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Iron oxide nanoparticles: a narrative review of in-depth analysis from neuroprotection to neurodegeneration

Ruchika Agarwal,[a] Satadal Adhikary,[b] Suchandra Bhattacharya,[c] Sohini Goswami,[a] Dipsikha Roy,[a] Sohini Dutta,[a] Abhratanu Ganguly, [iD] [a] Sayantani Nanda[a] and Prem Rajak [iD] *[a]

Air pollution is a major risk factor for neurological disorders. Both indoor and outdoor dusts comprise different types of iron oxides in the nano-scale range. Due to their small size and unique physico-chemical properties, iron oxide nanoparticles (IONPs) adopt the intracellular path to agglomerate inside the cell cytoplasm. Moreover, they can cross the blood–brain barrier to invade cortical tissues in the brain and impair neuronal functions. Hence, analysis of the effects of IONPs on the Central Nervous System (CNS) structure and functions is indispensable from medical perspective. A literature search was performed using three scientific databases: ScienceDirect, PubMed, and Google Scholar. Articles published till December, 2023 were screened for their relevancy. Analyses of the appropriate literature have revealed that IONPs are being employed in drug delivery systems and diagnosis of CNS-related ailments that favor neuroprotection. However, the inhalation of IONPs from air and other sources can lead to excessive accumulation of iron in the neuronal tissues, leading to a disturbance in neuronal signaling and augmenting the onset of neurodegenerative disorders. Therefore, it is essential to monitor and control the abundance of IONPs in the environment to combat adverse impacts on the human nervous system.

Environmental significance

Air pollution is a global issue that poses significant detrimental impacts on humans and other animals. Particulate matters of different shapes and sizes are the major air pollutants that harbor Iron oxide nanoparticles (IONPs). IONPs are extensively used in disease diagnosis and drug delivery to facilitate neuro-protection. However, environmental IONPs derived from vehicles and industrial processes are readily inhaled by the global population. IONPs, due to their small size and unique physico-chemical properties, can easily invade the central nervous system and accumulate inside neurons. IONP agglomerization fuels Fenton reaction that produces reactive free radicals such as hydroxyls, superoxides, and peroxides. These reactive entities injure the sub-cellular environment, leading to the induction of ferroptosis and ensuing neurodegeneration. Therefore, proper monitoring and control of the release of IONPs are essential to minimize IONP exposure.

1. Introduction

Air pollution is a decade-old environmental issue that threatens human health and prosperity. It has been known to fuel cardiovascular ailments, endocrine disruption, breathing issues, and reproductive failure.[1] Recently, air pollution has been shown to impair cortical networks of the brain implicated in depression and other mental disorders that have increased the incidence of suicides, mostly in urban areas.[2] More specifically, particulate matter (PM) with aerodynamic diameters ≤10

μm (PM10) and ≤2.5 mm (PM2.5) have been reported to affect the cognitive capability of humans by disproportionately augmenting stress-related changes in brain circuitry.[3] Particulate matter in the environment harbors iron oxides, even in the nanoscale range, that can enter the human body. The small size of particles enables their easy uptake into the subcellular environment and generates ROS *via* the Fenton reaction. The main reasons for Iron oxide nanoparticle (IONP) emission in the air are smelting and refining processes. In addition, IONPs are also released from brake wear on vehicles and various industrial sources.[1] IONPs can also be released in trace quantities from the fuels and lubricants. Therefore, roadside aerosol could be one of the major sources of IONPs. Higher iron fractions might go beyond 40% of the total mass of PM$_{2.5}$. Iron oxides have been detected as a dominant metal oxide in

[a]Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India. E-mail: prem.rjk@gmail.com

[b]Post Graduate Department of Zoology, A. B. N. Seal College, Cooch Behar, West Bengal, India

[c]Department of Chemistry, A. B. N. Seal College, Cooch Behar, West Bengal, India

particulate matter. IONPs were detected in the range of 10–100 nm in samples collected from Tokyo.[4] Indoor dust might carry magnetic IONPs that easily aggregate when coming in contact with lung fluid. It also has a tendency to produce more ROS, particularly hydroxyl radicals, leading to ferroptosis.

Different types of IONPs have been detected so far. FeO, Fe_3O_4, α-Fe_2O_3, and γ-Fe_2O_3 have been reported as the most abundant types of IONPs.[1] Therefore, it can be opined that environmental IONPs can easily be inhaled by humans where these nanosized particles make their way to sub-cellular moieties. Despite their detrimental impacts on health, IOPNs have several applications in disease diagnosis and pharmaceuticals. For instance, IONPs are widely employed as contrast agents in magnetic resonance imaging (MRI) for the detection of specific cell types. IONPs can cross the blood–brain barrier (BBB) to target carcinogenic growth and aids in treating tumors with magnetic hyperthermia.[5]

Ruchika Agarwal is a dedicated individual who completed her post-graduate studies from the Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India. She has academic specialization in Molecular and Clinical Toxicology. Her research interest includes toxicology of emerging environmental contaminants with special emphasis on nano-toxicology.

Ruchika Agarwal

Satadal Adhikary is currently working as Assistant Professor of Zoology at A. B. N. Seal College, West Bengal, India. His interests include toxicology and immunology. He has a teaching experience of more than eight years. Apart from teaching, he has published a number of articles in journals of international repute.

Satadal Adhikary

Dr Suchandra Bhattacharya is presently working as Assistant Professor in the Department of Chemistry, A. B. N. Seal College, West Bengal, India. She has expertise in graphene chemistry, heterocyclic chemistry, and organic synthesis. Her interests also include nanochemistry and toxicology. Dr Bhattacharya has many articles to her name in reputed international journals.

Suchandra Bhattacharya

Sohini Goswami has graduated from the Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India. She has academic specialization in Molecular and Clinical Toxicology. Her research interest includes toxicology of emerging environmental contaminants.

Sohini Goswami

Dipsikha Roy has graduated from the Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India. She has academic specialization in Molecular and Clinical Toxicology. Her research interest covers food toxicology.

Dipsikha Roy

Sohini Dutta, a diligent individual has completed Integrated B.Sc.-M.Sc. in Animal Science with specialization in Molecular & Clinical Toxicology from Toxicology Research Lab, Kazi Nazrul University, Asansol, West Bengal, India. She has research interest in the eco-toxicology of emerging contaminants.

Sohini Dutta

In the air, iron has been recognized in a variety of forms, including metallic Fe (α-Fe), maghemite (γ-Fe_2O_3), haematite (α-Fe_2O_3), magnetite (Fe_3O_4) and wüstite (FeO).[6] A variety of anthropogenic sources contribute to the discharge of IONPs into nature. Brake fume is the major source of airborne iron-bearing NPs in roadside areas. IONPs constitute around 50% of the total particle mass released from vehicle brake systems.[7] In addition, fiery coal, which is employed in producing 40% of total global electricity, is another main source of airborne IONPs.[8] The extremely abundant nanosized particle fraction in metropolitan air has a high bioreactivity and the capacity to invade almost all organs. IONPs are readily taken up by the

Abhratanu Ganguly has completed his Master of Science in Zoology from A. B. N. Seal College, Cooch Behar, West Bengal, India. Currently, Mr Ganguly is working as a Research Scholar at the Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India. His research interests include food toxicology and mitigation approaches.

Abhratanu Ganguly

Sayantani Nanda has graduated in Zoology from A. B. N. Seal College, Cooch Behar, West Bengal, India. Currently, Miss Nanda is working as Research Scholar at the Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India. Her research domain includes the eco-toxicology of emerging contaminants across the globe.

Sayantani Nanda

Dr Prem Rajak is currently working as Assistant Professor at the Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India. The research interests of Dr Rajak include Molecular Toxicology, Cell Biology, and Genetics. He has teaching and research experience of more than eight years. He has published a number of articles in journals of international repute.

Prem Rajak

neural tissues, which aggregate and induce pathogenic alterations, leading to neurodegeneration, mainly in metropolitan cities where the risk of exposure is high due to heavy traffic and industrial prevalance. In regions with higher traffic density and frequent braking, IONPs, mostly in the magnetite form, *i.e.*, Fe_3O_4 NPs are released into the nature. Fe_3O_4 NPs have been traced in brain autopsies and are thought to invade the neuronal tissues. Moreover, these IONPs suspended in polluted air could also reach the alveoli of the lungs following inhalation and invade the circulation to contaminate the brain by crossing BBB. This leads to the accumulation of IONPs that trigger oxidative and inflammatory reactions through the Fenton reaction to cause a variety of health issues.[9] It is becoming more and more likely that excessive amount of iron in certain brain areas like the frontal lobe, temporal lobe, parietal lobe, caudate nucleus, globus pallidus amygdala, cingulate cortex, and putamen contribute significantly to the pathogenesis of AD and other neurodegenerative illnesses.[10]

Although dementia is more common in established nations than in developing ones, it is spreading quickly around the globe. Notably, it has been opined that dementia will affect twice as many individuals between 2020 and 2040.[11] Air pollution has been associated with the onset of neurological disorders like Parkinson's disease (PD) and Alzheimer's disease (AD). Neuro-inflammation, altered immune response, BBB interruption, and amyloid plaque deposition are fuelled by long-term exposure to numerous air pollutants.[12] In neural tissues, iron exhibits dual functions. It is a vital biometal that is found in a variety of metalloproteins, including cytochromes and hemoglobin. Iron is crucial for the myelination of neurons and is involved in many aspects of neural function, including the transmission of nerve impulses, production of neurotransmitters, and generation of mitochondrial energy. Redox cycling and valence changes are used to mobilize and store iron, and complex regulatory mechanisms for storage, transit, and release govern these processes. These procedures are essential because labile iron, or iron that is free and redox-active, has the potential to harm living cells. Excessive iron-induced oxidation injures surface proteins, lipids, and DNA in neural cells. Additionally, IONPs can ignite inflammatory pathways in the brain, causing the discharge of cytokines and chemokines that promote neuroinflammation.[13]

In light of the information above, we seek to understand the various synthesis methods of IONPs and their beneficial and detrimental effects on the human brain. We also aim to unravel how these particles are transported to the brain and accumulate in various CNS sites, fueling protein aggregation, ROS production, and apoptosis in neuronal cells, ultimately leading to neurodegenerative diseases.

