

Plant-Polyphenol-Mediated Synthesis of Magnetic Biocompatible Iron Oxide Nanoparticles for Diagnostic Imaging and Management of Neurodegenerative Diseases

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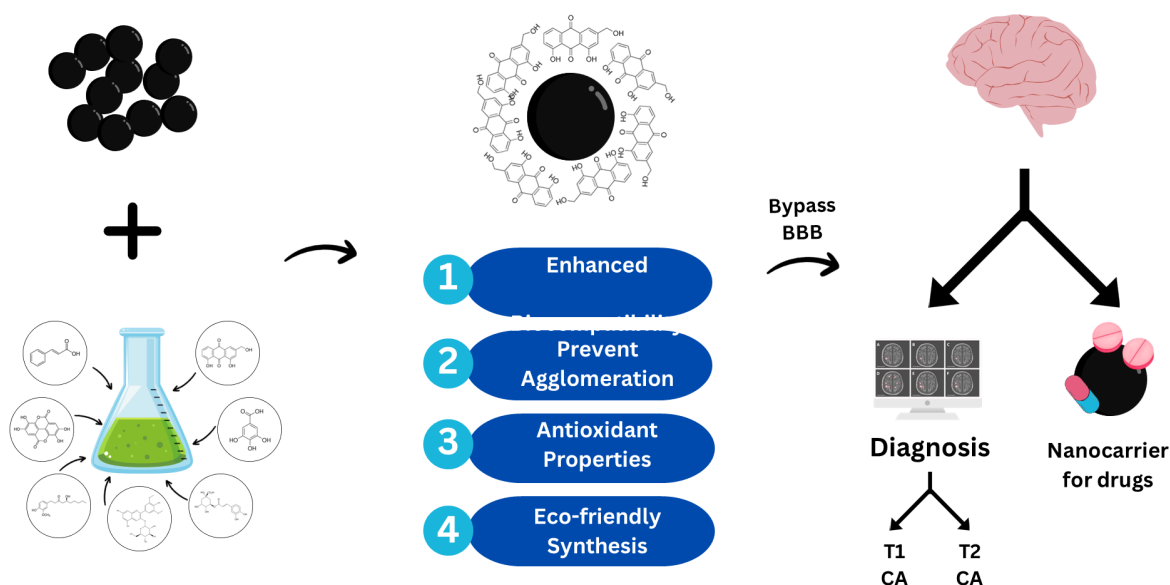
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Graphical abstract



Abstract

Neurodegenerative diseases (NDDs), including Alzheimer's disease (AD), Parkinson's disease (PD), and glioblastoma tumors (GB), represent a spectrum of disorders characterized by progressive neuronal degeneration. This gradual deterioration presents significant challenges in early diagnosis and treatment. As a solution, iron oxide nanoparticles (IONPs) have emerged as promising materials due to their diminutive size and inherent biocompatibility, which facilitates bypassing the blood-brain barrier (BBB), thereby serving as effective targeted nanocarriers for neuroprotective therapeutics, offering efficient delivery to the brain. Furthermore, IONPs demonstrate efficacy as T1/T2 contrast agents (CAs), offering a novel diagnostic tool for various NDDs, emphasizing GB. Despite the expanding potential of IONPs in the management of NDDs, a clear gap exists in developing environmentally sustainable synthesis methods. Such methods must adhere to ecological standards and enable the production of

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nanoparticles capable of efficiently crossing the BBB. This is essential for precisely delivering and monitoring therapeutic interventions in diseases such as AD, PD, and GB. This review systematically explores the potential of green-synthesized IONPs in the context of NDD treatment. In this review, we emphasize different functionalization techniques for IONPs, tackling how these functionalized IONPs can be effective therapeutic approaches for NDDs. Moreover, we discuss biosafety and biocompatibility by covering a range of in vitro biocompatibility studies to analyze the safety of green-synthesized IONPs for the human body. Furthermore, our thorough analysis discussed the current state of green-synthesized IONPs using plant extracts polyphenols, which also act as neuroprotective agents, as proved by studies mentioned in the review.

Keywords: Green Synthesis, Iron Oxide Nanoparticles (IONPs), Neurodegenerative Diseases, Blood-Brain Barrier, Magnetic Hyperthermia, Magnetic Reasoning Imaging.

Rationale, Purpose, and Limitations

The study is motivated by the need for early diagnosis and effective treatment of NDDs like AD, PD, and glioblastoma tumors. It aims to explore the potential of green-synthesized IONPs as targeted nanocarriers for therapeutics and as diagnostic tools, addressing their biocompatibility and biosafety. The goal is to develop environmentally sustainable IONPs that can cross the BBB efficiently. This research is significant as it offers insights into novel, eco-friendly methods for managing NDDs with IONPs while also emphasizing their diagnostic and therapeutic applications. The limitations include the development of environmentally sustainable methods for synthesizing IONPs. Additionally, there is a need for comprehensive in vitro & in vivo biocompatibility studies to assess IONPs' safety and long-term effects on human health.

