Review

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Iron chelators: as therapeutic agents in diseases

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Abstract

The concentration of iron is tightly regulated, making it an essential element. Various cellular processes in the body rely on iron, such as oxygen sensing, oxygen transport, electron transfer, and DNA synthesis. Iron excess can be toxic because it participates in redox reactions that catalyze the production of reactive oxygen species and elevate oxidative stress. Iron chelators are chemically diverse; they can coordinate six ligands in an octagonal sequence. Because of the ability of chelators to trap essential metals, including iron, they may be involved in diseases caused by oxidative stress, such as infectious diseases, cardiovascular diseases, neurodegenerative diseases, and cancer. Iron-chelating agents, by tightly binding to iron, prohibit it from functioning as a catalyst in redox reactions and transfer iron and excrete it from the body. Thus, the use of iron chelators as therapeutic agents has received increasing attention. This review investigates the function of various iron chelators in treating iron overload in different clinical conditions.

Keywords: iron, iron chelators, iron overload disease, redox reactions

Introduction

The chemical composition of iron chelators is widely diverse; they usually have oxygen, nitrogen, or sulfur atoms that form bonds with iron. The iron atom (Fe) can coordinate six ligands octagonally[1]. Biological ligands compete efficiently with iron chelators for binding iron. Therefore, the tendency of chelators to bind to iron and the stoichiometry of iron binding will significantly affect their activity as therapeutic agents[2,3]. Because of the ability of chelators to trap essential metals, including iron, they may be involved in diseases caused by oxidative stress, such as infectious diseases[4], inflammation[5], cardiovascular diseases[6], atherosclerosis, neurodegenerative diseases, and cancer[7]. As secondary antioxidants, chelating agents reduce the reduction potential and stabilize iron ions in their oxidized state. Several chelators are found in modern medicines, including those derived from microorganisms (siderophores), synthetic chelators, and plants[8]. A schematic diagram of this review is shown in Figure 1.

HIGHLIGHTS

- The concentration of iron is tightly regulated, making it an essential element.
- Various cellular processes in the body rely on iron, such as oxygen sensing, oxygen transport, electron transfer, and DNA synthesis.
- Iron-chelating agents, by tightly binding to iron, prohibit it from functioning as a catalyst in redox reactions and transfer iron and excrete it from the body.

Methods

The current study is a review article that deals with the latest findings about the function of various iron chelators in treating iron overload in different clinical conditions. In this review, Web of Science, Google Scholar, PubMed, and MEDLINE databases and keywords Iron, Redox reactions, Iron chelators, and iron overload conditions were referred to access articles, and during that, we accessed more than 100 articles.

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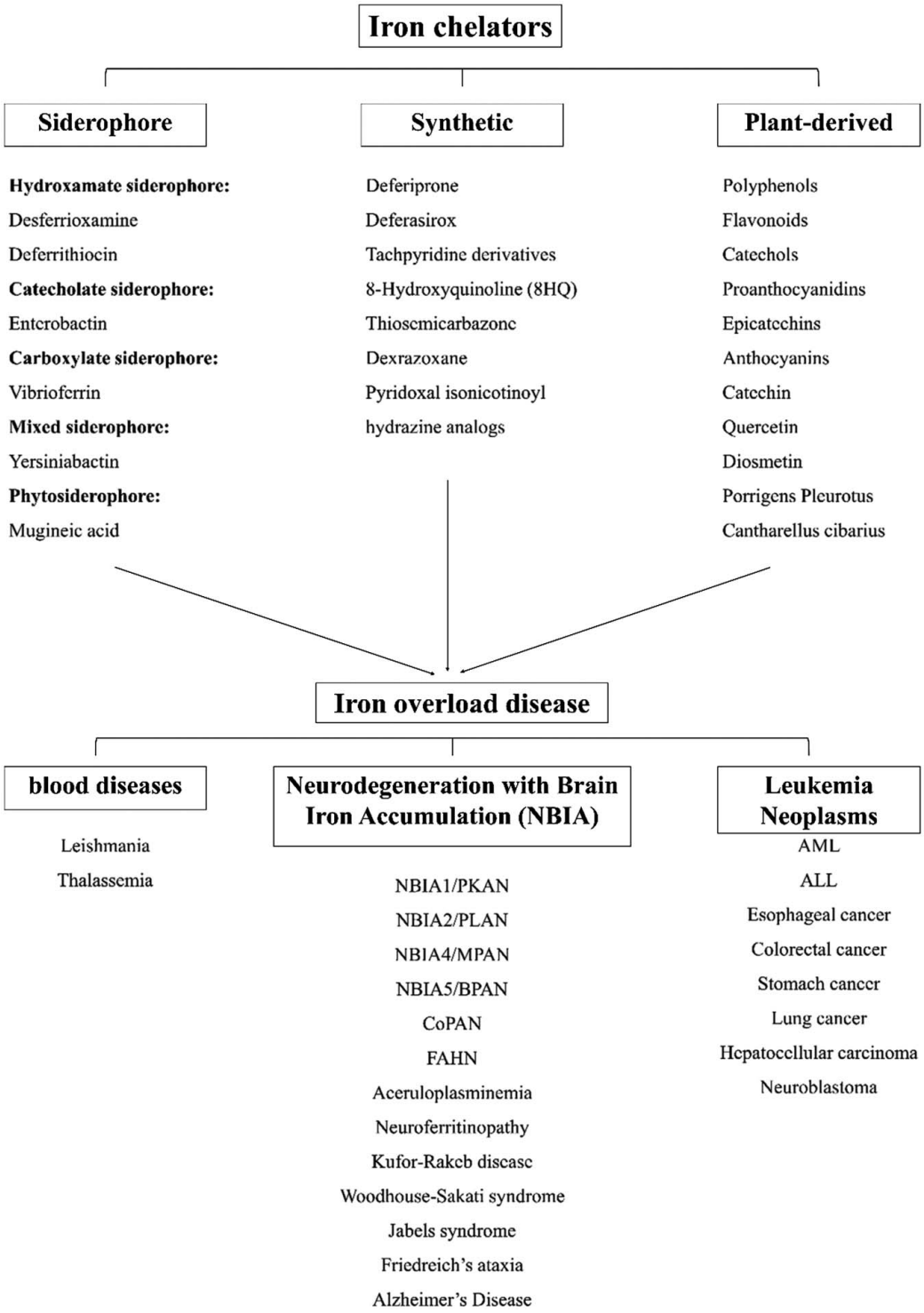