2. Methodology

Three scientific databases such as Google Scholar, ScienceDirect, and PubMed, were used to search relevant literature using the search terms which were Iron oxide nanoparticle; Iron oxide nanoparticle toxic impacts; Alzheimer's Disease; and Parkinson's Disease. Authors have carefully screened the original

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Identification

Records identified from databases
Google Scholar (1730),
ScienceDirect (1655),
PubMed (604).
n = 3989

Records in duplicate
(n=1432)

Screening

Records after duplicate removed
(n=2557)

Records screened
(n=2557)

Eligibility

Non-relevant records excluded
(n=2379)

Full text of articles assessed for eligibility
(n=178)

Number of records excluded
(n=31)
Seminar/Conference abstract (n=14)
Perspectives (n=7)
Encyclopedia (n=8)
Opinions (n=2)

Included

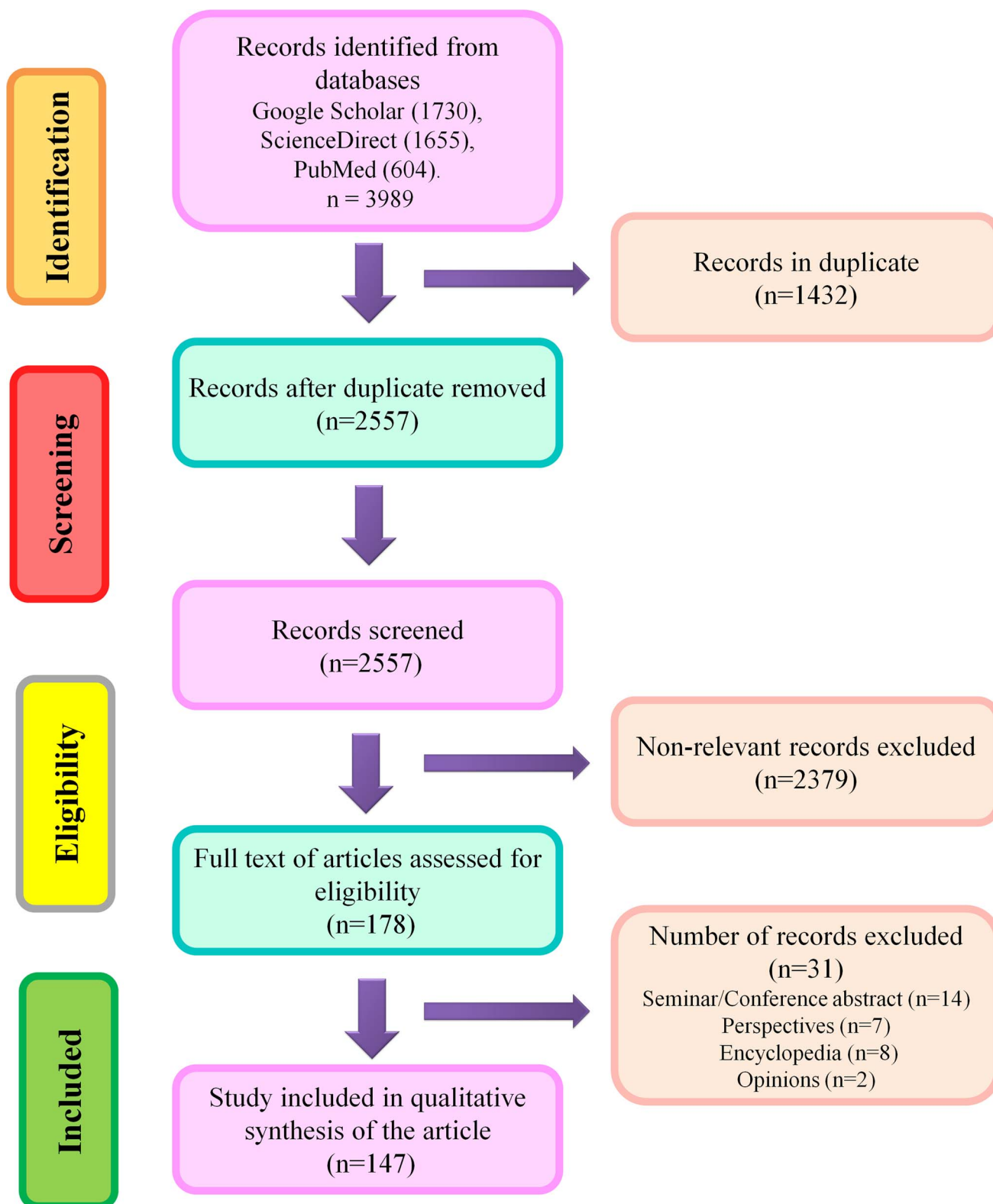Study included in qualitative synthesis of the article
(n=147)

Fig. 1   Workflow of literature search strategy.

articles published till December 2023, and based on titles, they eliminated identical results. Later, the title, abstract, and keywords were studied to evaluate relevant articles. Disputes

were settled following discussion and joint paper revision. Non-original papers, abstracts from seminars or conferences, book chapters, viewpoints, opinions, letters, and encyclopedias were
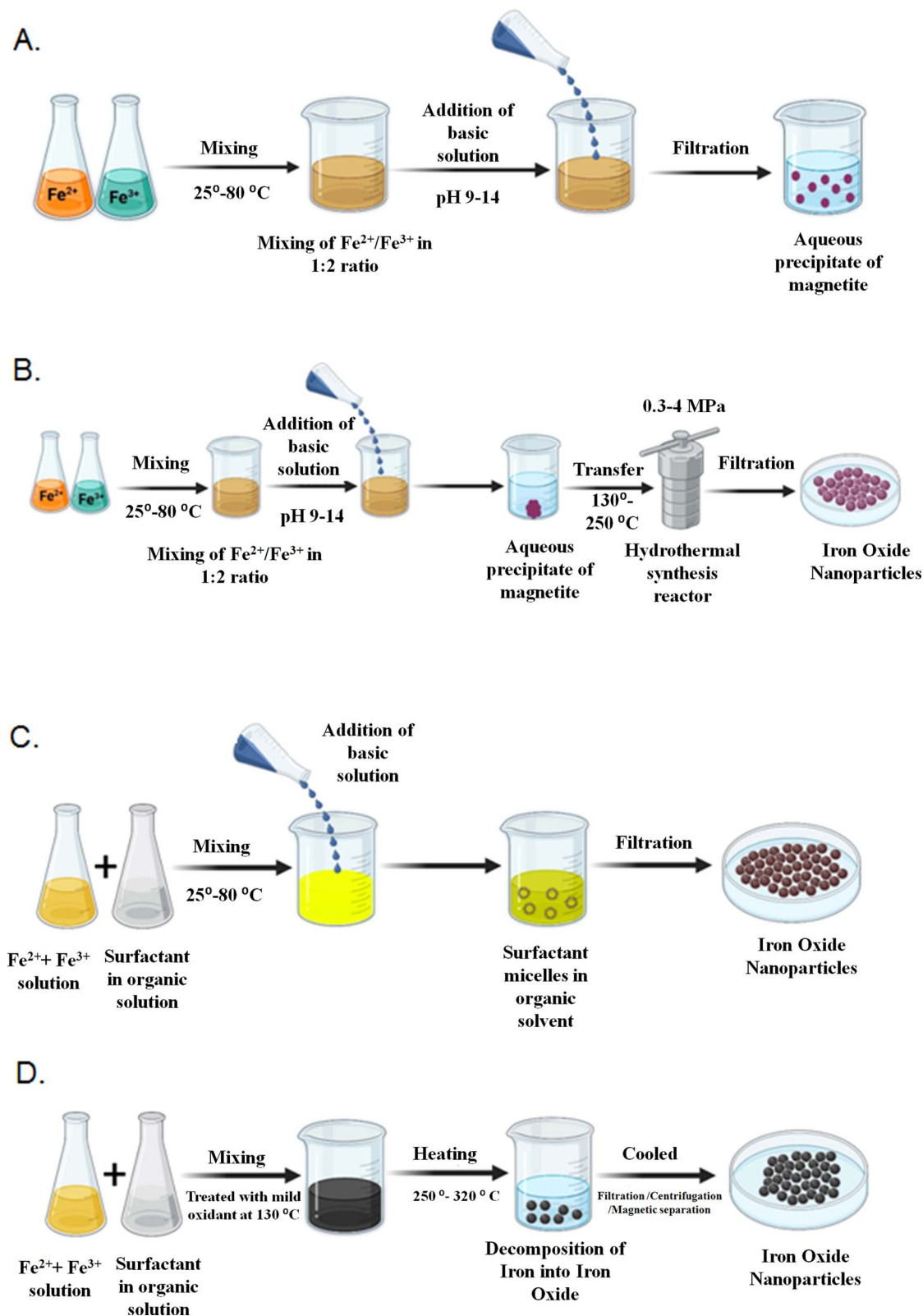
Fig. 2   (A) Artificial synthesis of IONPs by the co-precipitation technique. Utilizing a controlled chemical process to precipitate ions simultaneously, it is possible to create magnetic nanoparticles by this technique. (B) Synthesis of IONPs using the hydrothermal method. It is a controlled method of producing magnetic nanoparticles by chemical reaction at high temperatures and pressures. (C) Artificial synthesis of IONPs by the microemulsion technique. IONPs can be synthesized using microemulsions in an artificial way using a chemical method that produces stable dispersions of immiscible liquids known as microemulsions that enable the precise control of particle size and morphology. (D) Artificial synthesis of IONPs by the thermal decomposition technique. This technique is used to create IONPs artificially by decomposing precursor compounds and forming nanoparticles with desired properties by subjecting them to high temperatures.

excluded from further consideration. Following an early screening, the entire texts of relevant articles were accessed for the systematic synthesis of the present article.

Inclusion criteria: Articles covering the implications IONPs on neuroprotection, detrimental impacts of neurodegeneration on CNS, and alternatives to minimize IONP exposure were included in this study. Exclusion criteria: Abstracts from seminars or conferences, book chapters, viewpoints, opinions, letters, and encyclopedias were excluded from consideration. Any confusion in the selection of relevant literature was resolved through joint discussion. A schematic illustration of the screening process is given in Fig. 1.

3. Natural and artificial production of IONPs

NPs are abundant in our environment. They can be produced by both natural and artificial means.[14] Natural NPs are produced by natural processes, such as water mist, woodland fires, dust clouds, volcanic debris, and by biotic factors like bacteria and fungi. For instance, it was recently revealed that the bacteria *Actinobacter* sp. can synthesize γ-Fe_2O_3 when coupled with the ferric chloride precursors under aerobic surroundings.[15] IONPs have been widely studied over the previous few decades. Numerous studies have detailed effective synthesis techniques that result in shape-controlled, biocompatible, stable, and monodispersed IONPs. The popular techniques which can also be used to produce excellent IONPs, include microemulsion, thermal decomposition, co-precipitation, and hydrothermal synthesis. Additionally, other approaches can be used to synthesize these NPs, including laser pyrolysis techniques,[16] electrochemical syntheses,[17,18] microorganism or bacterial synthesis, particularly that of iron-reducing bacteria and magnetotactic bacteria.[15] Methods widely adopted for the synthesis of IONPs are discussed below.

3.1 Co-precipitation

Co-precipitation is the technique used very frequently to yield Fe_3O_4 or γ-Fe_2O_3. By combining ferric and ferrous ions in an extremely basic solution at either room temperature or a higher temperature, ferric and ferrous ions are combined in a $1:2$ molar ratio. The ferric and ferrous ion ratio, ionic strength of the media, pH value, and reaction temperature change the size and shape of the IONPs. Diverse types of salts like chlorides, perchlorates, nitrates, and sulfates are used during the synthesis. This technique would significantly impact the chemical and physical appearances of the IONPs. If there is no shift in ionic configurations, the saturation magnetization (MS) values observed in nanostructured ingredients are typically lower than those found in the equivalent bulk phase.[19] Furthermore, under ambient circumstances, Fe_3O_4 NPs are readily oxidized to Fe_2O_3 or dispersed into an acidic medium.

3.2 Hydrothermal synthesis

Hydrothermal synthesis encompasses a variety of wet-chemical methods for crystallizing substances in a closed receptacle from high-temperature aqueous solutions ranging from 130 to 250 °C at high vapor pressures ranging from 0.3 to 4 MPa. The method is also employed for synthesizing dislocation-free single-crystal particles. Grains produced in this procedure may have higher crystallinity than grains formed in other procedures, indicating that hydrothermal synthesis is more likely to produce extremely crystalline IONPs.[20]

3.2.1 Microemulsion.
The term "microemulsion" refers to an isotropic, thermodynamically stable dispersion of two incommensurable stages, *i.e.*, water and oil. A surfactant may form a monolayer at the contact point between the aqueous and oil phases, with hydrophilic head groups in the aqueous phase and hydrophobic tail groups in the oil phase. Self-assembled structures of various kinds, such as spherical and cylindrical micelles, lamellar phases, and discontinuous microemulsions, which may cohabit with primarily oil or aqueous phases, can be produced, just as in binary systems.[21] In this regard, the inverse micelles and microemulsion routes can be used to produce IONPs of a particular shape and size.

3.2.2 Thermal decomposition.
In order to yield higher-quality monodispersed IONPs, an organic solution phase decomposition pathway that involves the decomposition of $Fe(cup)_3$ (cup = *N*-nitroso phenylhydroxylamine), $Fe(acac)_3$ (acac = acetylacetonate), or $Fe(CO)_5$, followed by oxidation, has been widely used in the field of IONPs synthesis.