Introduction

Neurodegenerative diseases (NDDs) encompass a spectrum of disorders impacting the nervous system, involving central and peripheral neural pathways [1]. These conditions result in the gradual deterioration of nerve structures necessary for proper brain function, which can lead to significant morbidity and mortality [2], [3]. Parkinson's disease (PD), Alzheimer's disease (AD), vascular dementia, multiple sclerosis, and glioblastoma (GB) constitute the predominant NDDs [4]. These diseases significantly impact society, resulting in physical deterioration and an increased demand for home care services, which can be costly. Another problem is the early diagnosis of these diseases, and as a result, they often progress rapidly [5].

Although invasive surgeries and techniques have shown efficacy in treating NDDs, their application is limited because of concerns about potential long-term benefits and damage to the blood-brain barrier (BBB). Meanwhile, while there are medications approved for managing NDDs, the vast majority of them only address symptoms rather than stop the disease. The absence of therapies targeting the root causes of NDDs is largely attributable to the restrictive nature of the BBB, which prohibits 98% of drug substances from entering the brain [6]. The BBB serves as a vital physiological blockade, impeding the directed administration of diagnostic and therapeutic substances to cerebral tissue. Consequently, formulating methodologies for translocating agents across the BBB with minimal toxicological impact continues to be a formidable challenge [7]. Recently, nanotechnology has gained prominence as an innovative strategy for tackling NDDs, attributed to its favorable pharmacokinetic properties and biocompatibility. Nanomaterials, with sizes spanning 1 to 100 nm, are particularly adept at penetrating the BBB, thus enhancing their therapeutic efficacy in both central and peripheral nervous systems. Specifically, metal oxide nanoparticles have attracted considerable attention due to their unique physical and chemical attributes [8]. Iron oxide nanoparticles (IONPs) have been extensively employed in various medical applications, including other metal oxide nanoparticles [9]. Various physical and chemical techniques have been employed to synthesize IONPs, including co-precipitation [10], hydrothermal treatment [11], thermal decomposition [12], sonochemical reaction [13], and chemical vapor deposition [14].

Nonetheless, these methodologies are often constrained by the necessity for specialized equipment, elevated costs, limited production

efficiency, and substantial energy expenditure [15]. Furthermore, these approaches may harm environmental and human health, attributable to the employment of hazardous substances. These include toxic, corrosive, and flammable chemicals, such as organic solvents used to disperse and stabilize [16] capping and reducing agents [17]. Consequently, developing novel eco-conscious methodologies is imperative to mitigate these concerns. The green synthesis of IONPs has surfaced as a viable alternative to the limitations of traditional methods. This technique seeks to refine IONP production through more efficient, sustainable, and environmentally friendly processes [18]. This review highlights the significance of green synthetic techniques for producing biocompatible IONPs. Specifically, it focuses on the potential of green-synthesized IONPs to treat and diagnose NDDs. The review emphasizes PD, AD, and GB as the predominant NDDs. Furthermore, we will explore the ability of these IONPs to effectively pass through the BBB while maintaining their biocompatibility and safety for use in such diseases.

Neuronal Activity of Polyphenols

Recent studies have revealed that diverse plant extracts, abundant in polyphenols, hold the potential to enhance the accumulation of IONPs in the brain. This is achieved by employing appropriate polymer coatings, which facilitate the targeted delivery of IONPs to brain tissues. This enhancement positions them as prospective treatments for NDDs, such as AD and PD, in addition to GB. Notably, these polyphenols can influence the aggregation of amyloid proteins and exhibit antioxidant and anti-inflammatory properties. These properties are pivotal in mitigating oxidative stress and inflammation, which are closely associated with the pathways leading to neurodegeneration [19].

Furthermore, these compounds directly neutralize free radicals or indirectly enhance the body's endogenous antioxidant defenses, exemplified by the activation of nuclear factor erythroid-derived 2-related factor 2 (Nrf2) transcription factor pathways. Their mode of action also encompasses the modulation of signal transduction pathways and the exertion of influ-

ence on gene expression [20]. Table 1 lists various polyphenols that exhibit neuroactive effects, suggesting their utility as IONP coatings in NDD therapies. As a result, the combination of polyphenols with IONPs has surfaced as a potential therapeutic approach for NDDs.

Green Synthesis of IONPs

Green nanoparticle synthesis can be achieved by utilizing biological microorganisms, fungi, and plant extracts, with the latter being the most commonly employed technique. Extracts from diverse plant components, encompassing roots, leaves, seeds, flowers, fruits, peels, petals, entire plants, and seed husks, are abundantly rich with polyphenols, flavonoids, and terpenoids. These constituents are pivotal in their role as capping and reducing agents in synthesizing IONPs [42]–[45]. Capping agents derived from plants play a crucial role in controlling the size and form of nanoparticles. The phytochemicals found in these plant extracts are essential for the fabrication of nanoparticles, with each element having a unique function in reducing and stabilizing nanoparticles. In particular, flavonoids, water-soluble plant metabolites, are recognized for their ability to eliminate oxygen molecules, a property closely linked to their electron-donating capacity. Phenolic compounds, including organic carboxylic acids and phenolic rings, show affinity toward different metal ions and create bonds. This is observed in substances like caffeic acid, protocatechuic acid, and gallic acid. Additionally, Terpenoids supply hydroxyl groups that act as bioreductants for these metal ions. Concurrently, the availability of free amino and carboxylic groups in proteins enables their interaction with metal ions, thereby aiding in the synthesis of nanomaterials. Similarly, due to the intrinsic carboxylic and hydroxylic functional groups present in organic acids and alkaloids, these natural compounds can reduce metal ions, producing biofabricated nanoparticles. [46]. Moreover, specific polyphenols and flavonoids found in plant extracts, utilized for nanoparticle reduction, are believed to affect neuronal health positively. Notably, empirical evidence suggests a correlation between the intake of polyphenol-rich foods, including berries, grapes, cocoa, and green tea, and improved cognitive function [47]–[50].

