaging evaluations, which are hardly visible in images but whose effect is reliably seen.[12]

Structural lesions serve as generators for seizure onset in most patients with focal epilepsy. These lesions are usually considerably thin. The identification of the lesion and the planning of surgical treatment strategies are based on the identification of the structural lesion on magnetic resonance imaging (MRI).[16] Magnetic resonance imaging is a powerful and non-surgical tool in biomedical imaging and clinical diagnosis. It has a high spatial and temporal resolution. It is non-radiative when compared to imaging modalities such as computed tomography (CT) and single-photon emission computed tomography (SPECT)/positron emission tomography (PET). However, MRI sensitivity is limited for cellular and molecular imaging compared to optical imaging and SPECT/PET.[17]

Nanomaterials have unique properties such as a high surface area to volume ratio, adjustable size, biocompatibility, importance in targeted therapy, easy separation under external magnetic fields, and superparamagnetism. In addition to these features, their surfaces can be easily functionalized in different ways.[18,19]

The unique properties of magnetic nanoparticles, particularly their magnetic susceptibility and good biocompatibility, draw a significant amount of attention.[20] In recent years, they have become ideal for applications in biomedicine, biomedical engineering, and biomedical applications, including magnetic carriers for drug delivery systems and contrast-enhancing agents in MRI for diagnosis.[18-21] In the last few years, magnetic nanoparticles have been used frequently in bio nanotechnologies such as bio-separation, tumor hyperthermia, enzyme immobilization, MRI, diagnostic agents, magnetically guided target-specific drug delivery agents, and biomolecule immobilization.[22]

Magnetic iron oxide nanoparticles (IONPs) appear to be of particular interest in many biomedical applications due to their superparamagnetic properties and low toxicity. It shows superparamagnetic properties when its dimensions are below 20 nm. Its nanoscale diameter and excellent magnetic properties contribute to the various functions of superparamagnetic iron oxide nanoparticles (SPIONs).[23] Superparamagnetic iron oxide nanoparticles are also excellent MRI contrast agents with strong shortening effects and unique magnetic properties under longitudinal relaxation (T1) and transverse relaxation (T2).[17]

In the last few years, SPIONs are widely used in numerous clinical applications such as MRI, tissue repair, immunoassays, hyperthermia, gene delivery, detoxification of biological fluids, cell separation, and drug delivery (Figure 1).[22,23] Biocompatible, stable, non-toxic nanoparticles

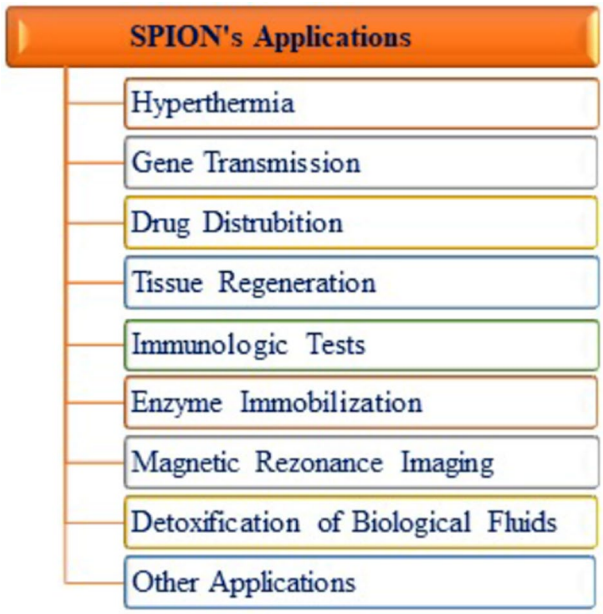

Figure 1. SPIONs applications.[22,23]
SPIONs: Superparamagnetic iron oxide nanoparticles.