According to Sun and Zeng,[22] a universal breakdown method based on the high temperature (265 °C) reaction of $Fe(acac)_3$ in phenylether in the occurrence of oleyl amine, oleic acid, and alcohol might be used to synthesize size-controlled monodispersed Fe_3O_4 NPs. The larger monodispersed magnetite NPs can be synthesized and distributed in a nonpolar solvent by seed-mediated growth technique using the smaller magnetite NPs as seeds. The method is easily scaled up for bulk manufacturing and does not need a size-selection process. By heating the synthesized Fe_3O_4 NPs clusters at a high temperature and in the incidence of oxygen for two hours, it is simple to convert them to γ-Fe_2O_3 NPs.

Even though the thermal decomposition technique offers a lot of benefits for creating extremely monodispersed particles with a limited size distribution, the main drawback is that the resulting NPs are typically dissolved in nonpolar solvents. The synthesis of IONPs has been represented in Fig. 2. Some of the artificial synthesis methods are summarised in Table 1.

4. Exposure and transportation of IONPs

Humans are exposed to IONPs through intravenous administration, ingestion, dermal uptake, and inhalation. All of these routes ultimately employ blood circulation to cross the BBB to enter and harm CNS. The transport of IONPs from the nostrils to the brain *via* the olfactory epithelium is a significant route to enter the CNS. Therefore, the nasal-to-brain route is a possible channel for the non-invasive delivery of therapeutic NPs straight to the brain, thereby avoiding the BBB. The machinery of transport includes two different pathways, as represented in Fig. 3.

Table 1 Artificial synthesis methods of IONPs and their merits and demerits

Method	Solvent	Temperature (°C)	Size range (nm)	Morphology	Advantages	Disadvantages	Reference
Hydrothermal synthesis	Water–ethanol	220	520	Spherical	Temperature-dependent synthesis occurs at very high temperatures	Yield is marginal, high pressure is needed	134 and 135
Laser pyrolysis	Organic	5–30	1100	Spherical less large	The production rate is high	In a water solution, the size of the particles is uncontrolled, and extremely high temperature	135
Co-precipitation	Water	20–90	15–200	Spherical	The production rate is high and the size distribution is narrow	A lack of good shape control	135
Thermal decomposition	Organic compounds	100–320	500–550	Spherical	Size distribution is very narrow, shape control is good, and the product is highly scalable	An inert atmosphere and a high temperature are required for this process	135
Sonochemical	Water	10–30	25	Spherical and rod shaped	Small-sized particles are produced	Requirement of high pressure and temperature	135
Microemulsion	Organic	20–50	4–12	Spherical or cubic	It has a narrow size distribution and a good shape control, which makes it a good product	Produced at a low rate	135
Spray pyrolysis	Organic	5–60	400–700	Spherical but aggregated	Simple and easy production, morphology is uniform, cost-effective	Increasing the temperature (1100 °C) leads to an increase in crystallinity	135 and 136
Arc discharge	Organic	5–30	1100	Spherical or less large	Particle shapes can be easily controlled	A lot of purification is often required	135
Sol–gel	Water	15–50	25–200	Spherical	Hybrid nanoparticles can be synthesized with desired shapes and lengths	Sol–gel matrix components are usually found on the surface of products	136 and 137

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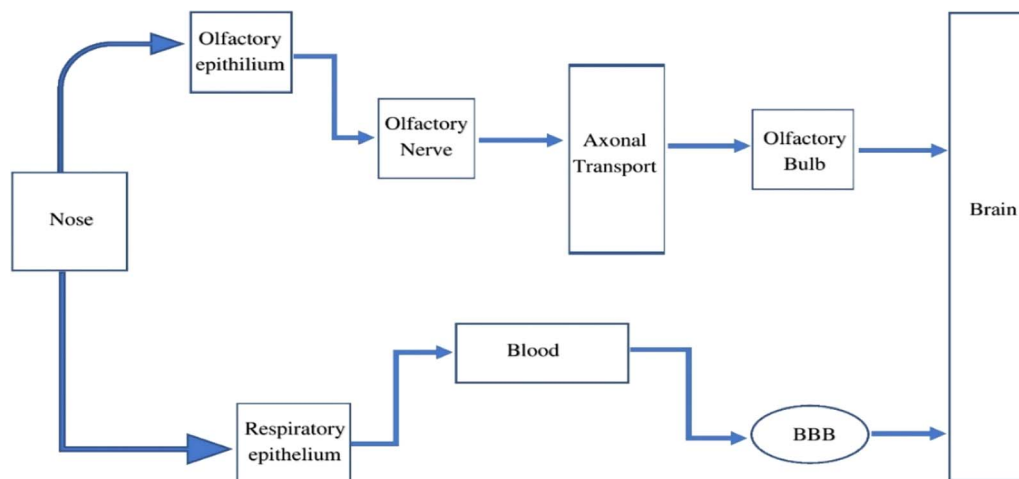*Environ. Sci.: Adv.*, 2024, **3**, 635–660 | **641**

Fig. 3 The pathway through which IONPs travel from the nasal cavity to the CNS, potentially involving olfactory nerve pathways or systemic circulation.

4.1 Olfactory pathway

The inhalation of environmental particulate matter can allow IONPs to contaminate the olfactory mucosa. Neuronal receptors in olfactory mucosa are found in the olfactory epithelium and are engaged in nerve impulse transmission. The cilia at the terminal of the olfactory receptor neurons are employed in signal transduction. Paracellular or transcellular mechanisms are used to transport molecules to the odor receptor neurons. Molecules generally cross the cell junctions between cells of the nose epithelium and invade the body *via* paracellular transport. The neural circuit is critical to constitute the route from the nasal to the brain. The olfactory bulb, on the brain's frontal region, becomes accessible by drug molecules/NPs traveling along an axon *via* a nerve bundle and crossing the cribriform plate. The olfactory bulb and cerebrospinal fluid can receive the drugs or NPs from the olfactory neurons.[23] By combining with the interstitial fluid in the brain, the drug or NPs can be transferred from the CSF to the brain. A substance or neuropeptide takes only a few minutes to reach the brain through olfactory transit. The olfactory neural pathway enters the brain *via* two distinct routes: the extra-neuronal pathway and the intraneuronal pathway.[24] Axonal transport constitutes the intraneuronal route that enables active compounds to reach the brain, and it might take from a few hours to days. Active molecules can reach the brain in just a few minutes when the transportation route involves perineural channels.[25] The cortex, cerebrum, and cerebellum are among the deepest brain regions that are innervated by the olfactory neuronal route.

4.2 Systemic pathway

Blood circulation also plays an essential role in the transportation of drugs or NPs to the brain from the nasal passage. Some amount of the drug or NPs are taken into the systemic blood through the nasal mucosa due to the abundant vasculature in the respiratory epithelium.[26] The respiratory portion comprises both uninterrupted and fenestrated endothelium,

permitting both small and large molecules to enter the bloodstream and be transported to the CNS by crossing the BBB. The BBB is a protective network of blood vessels and brain cells that effectively regulates blood flow to and from the brain. The primary physical barrier of BBB is made up of endothelial cells that are tightly placed. The 80 kDa glycoprotein transferrin (Tf) is the primary iron carrier protein in organisms. The molecule consists of two lobes and has two iron-binding sites consisting of two N- and C-terminal globular units. These sites are formed by the amino acid aspartate, histidine, and two tyrosine to create a 4-atom tetradentate ligand.[27] Nearly all iron transport and exchange in the body is carried out by Tf, and healthy adults normally have about 3–4 mg of circulating iron bound to Tf. Two Fe ions, oxidized by ferroxidase and diverted into the interstitium by ferroportin, are loaded into a single Tf unit, with only about 30% of all circulating Tf units engaged at any one time. Tf saturation occurs only with iron overload. Below 1% of circulating iron is typically not bound to Tf and is referred to as non-transferrin-bound iron (NTBI).[28]

The exact mechanism by which iron is exported from endothelial cells is unknown, but it might involve a reduction to Fe^{2+}, transfer across the endosomal cell membrane by divalent metal transporter 1 (DMT1), and export into the extracellular space by ferroportin (FPN1). Much of the Fe^{2+} that crosses the BBB is oxidized by ceruloplasmin (CP), which is located in astrocytic processes that surround brain endothelial cells. Thereafter, the oxidized form is bound by Tf, which is synthesized by oligodendrocytes. Neurons internalize the Tf-TfR1 complex into endosomes, where iron is isolated from Tf after acidification, transformed to Fe^{2+}, and transported into the cytosol *via* DMT1 to form part of the labile iron pool. Following that, the liberated iron may be utilized for various cellular functions, kept as ferritin cores, or expelled from the cell by FPN1. It is conceivable that cellular reductants like citrate or ascorbate, as well as circulating ferritin proteins, albumin, and ATP, reduce NTBI, which is discharged by astrocytes and later introduced by the DMT1 of oligodendrocytes. Oligodendrocytes have a lot of iron,
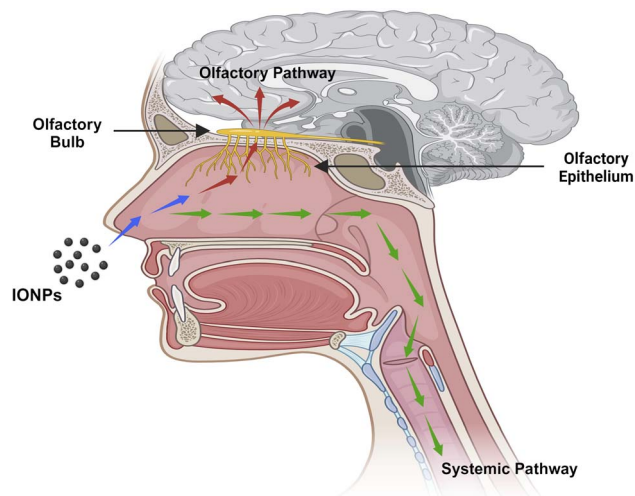
Fig. 4 Pathways through which IONPs travel from nose to brain. IONPs proceed from the nasal area to the brain *via* two different pathways. The olfactory pathway, which involves directly following the neurological connection, whereas the systemic approach involves entering the bloodstream and traveling to the brain *via* systemic circulation.

which is necessary for the myelination of axons. However, the mechanism explaining the intake of iron by glial cells is less understood. FPN1 combines with amyloid precursor protein (APP), which may act as a ferroxidase at the intracellular membrane of neurons, astrocytes, microglia, and astrocytes. Tf is recycled after Fe^{2+} release to attach with the Fe^{3+} in the circulation. CP on astrocyte membranes oxidizes Fe^{2+} to Fe^{3+} to bind with the Tf. Neurons absorb both Tf-bound iron and NTBI. NTBI may also attach to citrate and ATP derived from astrocytes in order to serve as an iron supply for oligodendrocytes and astrocytes. Tf is synthesized by oligodendrocytes and is involved in intracellular trafficking. Ferritin, a cytosolic iron storage protein, captures and deposits NTBI in brain cells[29] (Fig. 4).

5. Impact of IONPs on CNS

5.1 Beneficial effects

The ferrimagnetic family of magnetic materials, including IONPs, is used in various medicinal and bioengineering applications.[30] Mixed ferrites, γ-Fe_2O_3, and Fe_3O_4 are three distinct kinds of IONPs. Superparamagnetic IONPs (SPION) synthesized after surface modification can be employed in magnetic particle imaging (MPI), targeted drug and nucleic acid delivery, MRI, biosensing, hyperthermia, biomolecule separation, and tissue repair.[31] The magnetic properties of SPION enable its usage in several applications, as it can be synthesized in different shapes and sizes.[32] The magnetic moments of SPION are strong when they are subjected to an external magnetic field but disappear following the removal of the magnetic field. The BBB prevents many medications from penetrating the brain at a therapeutic level, which makes imaging, drug delivery, and treatment challenging in cases of CNS-related issues like brain tumors. The primary functions of BBB include protecting the CNS from

potentially harmful molecules and maintaining brain homeostasis. BBB protects CNS from hazardous substances and is also responsible for preventing many therapeutic molecules from passing through it to reach their targets in the brain. As a result, some molecules are allowed to pass through passive diffusion, while other essential substances, such as amino acids, glucose, and water, are selectively transported across the BBB to maintain the normal functions of neurons in the CNS.