Table 1. The Neural Activity of Different Polyphenols Can Be Observed in Plant Extracts.

Polyphenol	Natural Source	Neural Activity	Ref.
Genistein	Glycine max	Studies have demonstrated that Genistein can suppress the activity of the BACE1 enzyme, resulting in a decreased synthesis of amyloid-beta (A β).	[21], [22]
Chlorogenic Acid	<i>Camellia sinensis</i> <i>Melissa officinalis</i> <i>Ilex paraguariensis</i> <i>Ginkgo biloba</i>	Chlorogenic acid has demonstrated neuroprotective effects, as indicated by its ability to inhibit the formation of senile plaques and α -synuclein oligomers, restrict the activities of acetylcholinesterase and butyrylcholinesterase, and reduce inflammatory responses within the brain.	[23]–[27]
Anthocyanins	<i>Vaccinium</i> species <i>Vitis vinifera</i> <i>Ribes</i> Species	Neuroinflammation induced by A β and aggregation of tau is considered significant factors in the manifestation of pathological characteristics in the APP/PSEN1 mouse model for Alzheimer's disease. Furthermore, a study has indicated that aged rats that consumed diets enriched with berries containing a considerable quantity of anthocyanins showed enhancements in motor performance and augmented hippocampal neurogenesis.	[28], [29]
Gingerols	<i>Zingiber officinale</i>	The efficacy of a 6-Gingerol-rich fraction was evaluated for its potential to counteract acrylonitrile (AN)-induced neurotoxicity in rat models. This fraction demonstrated an ability to normalize aberrant levels of oxidative stress markers and to prevent the depletion of glutathione levels and antioxidant enzyme activities typically induced by AN.	[30]
Ellagic Acid	<i>Psidium guajava</i> <i>Punica granatum L</i>	A study showed that combining ellagic acid with glucose facilitates its transportation across the BBB, which consequently induces pharmacological effects in the central nervous system. Moreover, a study has indicated that ellagic acid exhibits protective effects on dopaminergic neurons against the pathological factors involved in Parkinson's disease.	[31]–[33]
Berberine	<i>Berberis vulgaris</i> <i>Argemone Mexicana</i>	In hippocampal regions of AD model mice induced by heavy metals, berberine has been observed to diminish the expression and activity of acetylcholinesterase. Moreover, berberine can normalize the levels of inflammatory factors, including tumor necrosis factor-alpha (TNF- α), IL-6, and IL-1 β .	[34]–[36]
Cinnamic Acid	<i>Cinnamomum cassia</i>	Cinnamic acid has exhibited the capability to hinder the accumulation of amyloid- β aggregates in AD. Additionally, research findings indicate that cinnamic acid can improve memory functions by reducing oxidative stress and addressing cholinergic deficits in the brains of diabetic mice.	[37]–[39]
Caffeine	<i>Camellia sinensis</i> <i>Theobroma cacao</i>	Caffeine exhibits neuroprotective properties by inhibiting glutamate release and decreasing A β levels. Research has also demonstrated its ability to activate PKC, increase phospho-CREB levels, and reduce phospho-JNK and -ERK expressions. These actions contribute to survival mechanisms in AD models. Moreover, caffeine protects against BBB disruptions in animal models of AD and PD.	[40], [41]

Green Synthesis Mechanism of IONPs

The synthesis of green IONPs can be explained in three principal stages: reduction, growth, and stabilization. Initially, in the reduction stage, phytochemical constituents within the extract mediate the reduction of metallic ions, a process propelled by electrostatic attraction. The growth stage involves the detachment of metal atoms from their precursors and their subsequent aggregation into nanoparticles, concomitant with the continued reduction of additional metal ions. This phase is essential for obtaining stable nanoparticles, but an extended reduction stage can result in nanoparticles with less-than-ideal morphologies. In the concluding phase, known as termination, biomolecules en-

dow the nanoparticles with stability and encapsulation [51]. An initial chelation reaction characterized the eco-friendly mechanism for the synthesis of IONPs. In a study conducted by Somchadie and Tedsree, a ferric chloride solution was combined with guava extract. During this process, Fe^{3+} ions formed complexes with the phenolic compounds present in the extract. Following this, the extract facilitated the reduction of these complexes, aiding in creating IONPs. Notably, to prevent the oxidation of the precursor solution, both the synthesis and storage of the nanoparticles were carried out under a nitrogen atmosphere, which preserved the reduced state of the nanoparticles. Figure 1 illustrates the mechanism through which plant polyphenols reduce and stabilize nanoparticles.