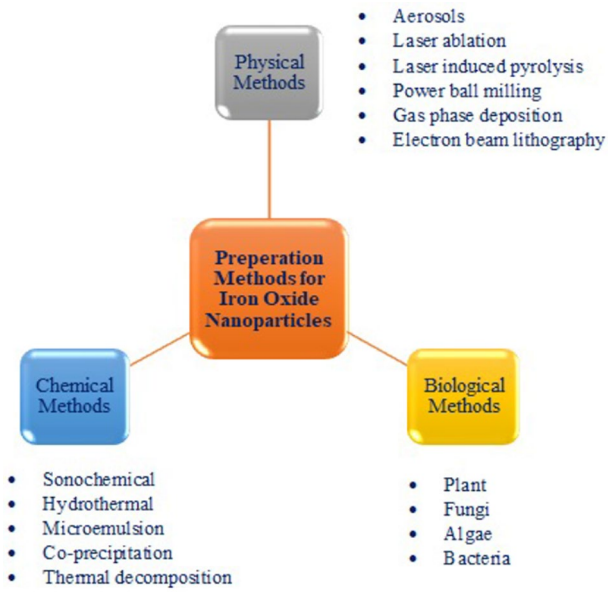

Figure 2. Preperation methods for iron oxide nanoparticles (IONPs).[25]

are used as efficient tools in the biological environment. Superparamagnetic iron oxide nanoparticles can be used as cancer therapeutics when designed in whole or in part.

Superparamagnetic iron oxide nanoparticles show features such as small size, high magnetization, biodegradable surface coating to prevent agglomeration, targeted attraction, therapeutically effective drug distribution, improved co-development for monitoring and imaging, and improved half-life.[23]

The main synthesis routes for preparing SPIONs have been well established over the last two decades. Some of these are readily available to produce semi-industrial quantities of IONPs, such as co-precipitation, light oxidative hydrolysis, and thermal decomposition.[24] The methods of preparing IONPs are shown in Figure 2. The properties of IONPs, such as differences in morphology, sizes, and shapes, affect their applications in biomedicine. The advantages and disadvantages of the basic methods used in the synthesis are known.[26]

Superparamagnetic iron oxide nanoparticles can also interact with different support materials; therefore, they can be enclosed with various groups. Superparamagnetic iron oxide nanoparticle-based MRI auxiliary agents are generally prepared by aqueous precipitation of ferric and ferrous ions in a basic medium in the presence of dextran or carboxy dextran. Hydrophilic polymer coating materials play an important role in determining circulation times and their distribution in the body. Without any surface coating, SPIONs are not stable colloidal elements in solutions, and they tend to clump or even precipitate in water and the physiological environment.[17]

Superparamagnetic iron oxide nanoparticles can be observed by forming structures in different ways, such as clinical validation in research or clinical tests and polymer micelle-based systems. Figure 3a, b show the molecules involved in the structure.[27]

As a drug delivery system, SPIONs show significant advantages in the treatment of many diseases, including epilepsy. The use of nanocarriers is prominent in bringing therapeutics directly to the target area and reducing systemic concentrations.[28]

Protein corona is a factor affected by the various physiochemical properties of the nanoparticles, and in turn, can affect the targeting abilities of SPIONs in imaging applications. In