Due to the BBB, some tumors, such as metastatic tumors and brain gliomas, cannot be chemotherapeutically treated. A variety of methods can be employed to overcome BBB in the case of chemotherapy drugs, such as the use of intrathecal drug administration or the use of olfactrogenic agents. The drugs can also be delivered through the BBB in small doses if the BBB is disrupted biochemically, osmotically, or using vasoactive substances such as bradykinin to increase the flow to the brain.[33] Certain diseases, such as cancer, are known for having poor prognoses or the failure to undertake early detection or anticipate their pathological pathways, thereby exposing patients to high morbidity and mortality rate, particularly for metastatic tumors. Therefore, there is an increased need for theranostics.[34,35] Theranostic drugs are safe, tolerable, and have both therapeutic and diagnostic potential in a single substance. Due to their distinctive characteristics and simple surface manipulation, IONPs have strong prospects for theranostic uses. Theranostic IONPs can be employed as a transport mechanism for cell replacement procedures, MRI-assisted tumor detection or surgical excision, and targetable gene transfer using an external magnetic field. An integrated theranostic system consisting of IONPs in MRI contrasting agent and doxorubicin (DOX) as a chemotherapeutic agent has been developed, which are useful in diagnosing and treating diseases.

Since uncoated IONPs with a size of 16 nm tend to precipitate or aggregate, IONPs are coated with biocompatible substances.[36] The process of cellular absorption and the fate of IONPs depend on the hydrophilicity and size of the surface-modifying materials. Particles having a size >100 nm are strongly phagocytosed, whereas those that are <30 nm undergo pinocytosis. Increased hydrophilicity lowers pinocytosis by hindering a particle from being transported through the hydrophobic lipid bilayer of the plasma membrane.[37]

Regarding toxicity, ultrasmall IONPs of size 2.3 and 4.2 nm have been demonstrated to be highly toxic. It shows toxicity at 100 mg kg^{-1} dosage in the mice model. On the other hand, no clear toxicity was reported for IONPs having a size of 9.3 nm. Additionally, the study also revealed that the toxicity of small nanoparticles could be diminished by splitting the dosage into four doses at five-minute intervals.[38]

BBB can also be breached by endogenous transport systems, including insulin receptor-mediated transcytosis, carrier-mediated transporters, such as glucose carriers and amino acid carriers, or by inhibiting active efflux transporters, such as P-glycoprotein. Vectors that target BBB transporters, for example, the transferrin receptor (TfR), are known to remain entrapped in brain capillaries rather than traveling through the BBB to the targeted location.[39] Several ways to transport
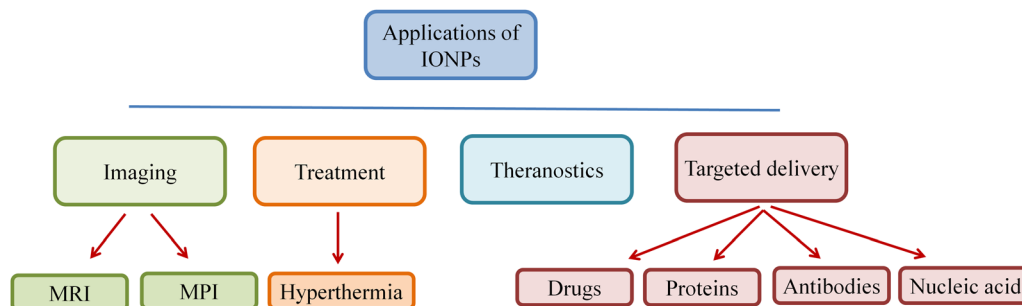
Fig. 5 Multiple applications including targeted drug delivery and diagnostic imaging of IONPs in medical science.

medications across the BBB include convection-enhanced diffusion and intracerebral insertion using needles. The beneficial effects of IONPs are illustrated schematically in Fig. 5.

IONPs often exert neuroprotective roles to ameliorate the nanotoxic effects of certain compounds. For example, a natural phytochemical, sulforaphane (SF) along with Fe_3O_4-NPs carrier (N.SF), was found to be beneficial against the chemotherapeutic drug cisplatin (CIS), which shows severe side effects of neurotoxicity. The intranasal administration of N.SF to the CIS-treated rats were found to have neuroprotective functions on the biochemical, histopathological (striatum and cerebral cortex), and behavioral aspects.[40] Other studies have shown the neuroprotective efficacy of Fe_3O_4-NPs in fruit fly models by executing catalase-like functions. Its neuroprotective roles have been established in PD and AD models in *Drosophila*. IONPs, when administered through the dietary route amongst aged *Drosophila*, ROS levels are diminished the flies performed better climbing performance, and their lifespan was increased. Additionally, IONPs have also been demonstrated to increase the life span of *Drosophila* in the AD model and alleviate the neurodegenerative condition. The neuroprotective role in the PD model was found to be exerted by means of retreating the
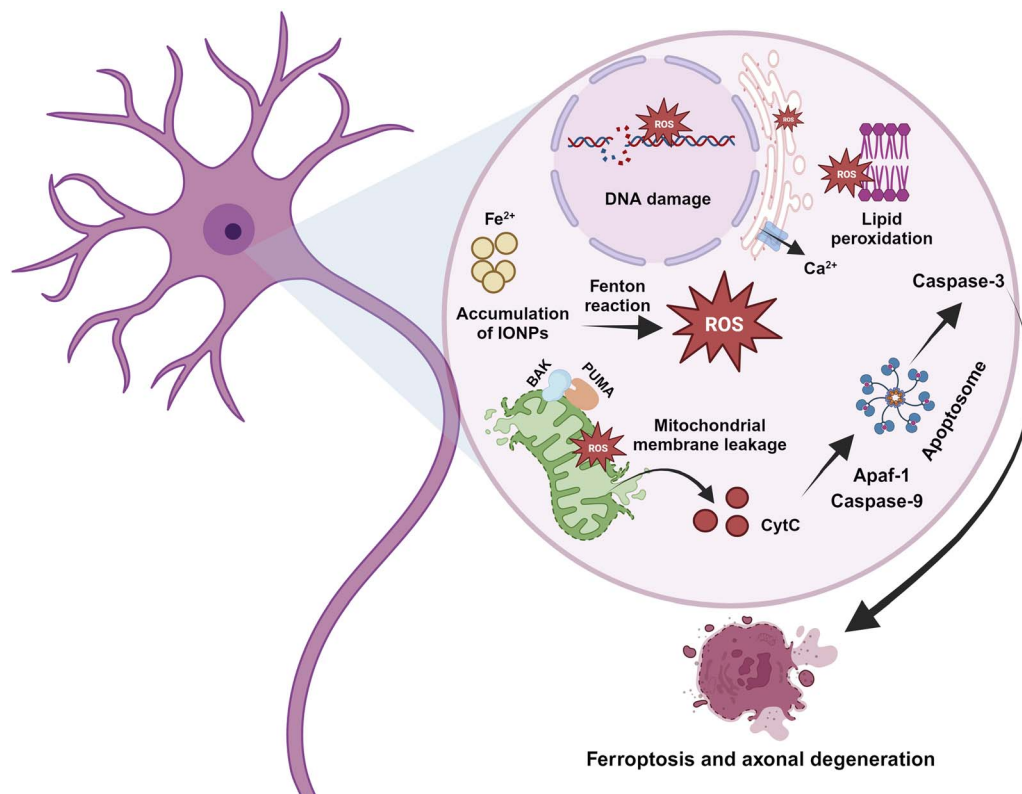

Fig. 6 Invasion of neurons by IONPs. IONPs can invade the neurons and aggregate to form clumps. IONPs catalyze the Fenton reaction to produce ROS and exert ensuing oxidative stress. ROS peroxidizes lipids of the cell membrane as well as the mitochondrial membrane. Moreover, ROS targets DNA and induces Ca^{2+} efflux from the endoplasmic reticulum. Mitochondrial membrane damage leads to the aggregation of BAK and PUMA, wich disrupts mitochondrial membrane potential. The leakage of matrix proteins, including cytochrome C, interacts with Apaf-1 and caspase 9 to produce functional apoptosomes. Apoptosome triggers the activation of caspase 3 that, along with other mediators, augment ferroptosis and neurodegeneration.

accumulation of α-synuclein and the activation of caspase-3.[41] Similar neuroprotective role of IONPs upon implantation at the lesion site and exposure to a magnetic field in an *in vivo* 6-OHDA rat model of PD have been established as demonstrated by the substantial improvement of mitochondrial functionality and healing of the scar.[42]

5.2 Detrimental effects

5.2.1 Iron accumulation. Cells may take up IONPs through phagocytosis, different types of endocytosis, or *via* diffusion.[43] While tiny IONPs are entered into a cell by pinocytosis, bigger IONPs are absorbed by endocytosis.[44] After being introduced into the endosome, IONPs are broken down and discharge iron ions into the cytoplasm.[45] Degradation of IONPs is notable in the endosomal medium, which has a pH of 4.7 and contains citrate. Acidic pH is unable to degrade IONPs without citrate. Liberated iron ions are introduced into the physiological pathways; for instance, they take part in the production of hemoglobin or are stored by ferritin in cells. IONPs affect iron hemostasis, which in turn affects the up or down-regulation of proteins involved in the storage and release of iron from the cells, like TfR1.[46] Nuclear ferritin levels rise in response to iron released by IONP breakdown, reducing the DNA-damaging effects of excessive iron. Additionally, the cells exposed to IONPs increase FPN1 expression and ferritin release to export iron.[47] This suggests that IONPs have an impact on the iron reserves in cells.

Several factors of IONPs, like the initial concentration, shape, size, functional group, coating, and cell type, affect the aggregation of iron inside a cell. Depending on the IONP dosage, the amount of iron in the cells increases.[48] Furthermore, the amount of IONPs also influences their retention time in tissues. When IONPs are administered in high amounts, it cannot be entirely removed from the systemic circulation. However, a small amount can be eliminated within three weeks.[49] As a result, the elevated dose of IONPs exposes the cells to IONPs for a long time. In the cell, comparatively small-sized IONPs may aggregate in greater concentrations than bigger ones.[50] Spherical NPs degrade more slowly than cubes because they have less contact area for degradation. Compared to citrate coating, dextran coating on IONPs reduces the degradation rate.

Positively charged IONPs with amine groups are more easily absorbed by the cells than the IONPs with negatively charged carboxyl or hydroxyl groups.[51] Cell type is a vital factor for IONP absorption. The brain endothelial cells absorb a smaller quantity of IONPs, whereas microglia absorb a large amount of IONPs.[51] Any element that alters IONP uptake or degradation rates can impact iron deposition in tissues or cells.