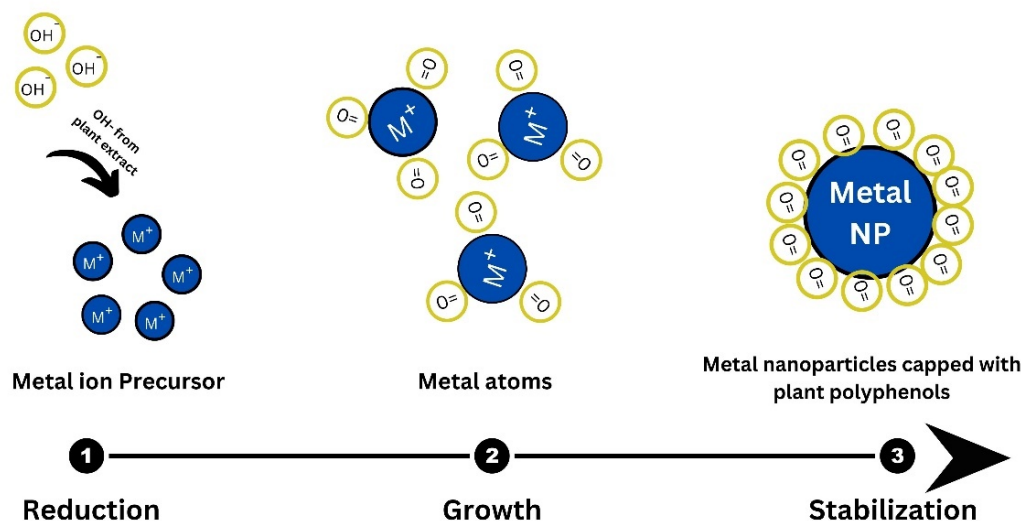


Figure 1. Schematic Representation of the Reduction and Stabilization of Nanoparticles by Plant Polyphenols.

Size and Magnetization of IONPs

The effective penetration of the BBB in treating central and peripheral nervous system disorders depends on the size of IONPs. Research indicates that the process of endocytosis, in which cells engulf external particles, is influenced by nanoparticle size, with smaller IONPs, particularly those under 100 nm, being more easily endocytosed by the BBB's endothelial cells. This feature is paramount because the BBB is essential for preserving brain homeostasis and ensuring neurological protection [52]. In the context of NDDs, there is frequently a compromise in the integrity of BBB, which results in heightened inflammation and accelerated neurodegenerative processes [53]. For ex-

ample, in acute medical scenarios such as traumatic brain injury or ischemic stroke, the disruption of BBB is a direct outcome of these incidents [54]. However, in chronic NDDs such as AD and PD, the role of BBB impairment is less clear. It is debated whether the BBB breakdown is a symptom of the disease or a contributing factor to its onset and progression [55], [56]. In this context, the ability of smaller IONPs to effectively penetrate the compromised BBB holds significant therapeutic potential. The diminutive size of these particles facilitates their evasion of BBB protective mechanisms, thereby potentially enabling the direct delivery of therapeutic agents to targeted areas within the brain. This targeted approach could

be instrumental in managing and possibly slowing the progression of neurodegenerative diseases, offering a novel avenue for treatment that directly addresses both the symptoms and the underlying pathophysiological processes. In light of this evidence, various plant extracts have been utilized to generate IONPs with dimensions smaller than 100 nm, resulting in biocompatible nanoparticles that do not exhibit cellular toxicity. Sudhakar et al. conducted a research study using *Canthium coromandelicum* leaf extract, forming IONPs below 20 nm in size [57]. In a separate research investigation, an extract from aloe vera leaves was utilized to synthesize nanoparticles, which were characterized by dimensions ranging between 7 and 8 nm [58].

Additionally, *Stevia rebaudiana* leaf extract was found to produce IONPs with a diameter of 20 nm [59]. These studies showed that IONPs can potentially treat NDDs and cross the BBB through endocytosis. Table 2 depicts previous papers that synthesized IONPs using plant extracts as reducing agents.

The inherent magnetization capability of IONPs helps enable their passage through BBB, whether acting autonomously or as vectors for medicinal compounds. Scientific investigations have established that, in animal studies, these magnetized nanoparticles can traverse the BBB efficiently and directly [60], [61]. Furthermore, these nanoparticles have demonstrated a propensity to accumulate in areas adjacent to the brain under the influence of an external magnetic field. This observation highlights the critical role of the magnetization properties of IONPs in biomedical contexts, especially concerning drug delivery and neurological treatments [62]. Various IONPs with high magnetization have been synthesized using different plant extracts, such as *Garcinia mangostana*, *Punica granatum*, *Phoenix dactylifera* L, *Zanthoxylum armatum*, and *Excoecaria cochinchinensis*, exhibiting magnetization values of 73.15, 69, 66.1, 128, and 55 emu/g, respectively [63]–[67].