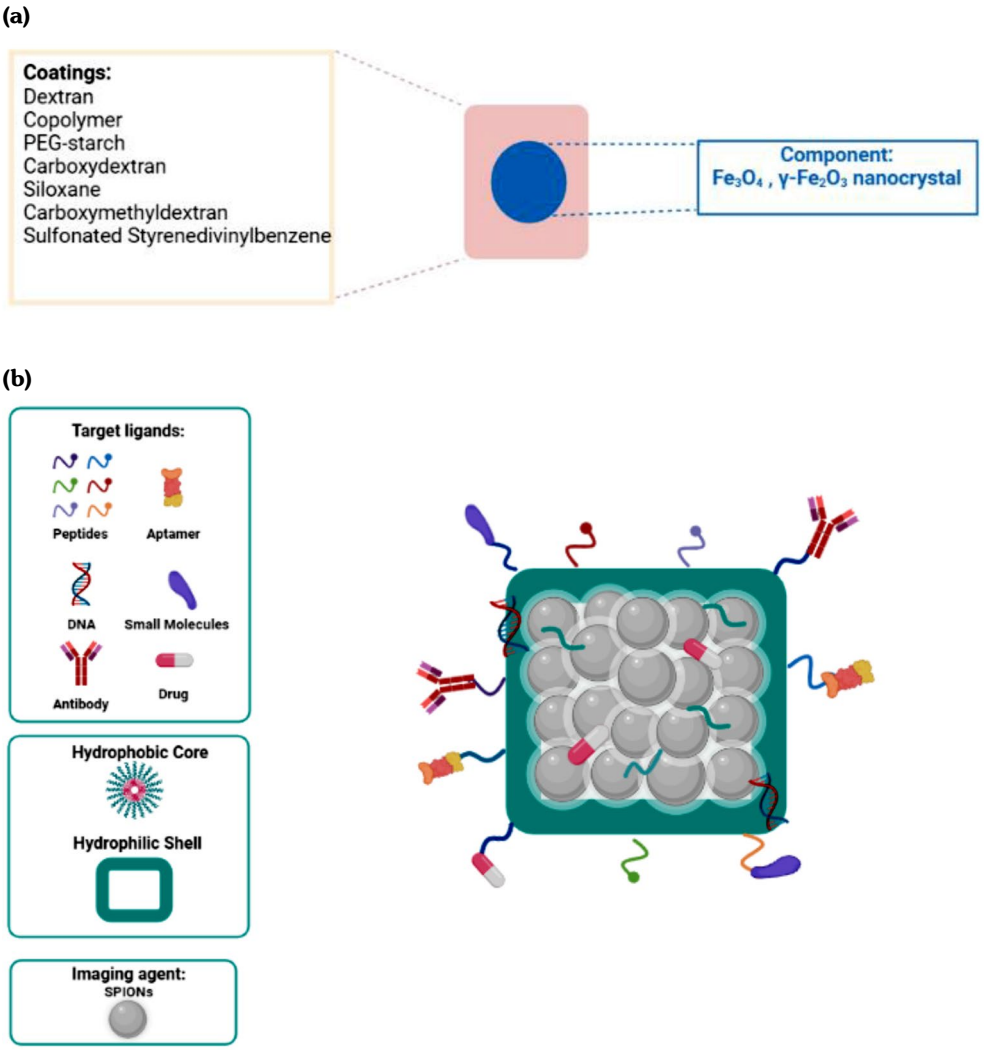

Figure 3. (a) SPIONs: Clinically approved or in clinical test. **(b)** SPIONs: polymeric micelle based system in research.[17]

addition, the different physiochemical properties of SPIONs affect their biokinetics and *in vivo* use. Protein corona not only alters the toxicity, uptake, targeting, and circulation time of SPIONs but can also affect the relaxation of SPIONs as MRI contrast agents. These changes can be observed in the intake, distribution, metabolism, and excretion of SPIONs.[29-32]

Treatment of lung diseases causes difficulties in the ability to limit the accumulation of inhalation aerosols to specific lung areas or local airways. To prevent this, it is essential to use magnetically charged aerosols to target the airway in the presence of an external magnetic field. In target-oriented work, the use of SPIONs is preferred and new strategies are developed (Figure 4).[33]

Long et al.,[34] in their study in 2015, primarily bone marrow mesenchymal stem cells (BMSCs) transplantation, have pronounced that a promising approach for the treatment of epilepsy. Moreover, they stated that there are limited studies on BMSCs labeled with ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles in the MRI follow-up of the TLE rat model. For this purpose, BMSCs were pre-labeled with USPIO nanoparticles and then cell apoptosis, proliferation, surface antigens, and multipotential were investigated.