In spite of its medical applications, the biomedical administration of magnetic IONPs has aroused critical concerns regarding their pharmacokinetics *i.e.* their distribution in
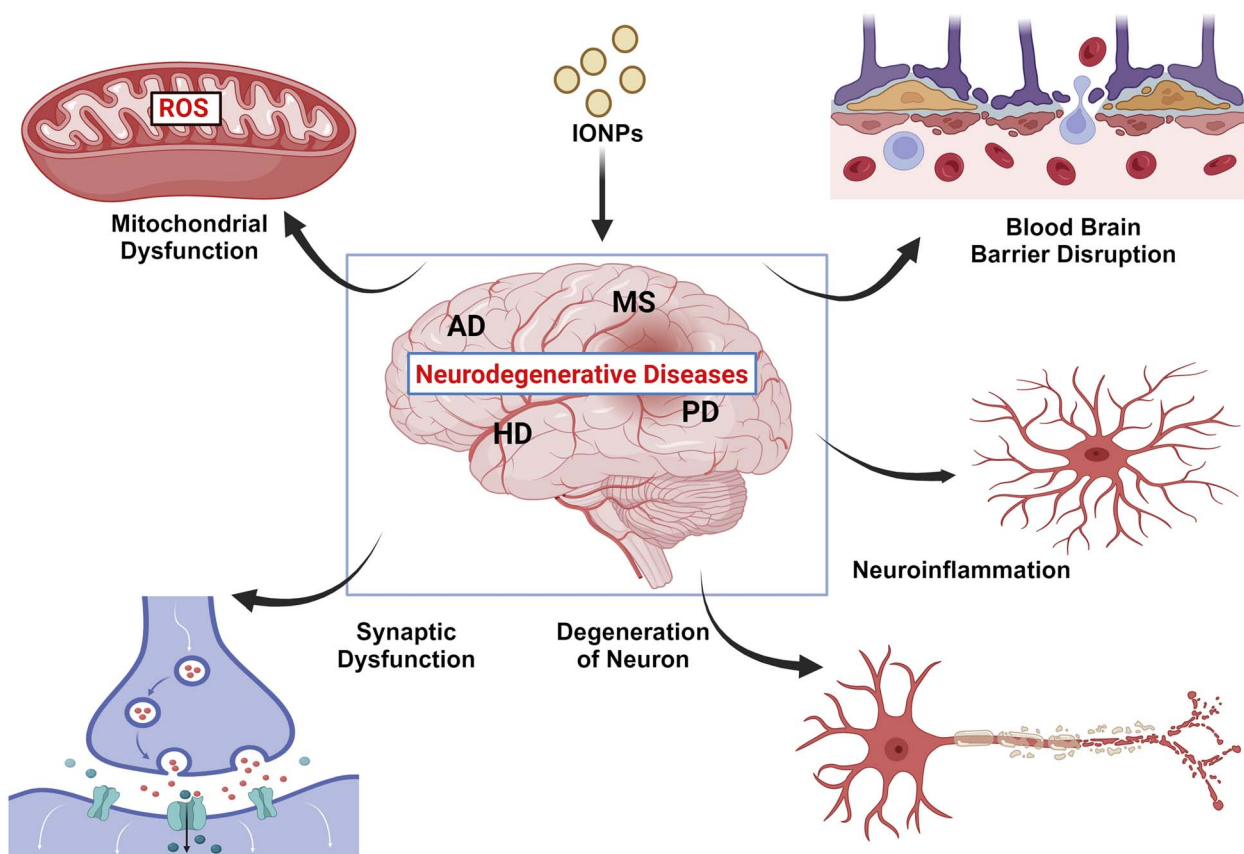
Fig. 7 Complications associated with IONPs in CNS. IONPs can impose various adverse effects on CNS, including neuroinflammation, neurodegeneration, disruption of the BBB, altered neuronal signaling, and ROS production through several cytosolic pathways.

various organs after absorption, eventual metabolism, and finally excretion, which as a whole contributes to IONP-induced toxicity. Adsorption of plasma proteins greatly affects the fate and distribution of IONPs after their administration. Human serum albumin when adsorbed to IONPs, showed longer circulation time in blood.[52,53] Endosomes/lysosomes are the sites where the IONPs reside after their uptake by the cell and subsequently liberate into the form of free iron and add up into the cellular iron pool. Overabundance of intracellular iron oxidizes and damages the cellular proteins and nucleic acids. Up-regulation of ferritin and down-regulation of transferrin receptors in labeled cells may protect cells from possible cytotoxicity led by higher intracellular iron concentrations.[54] Researchers have deployed colloidal IONPs like the

superparamagnetic iron oxide nanoparticles (SPIONs) and ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles as contrast agents (CA) in magnetic resonance imaging (MRI). SPIONs have their speciality in not showing magnetization without the presence of the external magnetic field. SPIONs, along with their features of high saturation magnetic moment and chemical stability also show minimized cellular toxicity.[55,56]

5.2.2 Oxidative stress. IONPs have a large surface area that can be used for redox cycling. Iron ions are removed from their surfaces by enzymes, which can also generate ROS. The Fenton reaction and the production of ROS from superoxide and H_2O_2 are both possible outcomes of the iron ions produced by IONPs.[57] Mouse fibroblastic cells were less affected by H_2O_2 when bare Fe_3O_4 was used as the catalyst.[58] Several factors,

Table 2 *In vivo* detrimental effects of IONPs in different organisms

Organism	Method	NP type	Size (nm)	Concentration	Coating	Functional group	Explanation	Reference
Rat	Intranasal	Fe_2O_3	36	20 μg μL^{-1}	APTS	Amine	IONPs are delayed in being removed from the stratum and hippocampal region because of increased oxidative stress	138
Rat	Oral	Fe_2O_3	30	30 mg per kg per day, 300 and 1000 mg per kg per day	Bare (none)	Hydroxyl	It inhibits Mg^{2+}, Na^+–K^+ and Ca^{2+} ATPases in the brain, reduces body weight, and inhibits acetylcholine esterase in the brain	62
Rat	Intravascular injection	Fe_2O_3	10	50 mg kg^{-1}	Bare (none)	Hydroxyl	Dopaminergic neurons were damaged and dopamine levels in the striatum were significantly decreased	51
Rat	Intratracheal instillation	Fe_3O_4	< 50	1 and 5 mg kg^{-1}	Bare (none)	Hydroxyl	Body weight reduction	139
Rat	Injection into stratum	Fe_3O_4	6.5 + 3.0	3 μ NP 2 μL^{-1} in a CSF	Bare (none)	Hydroxyl	A reduction in oxidative stress within the stratum and an increase in body weight	42
Drosophila	Exposure	Fe_3O_4	20	200 μg mL^{-1}	Bare (none)	Hydroxyl	The ROS levels of six-week-old flies were significantly reduced, and their climbing ability was enhanced, and their longevity increased	140
Mouse	Intravascular injection	Fe_3O_4	5	0.4, 2, and 10 μg kg^{-1}	PEG	Hydroxyl	Heart cells are induced to undergo DNA damage and oxidative stress	141
Water fleas (*Daphnia magna*)	Exposure	Fe_2O_3	33.3 50.4	10–100 mg L^{-1} 1–100 mg L^{-1}	Bare (none) Dimercaptosuccinic acid	Hydroxyl Thiol and carboxyl	A significant amount of toxicity is possessed by coated and uncoated IONPs when ingested and accumulated in the gastrointestinal tract	140
Green algae (*Raphidocelis subcapitata*)	Exposure	Fe_2O_3	33.3 50.4	1–100 mg L^{-1} 1–100 mg L^{-1}	Bare (none) Dimercaptosuccinic acid	Hydroxyl Thiol and carboxyl	IONPs coated or uncoated inhibit growth after 72 hours	140
Duckweed (*Lemna minor*)	Exposure	Fe_2O_3	33.3 50.4	1–100 mg L^{-1} 1–100 mg L^{-1}	Bare (none) Dimercaptosuccinic acid	Hydroxyl Thiol and carboxyl	In this range of doses, NPs have no effect	140

including size, functional group, coating, and oxidation state of iron, regulate the interaction of IONPs with cellular elements. An important factor in determining NP toxicity is the oxidation state of the iron, *i.e.*, Fe^{2+} or Fe^{3+}. Compared to Fe^{2+} in Fe_3O_4, Fe^{3+} in Fe_2O_3 is more toxic and inflicts DNA damage.[59] The cytotoxicity of IONPs may vary depending on their size. Small IONPs break down more quickly after cellular uptake than large IONPs. Large IONPs tend to aggregate more than small IONPs, making it easier for macrophages to engulf them. Smaller IONPs produce more ROS than larger particles because they have a more reactive surface.[59]

According to a study, endothelium cells exposed to 10 nm-IONPs may experience a marked rise in ROS levels.[51] However, the bare NPs in the 30 nm size induced the production of ROS, while the bare IONPs in the 5 nm size did not change the level of ROS.[48] Therefore, it is apparent that surface charge and coating determine the interaction of IONPs with cellular components.[52] Coating IONPs with aminopropyl trimethoxysilane (APTMS) can be detrimental to cell viability and DNA content. A greater amount of IONPs is endocytosed by cells and are concentrated in the cell as a result of surface amine groups. It is more likely that the positively charged APTMS coated IONPs interact with the negatively charged DNA.[44]

5.2.3 Protein aggregation. IONPs can induce oxidative stress and subcellular iron buildup. IONPs have the potential to promote protein aggregation because of the oxidative stress that affects the build-up of the proteins such as α-synuclein (αS) and amyloid beta (Aβ). Various factors influence the function of IONPs, including their coating, side-groups, and charge. Uncoated IONPs boost the development of αS aggregation, whereas lysine-coated IONPs inhibit protein aggregation. Uncoated IONPs can promote protein agglomeration by changing the ionic potential of soluble proteins.[60] Compared to neutrally- or negatively-charged IONPs, positively-charged IONPs may induce Aβ fibrillation due to their reduced concentration. Additionally, it has been suggested that the surface of IONPs with fluorinated, sulfated, or sulfonated groups can restrain the synthesis of Aβ fibril. Hence, the effects of IONPs on brain cells can be minimized using the appropriate coatings and side-groups. Based on oxidative stress, protein aggregation, and iron accumulation, there is a positive feedback loop where one component encourages the other by the initiation of iron aggregation, protein agglomeration, or oxidative stress. Additionally, IONPs may promote neurons to undergo apoptosis or neuronal death. IONPs may also be engaged in neurodegeneration due to oxidative stress, iron accumulation, protein aggregation, and ferroptosis (Fig. 6).

5.2.4 Ferroptosis. Neurological stem cell membranes are depolarized by IONPs, and mitochondrial membranes are hyperpolarized by IONPs on a long-term basis.[61] Na^+–K^+ ATPase, a transporter required to maintain the resting potential of the cell membrane, was inhibited due to membrane depolarization in rats.[62] In cells depolarized by calcium ions, *N*-methyl-D-aspartate (NMDA) receptors are activated, causing Ca^{2+} ions to enter and eventually cause apoptosis.[63] Exposure to IONPs results in the disruption of the mitochondrial membrane potential, release of cytochrome c from mitochondria, and activation of caspase 3.[64] As a result, IONPs may activate

ferroptotic pathways in cells through mitochondria-dependent mechanisms. Along with protein agglomeration, iron aggregation, apoptosis, and oxidative stress, IONPs can also inflict neuroinflammation, disruption of the BBB, degeneration of the neurons, dysfunction in mitochondria, and disturbance in neuronal signaling[12,13] (Fig. 7). The detrimental *in vivo* effects of IONPs in different organisms is represented in Table 2.

6. Association between IONPs and neurodegenerative diseases

6.1 Alzheimer's disease (AD)

AD is the most prevalent form of dementia worldwide. AD is a growing neurodegenerative disease that is first categorized by short-term memory loss, a stage referred to as mild cognitive impairment (MCI) and progresses to aphasia, and gradually to agnosia, *i.e.*, the inability to recognize people or things followed by apraxia, which is the inability to perform voluntary movements along with other memory and behavioral problems.[65] Clinically, the illness stage is evaluated by psychological assessments such as the mini-mental state examination (MMSE), which includes patients responding to a series of questions designed to measure their level of cognitive ability.[66]

The expected lifespan of a person diagnosed with AD is 3 to 10 years. The disease typically manifests around the age of 65; however, it can affect much younger people in cases where a familial link has been established.[67] The majority, *i.e.*, 95% of AD cases, are sporadic (SAD), with less than 5% being genetic or "familial" (FAD). There is a clear medical demand for the treatment of AD since present therapies merely provide symptomatic relief rather than treating the underlying illness cause. Currently, two types of AD therapeutics are utilized such as glutamate antagonists and acetylcholinesterase (AChE) inhibitors, like donepezil and rivastigmine.[68] Glutamate antagonists inhibit the overstimulation of glutamate in AD.[69]

Senile plaques, which are external Aβ deposits, and tangles of neurofibril, which are intracellular clumps of hyper-phosphorylated tau protein, are the two primary neurological symptoms of AD.[70] Other structural changes to the brain are also noted, including a reduction in the weight of the brain because of the loss of grey matter, a rise in ventricle size due to CSF aggregation, and a decrease in the thickness of the cortex.[71,72] The medial temporal lobe, which includes the hippocampus, entorhinal cortex, and amygdala, is one of the first brain regions affected by AD.