Table 2. Previous Studies of Nanoparticle Sizes and Magnetization in Various Plant Extracts

<i>Plant Extract</i>	<i>Part Used</i>	<i>Size</i>	<i>Magnetization</i>	<i>Ref.</i>
<i>Allium cepa</i>	Pearls	42.78 nm	95.6 emu/g	[68]
<i>Mimosa pudica</i>	roots	67 nm	55.402 emu/g	[69]
<i>Peltophorum pterocarpum</i>	Leaves	85 nm	89.8 emu/g	[70]
<i>Canthium coromandelicum</i>	Leaves	19.25 nm	20.32 emu/g	[71]
<i>Centella asiatica</i>	Whole plant	15.2 nm	13.8 emu/g	[72]
<i>Cymbopogon citratus</i>	Leaves	9 nm	28 emu/g	[73]
<i>Eichhornia crassipes</i>	Leaves	5 nm	53.65 emu/g	[74]
<i>Moringa Oleifera</i> + <i>Watermelon</i>	Leaves + Peels	14.6 nm	54.2 emu/g	[75]
<i>Camellia sinensis</i>	Leaves	7.5 nm	61.2 emu/g	[76]

BBB Penetration Capacity of IONPs

BBB is recognized for its restrictive nature, impeding the entry of most small and large molecules. It is estimated that approximately 98% of small molecules and a substantial portion of

large molecules cannot penetrate this barrier to access the brain [77]. Nevertheless, various strategies have been developed to augment the capacity of IONPs to traverse BBB. This facilitation is partly due to their small size, as numerous nanoparticles synthesized via green

methods are typically less than 100 nm in diameter.

Surface functionalization emerges as a key strategy to improve the permeability of IONPs through BBB. A range of coating materials, including Polyethylene Glycol (PEG), poly (lactic-co-glycolic acid) (PLGA), polyvinyl alcohol (PVA), Dextran, Polylactic acid (PLA), and polyglycolic acid (PGA), are employed for this objective [78]. For example, using PEG as a surface-coating material can provide multiple advantages, including an extended circulation period, enhanced brain penetration and accumulation, and minimal reticuloendothelial system detection. Moreover, PEG is a biocompatible and biodegradable polymer, ensuring its safety and absence of toxicity in the human body. Furthermore, PEG-coated IONPs can easily cross the BBB, making them a potentially effective treatment for neurological disorders [79]. In their study, Qiao and colleagues engineered a novel probe by attaching lactoferrin to PEG-coated IONPs. The efficacy of this modified probe was evaluated in a rat model under both in vitro and in vivo conditions. The findings revealed that lactoferrin-PEG-IONPs exhibited enhanced binding to lactoferrin receptors on cerebral endothelial cells compared to PEG-IONPs. This research concluded that receptor-mediated transcytosis represents a highly efficient mechanism for facilitating the transport of IONPs across BBB [80]. Another investigation was conducted to engineer a theranostic nanoplatform incorporating a surfactant-coated PLGA matrix. This matrix encapsulated doxorubicin hydrochloride (DOX) and IONPs, targeting specific glioma cell lines, including U87-MG, 9L/LacZ, and patient-derived neuronal stem cells. The findings indicated that this novel nanoplatform exhibited significant efficacy in the in vitro treatment of glioma cells, alongside its notable ability to traverse BBB effectively [81]. Green strategies have been implemented to synthesize similar nanocomposites to mitigate the toxicity of nanoparticles and minimize the use of hazardous chemicals. For example, Namasivayam et al. (2021) conducted a study employing a sustainable nanocomposite, PEG-IONPs, synthesized from gum acacia [82]. Furthermore, another study used *Spinacia oleracea* leaf extract to produce PEG-IONPs-DOX to enhance cancer chemotherapy [83]. These examples provide

evidence that eco-friendly IONPs synthesized from harmless and biocompatible materials have the potential to bypass the BBB and subsequently manage NDDs.

Furthermore, the efficiency of IONPs in penetrating BBB can be enhanced by synthesizing hybrid nanoparticles. These hybrid nanoparticles were designed to incorporate the properties of diverse nanomaterials into a unified platform. For example, IONPs can be combined with liposomes to yield magneto-liposomes (MLPs). Due to their inherent properties of targeting BBB and extending circulation time, liposomes present a compelling choice for integration into hybrid nanoparticles, primarily because of their biocompatible and biodegradable nature [84]. In a recent investigation by Marie et al., MLPs have demonstrated significant potential for magnetically targeting glioblastoma. They selectively accumulate in cerebral tumor lesions by exploiting the enhanced permeability and retention effect. Notably, it has been reported that these liposomes specifically target tumor tissues while completely sparing healthy brain tissue [85].

IONPs and Alzheimer's Disease

AD is a neurodegenerative disorder that worsens over time, leading to memory loss, spatial disorientation, and a significant decrease in cognitive function. The primary clinical features of this condition include the development of senile plaques outside cells, which are created by the buildup of amyloid-beta ($A\beta$) protein and neurofibrillary tangles within cells that are made up of tau protein that has undergone hyperphosphorylation, an increased inflammatory response, and the death of neurons due to oxidative stress, leading to apoptosis [86].