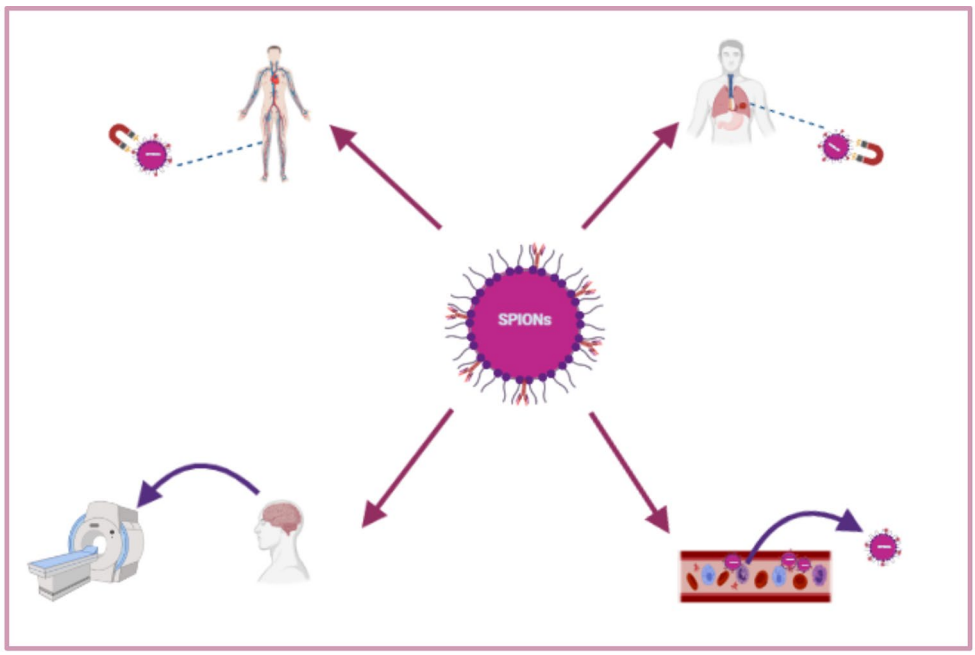

Figure 4. Use of SPIONs different researches in health.[28-33]
SPIONs: Superparamagnetic iron oxide nanoparticles.

It was determined that it is possible to trace transplanted BMSCs using MRI in a TLE rat model and demonstrated that USPIO labeling is a valuable tool for cell monitoring in the study of seizure disorders.

Fu et al.[35] stated that although active targeting of drugs using magnetic targeted drug delivery system (MTDS) with SPIONs is an effective treatment approach for tumors and other diseases, successful results in TLE have not yet been reported. A distinctive feature in the neuropathology of TLE is inflammation of the brain, particularly the activation of interleukin (IL)-1β by activated glial cells, which is considered a new mechanical target for therapy. They aimed to determine the feasibility of SPIONs functionalized with anti-IL-1β. In the study, they explained that this novel approach is an effective method in using SPIONs with its increased accumulation and anti-IL-1 therapeutic effect.

Yu et al.[36] considered the preliminary information that the regional overexpression of the multidrug transporter P-glycoprotein (P-gp) in epileptic brain tissues can reduce the antiepileptic drug concentrations in the target area and contribute to pharmaco-resistance in refractory epilepsy. In the study, they aimed to develop a nano-active compound by combining SPIONs with a near-infrared probe and pepstatin A targeting element, a peptide with a specific affinity for P-gp. The study demonstrated a suitable strategy for molecular imaging P-gp expression in the blood-brain barrier (BBB) with SPIONs, which specifically and effectively reveals regional changes caused by seizures. This suggests that this method may provide an experimental tool for understanding the mechanism of P-gp in multidrug-resistant diseases and locating the P-gp overexpressed focus. It also suggests that identifying additional reliable P-gp surrogate markers would greatly enhance the ability to diagnose, treat, and prevent P-gp overactivity.

Abbas et al.[37] directed clonazepam to the brain via the intranasal olfactory mucosa using nano lipid carriers loaded with SPIONs. They aimed to allow nanocarrier guidance to be directed by an external magnetic field and examined the peripheral effect of clonazepam with the intranasal method in the treatment of epilepsy. It was observed that nanostructured lipid carriers/SPION treatment was effective in reducing the side effects of clonazepam.

Temporal lobe epilepsy is closely related to inflammation. Alpha-methyl-1-tryptophan (AMT) is considered a candidate marker for epilepsy, characterized by high uptake in the epileptic focus. There are many advantages to using SPIONs with a MTDS in the treatment of many diseases, including epilepsy. Wan et al.[38] used an anti-IL-1β monoclonal antibody (mAb) chelated to AMT and SPIONs to pass it through the BBB. In the study, they investigated the effect of a targeted therapy. They found that SPIONs interacting with anti-IL-1β mAb has an improved therapeutic effect. The unique advantages of SPIONs and active position targeting of AMT were determined to be important in the anti-IL-1 of-mAb therapy of the acute TLE model.

In conclusion, the effects of SPIONs, biocompatible, stable, and non-toxic nanoparticles that provide new strategies in the biological environment, on TLE were discussed in this review. Superparamagnetic iron oxide nanoparticles have many advantages and disadvantages, and they can interact with different support materials; thus, they can be enclosed with different groups. They are considered advantageous candidates for new methods, particularly because of their biocompatibility and unique qualities. They also have a wide range of applications such as healthcare, biotechnology, and nanotechnology.

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