The metal hypothesis or ferroptosis hypothesis is one of the many theories proposed to cause AD. In contrast to other modes of cell death, like necrosis and apoptosis, ferroptosis is a type of programmed cell death. Iron overload is a defining feature of ferroptosis, a disorder where lipid peroxides build up to lethal quantities due to iron.[73] It involves brain iron accumulation, lipid peroxide, and glutathione depletion simultaneously, which causes a cascade of events that includes neuronal communication failure, astrocyte dysregulation, neurotransmitter oxidation, myelin sheath degeneration, dementia, and cell death.

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The changes in the morphology of cells undergoing ferroptosis include nuclear chromatin condensation, decreased mitochondrial membrane density, reduced or absent mitochondrial cristae, cell swelling, and ultimately, cellular as well as mitochondrial membrane disintegration.[74]

6.2 Parkinson's disease (PD)

PD is a neurological illness marked by a gradual degeneration of dopaminergic neurons in the substantia nigra (SN) of pars compacta. In addition to iron aggregation, increased production of inflammatory markers and ROS occur more often. These findings suggest that the dyshomeostasis of iron may be a major factor in neurodegeneration. A growing number of people are affected by PD, which affects one in ten people over the age of 60, due to the increase in life expectancy in nations with a huge number of industries.[75] Aceruloplasminemia and neuroferritinopathy are conditions associated with iron accumulation in certain brain areas, like SN, leading to PD. Animal models of PD show an increased level of iron in the SN when treated with 6-hydroxydopamine (6-OHDA). These data show a connection between iron accumulation and neurodegenerative disorders.[76] The accumulation of iron in the brain of PD patients correlates with a decline in Tau and APP levels. Tau interacts with APP to enhance iron export, while APP stabilizes FPN1 on the cell membrane.[77] This suggests that a disturbance in the iron homeostasis in the brain may be a factor triggering iron accumulation in PD.

6.3 Multiple sclerosis (MS)

MS is a degenerative and inflammatory condition that impairs the myelin sheath that surrounds axons and the oligodendrocytes that produce myelin. Several factors are identified that contribute to the neurodegeneration occurring in MS, including inflammatory molecules, protease dysfunction, mitochondrial dysfunction, and glutamate excitotoxicity. MS is increasingly associated with iron metabolism dysregulation and its cytotoxicity. MRIs are employed to examine the deposition of iron in the brains of patients suffering from MS. Increased iron concentration in deep grey matter areas has been discovered using MRI and is linked to grey matter atrophy. MRI results indicate the presence of oxidative damage and iron accumulation in deep grey matter. The mitochondrial function is further impaired in patients with MS, which is caused by frequent damage to mitochondria and the subsequent rise in ROS, which

Table 3 Diseases of the CNS caused by iron overload and the regions of the brain affected by the iron accumulation

Neurodegenerative diseases	Description	Brain regions affected	References
Alzheimer's disease	Alzheimer's disease leaves people unable to perform even the most basic tasks due to the slow deterioration of memory and thinking abilities	Iron elevation in cortical, hippocampal, and cerebellar neurons	142
Parkinson's disease	Parkinson's disease (PD) is a neurological disorder marked by a gradual loss of dopaminergic neurons in the pars compacta of the substantia nigra (SN)	Pars compacta of the substantia nigra	143
Huntington's disease	Huntington's disease (HD) refers to a progressive neurodegenerative disorder which is characterized by psychiatric, cognitive, and motor dysfunction that leads to dementia	Striatum and cerebral cortex	144
Neuroferritinopathy	In neuroferritinopathy (NF), abnormal excessive iron accumulation occurs primarily in the basal ganglia of the brain due to mutations in the ferritin light chain 1 (FTL1) gene	Basal ganglia	145
Amyotrophic lateral sclerosis (ALS)	Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by motor neuron loss	Cerebral cortex, spinal cord, and brain stem	146
Pantothenate kinase-associated neurodegeneration (PKAN)	A mitochondrial pantothenate kinase 2 gene mutation, located at locus 20p13-p12.3, leads to pantothenate kinase-2-associated neurodegeneration	Globus pallidus	147
Multiple sclerosis	Multiple sclerosis (MS) is a degenerative and inflammatory condition that causes damage to the myelin sheath which surrounds axons and the oligodendrocytes that produce myelin	Elevated level of iron in deep grey matter, *i.e.*, putamen and caudate	14

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in turn leads to the loss of genomic integrity and further impairments to mitochondrial function due to iron-mediated oxidative damage.[78,79]

6.4 Huntington's disease (HD)

HD is a growing neurodegenerative disorder characterized by cognitive, psychiatric, and motor dysfunction, leading to dementia. Brain areas in HD, particularly the cerebral cortex and striatum, experience gradual degeneration beginning several years prior to clinical onset.[80] In order to account for the pathogenetic mechanisms of HD, a number of factors have been implicated, including oxidative stress, dysfunction of oxidative phosphorylation, transcriptional dysregulation, and defects in axonal transport.[81–83] The caudate striatum and putamen are believed to be the first structures to show signs of neuronal degeneration in HD. Once the caudate and putamen striatum structures are affected, the degeneration spreads to other myelinating regions, with the medial temporal lobe being considerably less affected.[84] Due to a surge in iron deposition in the basal ganglia, several neurological disorders have been linked with injuries in the tissue. These diseases include PD, MS, AD, and other metabolic disorders.[85] HD is also known to be associated with alterations in iron metabolism. Gene knockdown models have shown iron-dependent localization, oxidation, and structural organization of mutant htt inclusion bodies produced by knockdowns of the human htt gene.[86] Some diseases of CNS are caused by iron overload, and the affected areas of the brain are summarised in Table 3.

7. Molecular mechanism of IONP-induced neurodegeneration

IONPs enter the BBB through the cells that line its endothelium *via* the TfR1-mediated endocytosis of Tf, independently as NTBI, or as a low molecular weight complex.[87] As circulating diferric-transferrin binds to transferrin receptors lining the cerebral lumen, IONPs are likely to be taken up by brain vascular endothelial cells by receptor-mediated endocytosis. Astrocytes are positioned perfectly to absorb iron from the blood and circulate it to different cells present in the CNS. Astrocytes contain the iron efflux as well as the influx mechanism necessary for cell-to-cell iron transfer. The expression of DMT1 by astrocytes is thought to mediate the iron influx into the glial cells.[88] Iron that is stored in astrocytes as ferritin is exported by a mechanism that employs CP as well as FPN1.[89] Oligodendrocytes take up iron *via* the non-vesicular iron import mechanism, or NTBI *via* DMT1, or ferritin receptor Tim-2. Iron can be influxed into neurons and microglia *via* Tf-TfR-mediated uptake and effluxed *via* FPN1.[87] The iron, exported from the endosomes *via* DMT1, contributes to the labile iron pool, which
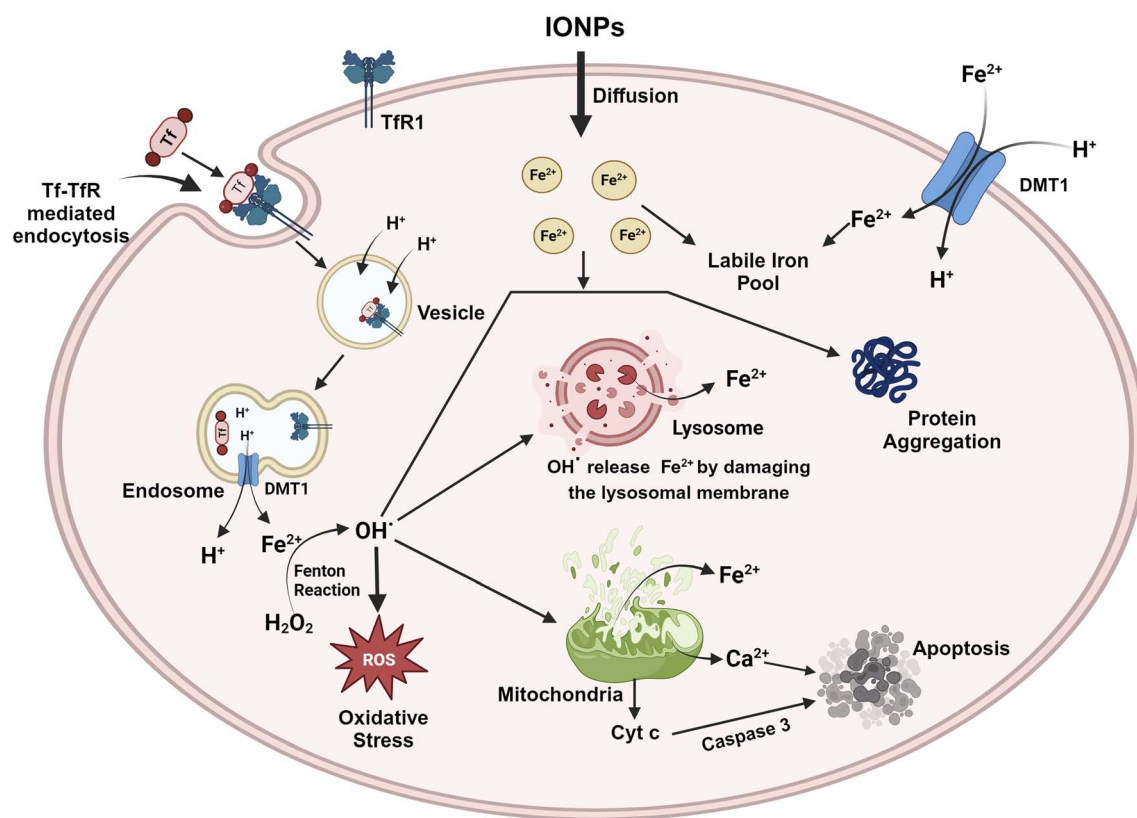
Fig. 8 Subcellular entry of IONPs through receptor–mediated endocytosis triggers the production of ROS through the Fenton reaction and switches on various cytosolic cascades, leading to protein aggregation, oxidative stress, iron accumulation, and apoptosis. All of these events are orchestrated together to favour the onset of neurodegenerative diseases.