The remarkable magnetic characteristics of IONPs with diameters ranging from 60 to 150 nm have garnered significant attention for their prospective application in AD diagnostics. In light of the detrimental impacts linked to the utilization of Gd^{3+} complexes, various research entities are increasingly focusing on IONPs due to their superior magnetic properties [87]. Due to their capacity to traverse BBB, IONPs also present a promising strategy for detecting $A\beta$ proteins and mitigating their aggregation. It has been proposed that IONPs can be tailored for diagnosing AD by modifying their surface with specific molecules that exhibit selective affinity

for A β plaques. An illustrative example involves using monocrystalline IONPs conjugated with A β (1-40) peptides, demonstrating efficacy in identifying A β plaques. However, this approach required the disruption of the BBB [88]. Within the framework of green chemistry, many polyphenolic compounds have been identified as effective modulators of amyloid protein aggregation, simultaneously contributing to the reduction of oxidative stress and inflammation, factors intimately associated with the onset and advancement of AD. The aforementioned compounds can be efficiently delivered to the brain and cross BBB by leveraging IONPs as nanocarriers. This approach significantly enhances their localization within the brain, optimizing their neural therapeutic potential. For instance, Rutin, a polyphenolic compound prevalent in plant extracts such as *Sophora japonica* and *Fagopyrum esculentum*, has been empirically demonstrated to impede the aggregation of β -amyloid into fibrillar formations, a hallmark pathology of AD [89]. In vitro studies have shown that IONPs modified with Congo red and Rutin substantially mitigate the cytotoxic effects instigated by A β while also reducing the synthesis of nitric oxide and reactive oxygen species, which are key contributors to the oxidative stress characteristic of AD. Notably, the intravenous administration of these Congo red/Rutin-modified IONPs has facilitated the identification of numerous amyloid plaques and demonstrated a notable enhancement in memory deficits [90]. Moreover, Epigallocatechin gallate (EGCG), a catechin present in significant quantities in black, green, and white tea, has been identified as a promising candidate for inhibiting several amyloidogenic proteins, including transthyretin, α -synuclein, and huntingtin, which are known to play critical roles in the pathogenesis of AD [91]. Research undertaken by Mareedu et al. in 2021 using green and black tea extracts effectively synthesized biocompatible IONPs [92]. EGCG is abundant in all tea types, so coating IONPs with EGCG can inhibit amyloid formation in AD. Additionally, owing to the presence of IONPs, the resulting nanocomposite (1-100 nm) can cross the BBB. Curcumin, a polyphenolic compound derived from turmeric, can interact with the beta-pleated sheet structure of amyloids. This interaction is a key mechanism

through which curcumin contributes to reducing plaque accumulation in various models of AD pathogenesis [93] [94]. In addition, curcumin can bind to A β and reduce toxic aggregates by regulating amyloid aggregation. Moreover, the natural fluorescence of curcumin may help monitor the progression of NDDs, particularly through the analysis of retinal plaques, which may reflect brain plaque deposition. A research study assessed the efficacy of combining curcumin, known for its neurogenesis properties, with dextran-coated IONPs on the neuronal branching morphogenesis of PC12 cells without nerve growth factor. The results indicated that the synergistic application of IONPs and curcumin successfully induced neurogenesis in PC12 cells without nerve growth factors. This finding implies that such a nanoformulation could represent a novel therapeutic strategy for managing various NDDs [95]. Considering that the progressive degeneration of neurons marks AD, the potential of this combination to stimulate neurogenesis may offer significant advantages in alleviating the impacts of AD.

Mahmoudi et al. conducted a study in 2013 to explore how the physicochemical attributes of IONPs, specifically surface charge and coating thickness, influence the fibrillation kinetics of A β protein. The research focused on assessing the effects of charge variations on the dextran polymer coating of IONPs and the investigation of single versus double layer coatings on A β fibrillation. The findings revealed that IONPs with a positive charge accelerated fibrillation at lower particle concentrations than their negatively charged or neutral counterparts. Consequently, the study recommends that for in vivo medical imaging applications, IONPs should preferably possess a negatively charged or neutral surface coating to minimize adverse effects like protein fibrillation while preserving their magnetic functionality [96].

IONPs and Parkinson's Disease:

PD is a commonly occurring neurodegenerative disorder, holding the position of being the second most prevalent of its kind. The pathological aggregation of α -synuclein proteins within Lewy bodies and Lewy neurites characterizes it. Additionally, there is a notable degeneration of dopaminergic neurons within the substantia nigra. As a result of these pathological changes, patients with PD often present with

hallmark symptoms, including resting tremors, bradykinesia, a stooped posture, and, in certain instances, dementia [97]. Flavonoids can modulate neuronal function and potentially treat PD'. Quercetin, a flavonoid compound found in various plant extracts, including *Ginkgo biloba*, *Malus domestica*, and *Vitis vinifera*, has been proposed to augment neurotransmitter levels. This effect is attributed to its capacity to mitigate oxidative stress by enhancing antioxidant enzyme activities. Such biochemical alterations have been associated with improvements in motor activities and cognitive functions, as well as a reduction in depressive behaviors. Several studies have effectively produced IONPs using quercetin as a reducing and capping agent [98]–[100]. Based on prior investigations that have explored the properties of quercetin as a standalone compound, the resultant IONPs-quercetin composite may hold potential in treating neurodegenerative conditions, particularly PD.