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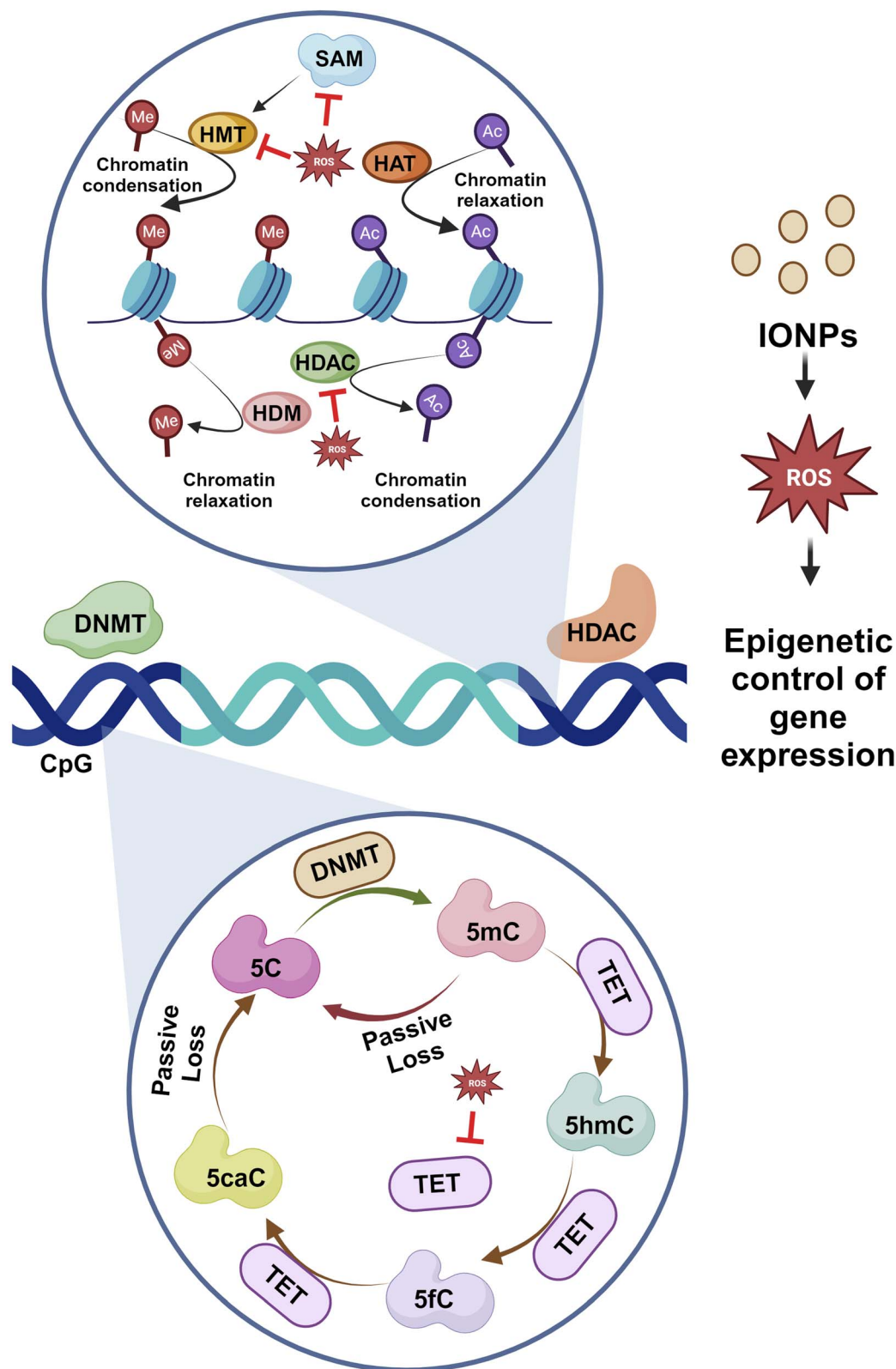
Fig. 9 Epigenetic modulation of gene expression by IONPs. IONPs trigger ROS production through the Fenton reaction that imposes modulatory impacts on determinants of gene expression or silencing. Both events, such as transcriptional activation or repression, are dynamic processes that are mediated by a group of enzymes like histone methyl transferase (HMT), DNA methyltransferase (DNMT), histone acetyltransferase (HAT), histone demethylase (HDM), and histone deacetylase (HDAC). Methyl groups are added to histones and DNA by HMT and DNMT, respectively. SAM acts as the methyl donor. Methylation is associated with heterochromatin formation and gene repression. It has been shown that ROS induced by IONPs can target HMT, HDAC, and DNMT and hence promote hypomethylation. DNMT mainly methylates at CpG islands of promoters, leading to the formation of 5 methyl cytosine (5 mC). mC can be converted into a series of intermediates to affect DNA methylation. It has been reported that ROS can impede the catalytic activities of both DNMT and TET and hence trigger epigenetic alterations, leading to abrupt gene expression and repression. Such abnormal events could be linked to neurodegeneration.

constitutes the iron content available in neurons. A major iron storage protein within neurons, ferritin, is regulated by iron-binding and cellular metal-sensing proteins, and then iron is recirculated by apo-Tf.[13] The high incidence of iron can be toxic to the brain even though iron plays a crucial role in many metabolic processes. Thus, any change in the iron level may be detrimental to human health. IONPs can lead to oxidative stress, iron aggregation, and protein agglomeration. The surface area of IONPs is large, allowing them to participate in redox cycling. Additionally, the iron ions generated by IONPs could potentially participate in the Fenton reaction, producing OH from H_2O_2 and ultimately causing oxidative stress. ROS can directly impair the cell membrane, the membrane of the organelle, and DNA. ROS leads to the release of cytochrome C and Ca^{2+} from mitochondria and hence induces apoptosis.[63] In addition, ROS leads to iron aggregation in the cytosol, and the iron is released from mitochondria as well as lysosomes by destroying the membranes of the organelles.[90] ROS and free iron affect several proteins, which alter their conformation and facilitate aggregation. Several iron-sensitive brain areas can be damaged by iron dyshomeostasis. Neurodegeneration is associated with iron accumulation in the brain as a result of iron overload in the basal ganglia. PD along with AD are two sporadic neurodegenerative diseases that have been linked to high levels of iron and pathogenic triggers that are related to iron. Between oxidative stress, iron accumulation, and protein aggregation, there is a loop with positive feedback where one element encourages the other. By inducing protein agglomeration, oxidative stress, or iron aggregation, IONPs can turn on this loop. Additionally, IONPs may cause the neurons to undergo apoptotic cell death. The molecular mechanism is represented with the help of Fig. 8.

IONPs tend to modulate the epigenetic activation of transcription by activating enhancers. In a study, IONPs like Fe_2O_3 and $Fe_2O_3@Co$ NPs alter the genomic distribution of H3K27ac, which causes alterations in the activity of enhancers.[91] In some cases, exposure to γ-Fe_3O_4 NPs could increase the cytosine methylation in the genome while disrupting genomic stability.[92] Gene expression is controlled by a precise balance between methylation and acetylation events. DNA methylation is a dynamic process that covalently adds methyl groups to C5 of cytosine, mainly at CpG islands of promoters, leading to the generation of 5-methylcytosine (5-meC). Enzymes, mainly DNA methyltransferase, DNMT1, DNMT 3A, and DNA methyltransferase DNMT3B, play crucial roles in such events. Here, S-adenosyl-L-methionine acts as the methyl donor. Another enzyme referred to as ten-eleven-translocation (TET) catalyzes the conversion of 5-meC to 5-hydroxymethylcytosine (5-hmeC) and 5-carboxycytosine to assist in the demethylation process. Exposure to IONPs can trigger the methylation of histone, H3K9, and H3K27 as well as the reduced methylation of histone K3K4 and H3K36 at the 5′ end. In addition, metal NPs can contribute to the demethylation of cytosine that contributes to epigenetic changes and aberrant gene expression.[93] Many of the miRNAs are essential to promote neural development. IONPs have been documented to reduce expressions of miRNAs that could significantly affect the entire epigenetic landscape.[94]

miRNA-124 suppresses PTBP1, leading to differentiation in neuronal cells rather than non-neuronal cells. Certain miRNAs also control the development and maturation of synapses and dendrites. Therefore, unusual alterations in DNA methylation and acetylation process through changes in enzymes and regulatory RNA activities can impact neurons, and such re-editing events contribute to neurodegenerative diseases.[95]

DNA methylation is crucial for memory acquisition and storage.[96] The loss of function in DNMT1 and DNMT3A is associated with perturbed hippocampus-mediated memories.[97] The methylation of CpG islands at promoter sites results in the formation of 5-methyl-cytosine (5mC), which is further converted into 5hmC, 5-formyl-cytosine(5fC), and 5-carboxy-cytosine (5caC) by methylcytosine dioxygenases ten-eleven translocation proteins (TET).[98] The increased activity of DNMT1 is linked to the enhanced methylation of the gene for α-synuclein (SNCA). Reduced SNCA methylation at intron 1 is evident in sporadic patients.[99] Histone acetylation is inhibited when SNCA binds to H3. Therefore, blocking the activity of HDAC could help prevent neurotoxicity. Studies have revealed that the inhibition of HDAC Sirtuin 2 reduces SNCA-mediated neuronal damage.[100] SNCA also downregulates genes encoding for histones H1, H2B, and H4.[101] Increased activities of HDAC2 and HDAC6 in the hippocampus and prefrontal cortex of AD are associated with impaired cognition. Reduced methylation, as evidenced by less 5mC, 5Fc, 5hmC, and 5caC in the entorhinal cortex and cerebellum, is linked to the onset of AD.[102] Reduced methylation of cytosine residues at 207–182 of amyloid precursor protein results in elevated amyloid-β (Aβ) deposition in the brain, contributing to AD. The epigenetic modification of histones like H3 methylation, H2B ubiquitination, and H4 acetylation has been associated with Huntington's disease.[95] Therefore, histone modification is critical in PD development (Fig. 9).

8. Future prospective to minimize IONP exposure

Exposure to IONPs impart negative impacts on human health, especially if it involves the CNS. As a result, it is extremely important to take the necessary precautions to lower the exposure of humans to IONPs as much as possible. Individuals can be protected against exposure to IONPs through several measures, some of which are discussed in the following subsections.

8.1 Personal protective equipment

Workers dealing with high levels of iron oxide emission in industries are routinely exposed to these hazardous particles. The amount of iron oxide that enters the body through the nasal route or skin contact can be reduced using personal protective equipment, such as gloves, respirators, and protective clothing, when exposure to iron oxide is unavoidable.

It may be necessary to wear a half-facepiece respirator with a particular filter with a National Institute for Occupational Safety and Health (NIOSH) type N95 or better filter if the exposure limit is expected to be breached and engineering controls are unfeasible. It is permissible to use this respirator

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up to ten times the maximum exposure limitation or the highest permitted concentration specified by the regulatory body or respirator manufacturer, whichever determines the lower exposure limit. In the case of particulate respirators with full-face pieces, such as NIOSH-type N100 filters, the maximum exposure limit can be 50 times the highest concentration outlined by the regulatory body or respirator manufacturer. A NIOSH-type P or R filter should be used if oil particles, such as glycerine, cutting fluids, and lubricants, are found.

It is recommended to wear a clean garment that covers the entire body and protective gloves in order to protect the skin. Safety goggles should be worn when handling chemicals. The work area should have an eye wash fountain and a quick-drill facility to add further safety.[103]

8.2 Electric brakes replacing conventional brakes

During the frictional braking system operation, a large volume of dust containing IONPs is emitted into the environment, which manifests in people in the form of lung diseases and several neurodegenerative diseases like Parkinson's disease (PD), Alzheimer's disease (AD), Multiple sclerosis (MS) and Huntington's disease (HD). There is no doubt that electric and hybrid vehicles need brake systems as well as their combustion engine counterparts; however, those vehicles are equipped with electric motors that facilitate the electric braking system and are known as regenerative brake systems. Unlike friction brakes, the regenerative brake system does not demand friction pads, which can lead to cleaner operation and better conversion of the braking energy into electric energy. In a handful of studies, a variety of control methodologies have been utilized to control the electric brake system, resulting in a reduction of 70–80% of mechanical brake participation. In order to minimize the contribution of frictional brakes in a conventional vehicle, the technology for braking electric automobiles can be incorporated into the automobile braking system so as to reduce brake dust emission into the air that occurs during friction braking.[104]

8.3 Regular maintenance of braking systems, equipment and machinery

The regular maintenance of braking systems may be effective in reducing the quantity of IONPs that are released during the operation of the vehicle. The rotors, brake pads, and other components of the automobile braking system must be thoroughly inspected and replaced when necessary. When low-dust brake pads are used, fewer particles are created when they come into contact with the rotor, resulting in a reduction of IONPs that is liberated into the atmosphere.[105] Keeping equipment and machinery in good working condition can help reduce the emissions of IONPs and eventually minimize the exposure. A part of this process involves cleaning and changing filters, inspecting and fixing equipment, and taking preventive maintenance measures to ensure everything runs smoothly.