The primary therapeutic strategy for PD focuses on elevating dopamine levels within the brain. However, recent advancements in stem cell-based therapies have garnered significant interest due to their potential for in vivo tracking in cell replacement treatments targeting PD. The application of magnetic nanoparticles in MRI is particularly advantageous because of the various methodologies available for in vivo stem cell monitoring. This is because these nanoparticles facilitate tracking of cell viability, physiological response, and spatial distribution. Importantly, the use of IONPs in tracking during cell transplantation processes offers the distinct advantage of not necessitating any genetic modification of the transplanted cells [101]. In a recent scientific study, human adipose-derived stem cells were tagged with newly formulated ultrasmall IONPs encapsulated with PAA and methoxy-PEG. These tagged stem cells remained detectable via MRI for up to three weeks post-transplantation. Furthermore, these labeled cells demonstrated a significant mitigation of behavioral deficits in PD models, concurrently facilitating an increase in the population of dopaminergic neurons within the substantia nigra [102]. Additionally, it has been established that applying IONPs with appropriate coatings can augment the therapeutic potential of mesenchymal stem cells (MSCs). A research

study conducted by Chung et al. in 2018 elucidated that the use of dextran-coated IONPs notably enhanced the migratory abilities of human MSCs (hMSCs) towards lesioned dopaminergic neurons in a mouse model of PD, which was induced by 6-hydroxydopamine. In situ analyses disclosed that Dex-IONPs not only elevated the protective effects of hMSCs on the degeneration of host dopaminergic neurons but also promoted the targeted migration of hMSCs to the affected neuronal sites and stimulated their differentiation into dopaminergic-like neurons within the afflicted regions [103].

IONPs and Brain Tumors

In individuals with certain diseases, the normal functioning of BBB can be disrupted. Brain tumors, whether primary or metastatic, are considered one of the fatal pathologies that can affect normal angiogenesis in the central nervous system (CNS) or other organs. Consequently, BBB becomes compromised, leading to the formation of a “blood-tumor barrier,” which is also known as BTB [104], [105]. GB are among the most frequently occurring types of brain tumors. These entities are characterized by their aggressive and invasive properties, leading to adverse clinical outcomes and a heightened likelihood of tumor recurrence. This remains the case even following the implementation of maximal safe surgical resection, chemotherapy, and radiation therapy [106].

When it comes to the diagnosis of GB, IONPs are a promising tool for brain tumor MRI scans. These nanoparticles function as negative contrast agents (CAs), effectively augmenting image contrast by reducing the T2 relaxation time in MRI. The core size and coating of the IONPs can be adjusted to enhance the relaxivity. This allows for improved visualization and detection of glioblastoma tumors. Diverse ligands and bioactive molecules capable of identifying specific receptors expressed on cancer cells can be conjugated to the surface of IONPs to enhance tumor imaging specificity. This enables the IONPs to bind specifically to the cancer cells, improving their detection and imaging. Tumor-associated ligands, including lactoferrin, neuropilin-1, and the epidermal growth factor receptor variant III (EGFRvIII), are frequently employed as prime candidates for active tumor targeting. These specific ligands facilitate the targeted binding of IONPs to receptors present on

Table 3. Biocompatibility Evaluation of Cytotoxic Effects of Various Plant-Extract Synthesized IONPs on Different Cell Lines

IONPs / IONPs-Based Materials	In Vitro-Assay	Cytotoxicity Evaluation	Cell Lines	Ref.
Fe ₃ O ₄ - <i>Sumac</i> Extract	MTT Scratch	IONPs produced showed non-toxicity and growth inhibition, with potential antimetastatic properties, against MCF-7 cells.	MCF-7	[115]
Fe ₃ O ₄ - <i>Jatropha curcas</i> latex Extract	MTT	IONPs showed no significant change in the percentage cell viability of both cell lines, indicating no cytotoxicity.	SW480, HeLa	[116]
99mTc-labeled Fe ₃ O ₄ - <i>Cydonia oblonga</i>	MTT	<i>Cydonia oblonga</i> seed/IONPs did not exhibit any toxic effect on A549 cells at all tested doses (0.39-100 mg/mL), with a concentration-dependent decrease in cytotoxicity. The IONPs were well tolerated by the A549 cells, even at the highest concentration of 100 mg/mL.	A549	[117]
Fe ₃ O ₄ and NiFe ₃ O ₄ - <i>Illicium verum</i> extract	MTS	The IONPs did not exhibit any cytotoxic effects on the cell viability of both HepG2 and A549 cells at all tested concentrations, even at the maximum concentration (1000 µg/mL), as determined by the MTS assay. Moreover, IONPs showed high cellular metabolic viability.	HepG2, A549	[118]
Fe ₃ O ₄ - <i>Aloe Vera</i> and <i>Flaxseed</i> Leaves	MTT	The toxicity assessment conducted through MTT assay demonstrated that the in vitro cytotoxic effects were contingent on the dosage. At concentrations lower than 4.7 µg/mL, biogenic IONPs synthesized from <i>Aloe Vera</i> leaves and <i>Flaxseed</i> displayed minimal cytotoxicity.	MCF-7	[119]
Fe ₃ O ₄ - <i>Nigella sativa</i> seeds	MTT	Using the MTT assay, no notable cytotoxicity was observed in cells treated with green-synthesized IONPs at concentrations of 12.5 to 200 µg.mL ⁻¹ for 48 hours, highlighting the biocompatibility of these nanoparticles.	Vero Cells	[120]
Fe ₃ O ₄ - <i>Cardiospermum halicabum</i> Leaves	MTT	The results showed that at a 100 µg/mL concentration, green-synthesized chemically synthesized IONPs recorded cell viability of approximately 84.04 ± 0.94% and 53.68 ± 1.50%, respectively. Hence, according to the ISO 10993-5:2009 guidelines, substances are deemed non-toxic if cell viability exceeds 70%, underscoring the superior biocompatibility of green IONPs in contrast to their chemically synthesized counterparts.	PBMCs	[121]

the surface of tumor cells. This targeted approach enhances the efficacy of tumor imaging and diagnostic procedures [107]. Coating IONPs is typically advantageous and positively impacts clearing cancer cells, particularly GB cells, while also increasing the number of IONPs inside brain cells for diagnostic purposes. For example, in one study, chitosan was

utilized for surface modification to enhance the surface charge of dextran-coated IONPs, which led to increased internalization in GB cells. Additionally, it has been demonstrated that IONPs composed of a chitosan-dextran hybrid exhibit pronounced MRI contrast enhancement capabilities. This characteristic effectively delineates tumors more accurately [108].

At high frequencies of alternating magnetic fields (AMF), IONPs can generate enough heat to raise tissue temperatures to between 40 and 45°C, a process known as magnetic hyperthermia. When temperatures exceed 45°C, it is defined as magnetic thermoablation. On the other hand, lower frequencies of AMF can induce hyperthermia to aid in the opening of the BBB junctions. Establishing that the permeabilization of BBB is both localized and reversible is crucial for validating the clinical applicability of this technique [109]. In the case of glioblastoma tumors in the brain, effective heating of the tumor using minimal amounts of IONPs is a significant challenge in magnetic hyperthermia. It is preferred to administer smaller quantities of IONPs to reduce potential adverse reactions and facilitate their elimination from the body [110].

Biocompatibility of IONPs

The increasing prevalence of NDDs has spurred research into novel therapeutic and diagnostic strategies. Nanoparticles, particularly IONPs, have shown potential in bio-imaging and diagnostics specific to neurodegenerative conditions [111]–[113]. However, concerns around biosafety have limited their broader application. Conventionally synthesized IONPs can be biologically incompatible, posing risks to healthy neurons and potentially exacerbating

neurodegenerative processes. For example, it has been reported that IONPs are characterized by an extensive surface area, which facilitates the enhanced generation of reactive oxygen species (ROS), including free radicals like hydroxyl radicals, superoxide anions, and non-radical hydrogen peroxide. These ROS can induce intracellular and in vivo toxicities in IONPs. The potential impact of such oxidative stress includes detrimental effects on cellular components, such as proteins, lipids, and various organelles, including mitochondria, nuclei, and endoplasmic reticulum [114].

On the other hand, plant polyphenols act as reducing, stabilizing, and capping agents, making the IONPs more biocompatible and having intrinsic antioxidant properties. Given the role of oxidative stress in the pathogenesis of many NDDs, such as Alzheimer's and Parkinson's, the antioxidant activity of polyphenol-derived IONPs could offer dual benefit-enhancing diagnostic capabilities while potentially mitigating disease progression. Several studies have evaluated the biocompatibility of these eco-friendly IONPs in the context of cell viability and cytotoxicity, especially concerning neural cells. Table 3 details the prior assessments of biogenic IONPs' compatibility derived from plant extracts, highlighting their potential in the realm of NDD research and therapy.

Conclusion and Future Directions

In conclusion, the exploration of IONPs in the treatment and diagnosis of neurodegenerative diseases such as Alzheimer's, Parkinson's, and glioblastoma has opened up promising avenues in medical research. The ability of IONPs to traverse the BBB for drug carriage and functioning as T1/T2 contrast agents makes them particularly valuable in diagnosing and managing these conditions. However, developing environmentally sustainable green synthesis methods for these nanoparticles remains a significant challenge. This approach is essential to minimize ecological impacts while producing effective, biocompatible agents for therapeutic use. For the future, it is imperative to focus on methods that are environmentally friendly and yield nanoparticles capable of efficient BBB penetration and targeted delivery. This involves refining synthesis protocols to optimize the size, surface characteristics, and functional capabilities of IONPs. In addition, there is a pressing need to explore various surface functionalization techniques that can enhance the specificity, biocompatibility, and effectiveness of IONPs in treating NDDs. Such advancements would allow for more precise targeting of neurodegenerative areas and improve therapeutic outcomes. Furthermore, extensive in vitro biocompatibility studies should aim to comprehensively understand the interactions of IONPs with biological systems, ensuring their safety and efficacy when administered to humans. This research should include further evaluation of the potential cytotoxicity of IONPs and their long-term effects on human health. Ultimately, the future of NDD treatment and diagnosis lies in the delicate balance between technological advancement and biosafety. By addressing these challenges, researchers can unlock the full potential of IONPs as neuroprotective agents, announcing a new era in managing debilitating conditions like Alzheimer's, Parkinson's disease, and glioblastoma.

Conflict of interest

The authors declare no conflict of interest. For a signed statement, please contact the journal office at editor@precisionnanomedicine.com.

Author Contributions

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