8.4 Biological remediation of IONPs

Biological remediation refers to the removal of pollutants and neutralizing it using living organisms. Through the process of biocorrosion, *Bacillus* sp. (SO-10) can facilitate the bioremediation of iron contaminants.

There are several processes that occur naturally to break down iron and other metals, and biocorrosion is one of them. Using iron as a source of energy and nutrients, these bacteria produce metabolic by-products, causing metal structures to corrode faster. While this may seem like a very undesirable aspect of bioremediation, the goal of bioremediation is not to encourage biocorrosion but rather to utilize the metabolic processes of these bacteria to eliminate or neutralize the iron contamination present in the environment. An example of this is the introduction of *Bacillus* sp. (SO-10) into soil or water that has been contaminated with iron-based pollutants in order to degrade or transform the pollutants into less hazardous forms.

It is essential to consider that the effectiveness of bioremediation in the use of *Bacillus* sp. (SO-10) depends upon a lot of different factors, such as the types and concentration of the contaminants, the environment, their pH, and the availability of nutrients, *i.e.*, a carbon source. To ensure that bioremediation is successful, it is also essential to monitor and manage the bacteria carefully to ensure that any possible risks or unforeseen repercussions are reduced to a minimum.

As a whole, bioremediation with *Bacillus* sp. (SO-10) can be an effective tool to address iron pollution in various settings, including wetlands, industrial sites, and ecosystems in general. However, there is a need to carefully assess the potential risks and feasibility of this approach in each specific circumstance to avoid any unforeseen consequences.[106]

9. Limitations

The safety of IONPs for human use is one of the major challenges preventing its clinical translation. In spite of the fact that IONPs have been approved and used in clinics, such as contrast media and iron replacements,[107,108] various studies have found that factors such as size, composition, route, surface, properties, and dose of administration can potentially affect their safety. According to several studies, most IONPs do not leave the body and accumulate in vital organs such as the spleen and liver and cause toxic effects.[109] Cell toxicity has been demonstrated to be significantly affected by the size and shape of IONPs. Small-sized IONPs, *i.e.*, less than 5 nm, are responsible for generating ROS through Fenton and Haber–Weiss reactions. In addition, rod-shaped and nano-sized IONPs pose a greater risk of toxicity than micrometric and sphere-shaped particles.[110] Furthermore, IONPs have a tendency to be cytotoxic or genotoxic depending on their surface charge. A positive charge on IONPs increases their intracellular accumulation and decreases the integrity of cellular membranes due to nonspecific interactions and adsorptive endocytosis.[111] Creating IONPs that are capable of high load capacities while ensuring that the payload is efficiently encapsulated within them is a challenging task. In some cases, as the load capacity increases, the encapsulation efficiency decreases, which might result in an inefficient delivery of drugs.

An additional challenge to IONP-targeted gene delivery is the adsorption of biomacromolecules on the surface. For example,

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to improve nucleic acid drug loading efficiency, IONPs are modified with a positive charge at their surfaces. In blood circulation, these positively charged nanocomplexes quickly adsorb on the negatively charged plasma proteins, creating a phenomenon known as the formation of protein corona on NPs.[112–114] Apparently, protein corona negatively impacts the speed of circulation and the effectiveness of payload delivery.[115–117] For example, NPs may interact with plasma proteins, altering their uptake and clearance.

Modifying IONPs might seem like a good solution; however, adding additional synthesizing steps might increase the complexity of the process and the cost of production. The cost of producing high-quality IONPs for biological applications is relatively greater because of a variety of factors, one of which is the method in which the IONPs are synthesised. Thermal decomposition and co-precipitation require controlled environments and specialized equipment, which can lead to higher production costs.[118] In preclinical research, IONPs are almost always prepared in small quantities, and their large-scale production might not yield particles of the same quality. In the past decade, thermal decomposition methods have been developed for the controlled synthesis of IONPs; nevertheless, they have limited reproducibility at larger scales because of the complex synthesis process. In lab-scale systems, continuous high-temperature syntheses may reduce production costs; however, it is difficult to predict any reductions in costs at the industrial scale.[119]

10. Strength and recommendations

Magnetic NPs are often known as IONPs or MNPs. MNPs may be found in a variety of forms, such as ferrites (MFe_2O_4), where M might be Co, Cu, Ni, Mn, and Mg, metal oxides (Fe_3O_4, γ-Fe_2O_3), metal alloys (FePt, CoPt), and pure metals (Fe, Co, Ni, and Mn). Pure metals are unsuitable for *in vivo* application due to their high degrees of toxicity and oxidative properties. Because of these factors, IONPs like Fe_3O_4 and γ-Fe_2O_3 are utilized in a number of healthcare sectors. Aside from their biocompatibility and chemical stability, SPIONs can also significantly reduce the T1 and T2 proton relaxation times when the surface of γ-Fe_2O_3 and Fe_3O_4 are modified. Due to these characteristics, SPIONs are frequently utilized for MRI contrast enhancement, hyperthermia, targeted drug administration, nucleic acids, antibodies, tissue healing, biomolecule separation, and biosensing.[120,121] A relatively large amount of MRI has been used in the diagnosis and staging of MS to assess the integrity of the BBB and to identify inflammatory lesions in the brain. In this context, IONP contrast agents are advantageous over other contrast agents based on gadolinium because they are able to detect macrophage or monocyte infiltration, which is a hallmark of the progression of MS.[122–124]

Conventional cancer treatment has a number of drawbacks, including side effects, a lack of drug availability at the site of action, drug resistance, rapid renal clearance, and several other issues. As a result of these challenges, researchers have been able to combine hyperthermia with radiotherapy and chemotherapy. In magnetic hyperthermia, a magnetic field exposes the

intratumorally injected IONPs to a heating effect, resulting in cell death near the tumor area.[125,126] Due to their poor cellular architecture, cancer cells are very susceptible to damage from slight temperature changes. Furthermore, hyperthermia can also increase the temperature of the surrounding environment to 55–60 °C, which can be tolerated by healthy cells; however, cancerous cells are susceptible to increased temperature.

The unique properties of NPs enable them to be used in effective cancer therapy. Since IONPs have a number of structural advantages, they have gained global interest for nanomedicine applications, including stability in colloidal suspension, resistance to degradation *in vivo*, synergistic activity in improving drug sensitivity, the ability to deliver drugs at high dosages, and the ability to reverse cancer cell resistance.[127,128] The cryoablation efficacy may be enhanced by Fe_3O_4 NPs. In cryoablation, cancerous cells are treated with extreme cold temperatures. Fe_3O_4 NPs can change the ability of intracellular ice formation during freezing, thawing, and recrystallization, resulting in the increased death of cancerous cells like MCF-7.[129] MCF-7 is a human breast cancer cell line possessing receptors for glucocorticoids, progesterone, and estrogen.[130] Therefore, IONPs may be successfully implemented to efficiently treat tumors.[129]

Gene delivery is a method of treating diseases utilizing nucleic acids rather than drugs or surgery. Generally, delivering biological materials like siRNA and plasmid DNA to the cells or tissues of interest without being damaged by nucleases is very challenging. Consequently, to mitigate the damage, nanocarriers involving IONPs have been employed to carry the genes and release them at the desired target sites.[131] An innovative vector for the delivery of therapeutic genes to tumors has been developed. In order to deliver the desired gene to the target region, the gene carrier contained IONPs that were bound to lentiviral (LV) vectors. To check the effectiveness, this nanocarrier along with a reporter green fluorescent protein gene was injected into mice-carrying tumors, which caused sustained gene expression in areas close to the target. The results of this research open the possibility that LV-IONPs may be capable of delivering therapeutic genes to selectively inhibit tumor growth.[132]

11. Future prospects

Advances in the synthesis of novel nanocomposites with multifunctional modalities will enable IONPs for usage in biomedicine. IONPs hold great promise for future applications in biomedical science, including the early detection and diagnosis of diseases, delivery of drugs or genes, the imaging of surface and deep tissues, and the development of multifunctional drugs. There is a need to develop more IONP-based materials for the consumer market, and more research needs to be conducted in this area. In order to make a product sustainable in the market, there is a requirement for a positive cost-benefit balance. Therefore, different techniques should be developed to produce IONPs at a larger scale that are more cost-effective. In molecular medicine, it is essential to develop new tools for the early detection of diseases. NPs, such as IONPs,

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could further enhance theranostic platforms, which combine diagnostics and therapeutics approaches. The primary benefits of such efforts would be to simplify and reduce the level of invasiveness of the diagnostic process. An increasing number of groups are paying attention to personalized medicine, and it is anticipated that nanotechnology will play a crucial role in achieving a positive impact across all aspects of health care. Therefore, multifunctional IONPs might become a popular material for biomedical applications in the near future.

At present, assuming an 8 hour of working period in a day, exposure of 14 mg m^{-3} has been set as the permissible limit for fine iron oxide by the Occupational Safety and Health Administration (OSHA). The recommended exposure limit (REL) is 5 mg m^{-3} for iron (in iron oxide) for a 10 hour working period in a day, while it is 5 mg m^{-3} for the respirable fraction of iron oxide over an 8 hour workday set by The National Institute for Occupational Safety and Health (NIOSH) and American Conference of Governmental Industrial Hygienists (ACGIH), respectively. Unfortunately, due to the unavailability of concrete hazard and toxicity assessment data for IONPs, there is no separate recommended exposure limit (REL) set for IONPs. Therefore, it is essential to set REL for IONPs in the near future since a lack of defined REL may put the workers at the verge of serious health issues.[133]

12. Conclusions

IONPs can either be a benediction or a curse to the human CNS depending on their physicochemical characteristics, concentrations, modes of exposure, and processes of cellular absorption. IONPs are useful in the identification and treatment of CNS disorders; nonetheless, they could also be harmful to the CNS. Studies have confirmed that IONPs can cause inflammation, oxidative stress, and ferroptosis following sub-cellular entry, potentially damaging the CNS. Moreover, the IONPs are so small that they can cross the BBB and accumulate in the brain, potentially causing neuronal death and ensuing neurodegenerative disorders. However, measures can be implemented to reduce the potential toxicity of these NPs by controlling their size, shape, and surface chemistry. Monitoring and controlling the abundance of IONPs in the air is also vital to reduce chronic exposure. Moreover, the safety of IONPs should be carefully evaluated before they are employed for clinical purposes, and strategies should be developed to minimize the potential toxicity of IONPs. Studies have proposed plausible molecular events that are engaged in IONP-induced neurodegeneration. However, many such predictions require further validation. Therefore, it would be of great importance to encourage studies for dissecting the underlying mechanism of neurotoxicity as well as to develop safer IONPs.

Abbreviations

6-OHDA:	6-Hydroxydopamine
AD:	Alzheimer's disease
APTMS:	Aminopropyl trimethoxysilane
BBB:	Blood brain barrier
CNS:	Central nervous system
CSF:	Cerebrospinal fluid
DMT1:	Divalent metal transporter 1
DOX:	Doxorubicin
FAD:	Familial Alzheimer's disease
FPN1:	Ferroportin
IONP:	Iron oxide nanoparticle
MCI:	Mild cognitive impairment
MMSE:	Mini-mental state examination
NMDA:	N-Methyl-D-aspartate
NTBI:	Non-transferrin bound iron
PD:	Parkinson's disease
PM:	Particulate matter
ROS:	Reactive oxygen species
SAD:	Sporadic Alzheimer's disease
SPION:	Superparamagnetic IONPs
Tf:	Transferrin
TfR:	Transferrin receptor
αS:	α-Synuclein

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

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