Figure 1. The schematic diagram of the review. ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; BPAN, beta-propeller protein-associated neurodegeneration; CoPAN, COASY protein-associated neurodegeneration; FAHN, fatty acid hydroxylase-associated neurodegeneration; NBIA, Neurodegeneration with Brain Iron Accumulation; PKAN, pantothenate kinase-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration; MPAN, mitochondrial membrane-protein-associated neurodegeneration.

The classification of iron chelators

Siderophore

Iron-dependent microorganisms have solved biological problems and iron toxicity via synthesizing siderophores (specific chelators with low Fe^{3+} mass) to absorb and store iron[9]. Extracting iron from stainless steel by microbial means is possible since siderophores have iron-binding constants exceeding 1030 M[10]. Siderophore is the most common type of drug in medicine[2,3,9]. Desferal [deferoxamine mesylate (DFO)] is produced by the fermentation of *Streptomyces* bacteria[11]. Its half-life is 5–10 minutes[12], and it has three active hydroxamic acid groups that can chelate Fe^{3+} with six orbitals (Fig. 1).

Desferrithiocin showed vigorous anti-pathogenic activity in hepatocellular carcinoma in laboratory conditions, while it had the most negligible cellular toxicity for normal liver cells. The high activity of oral Desferrithiocin has made it a good structure[13] (Fig. 2).

Synthetic chelators

Among the synthetic iron-chelating compounds, we can mention Deferiprone (L1), Deferasirox (DFX), Tachpyridine derivatives, 8-Hydroxyquinoline (8HQ), Thiosemicarbazone, Dexrazoxane, and Pyridoxal isonicotinoyl hydrazine analogues. L1 quickly penetrates different tissues. Three L1 molecules with six orbitals are needed to chelate the Fe^{3+} ions. The half-life of this drug is relatively short, less than 2 h[14] (Fig. 3). The U.S. Food and Drug Administration (FDA) has licensed a new oral medicine, DFX, to treat chronic iron overload in patients who need long-term blood transfusions. Two molecules of DFX are combined with iron in the blood and then removed from the body by the kidneys[15] (Figs 4, 5).

Plant-derived chelators

Studies are incomplete in most cases, but the results indicate that foods containing plant polyphenols and flavonoids may act as antioxidants and iron chelators, which have their benefits[16]. In addition to catechols, proanthocyanidins, epicatechins, flavonols, and anthocyanins contain iron-binding patterns similar to catechols[17]. According to studies, flavan-3-ols and their polymer condensation products and proanthocyanidins are the most common flavonoids in the American diet and have antioxidant,

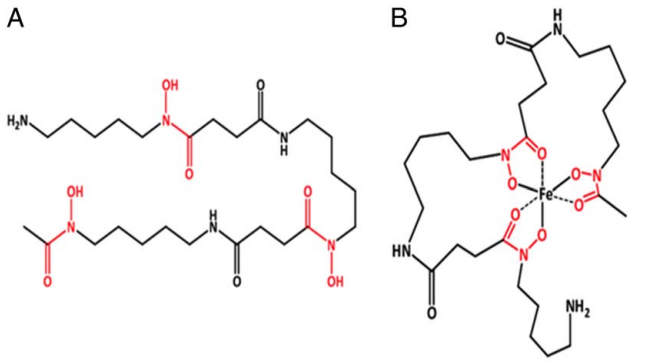

Figure 2. Chemical structure of (A) deferoxamine and deferoxamine (its iron complex) (B). Hydroxamic groups, responsible for metal chelation, are evidenced in red.

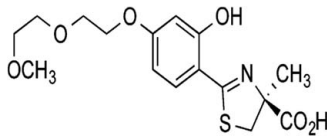

Figure 3. Chemical structure of desferrithiocin.

anticancer, heart-protecting, antimicrobial, antiviral, and neuroprotective properties[18]. Ebrahimzadeh *et al.*[19] studied the iron ion scavenging capacity of two mushroom species, *Pleurotus porrigens* and *Cantharellus cibarius*, *in vitro*. Their studies showed these two mushrooms have great power in chelating iron. Various studies have shown that flavonoid compounds like catechin, quercetin, and naringin can chelate iron ions in iron-overloaded rats[20–22]. Natural chelators and their metabolites are good antioxidants due to their lower toxicity and greater stability than synthetic chelators[23]. Although many of the reported results of phytochemical compounds are very encouraging, caution is needed in the interpretation of some of these studies. Medicinal plant extracts have a significant therapeutic role due to the presence of a mixture of different phytochemical compounds. However, in such studies, effects cannot always be attributed to a specific phytochemical compound.

Iron chelator and blood diseases

Leishmania

Leishmania sp., like all living organisms, needs iron to survive and grow[24]. *Leishmania* parasites multiply within macrophage phagosomes, which are intracellular parasites[25]. The global prevalence of all forms of the disease is 12 million, with 1.5–2 million new cutaneous cases added annually, 500 000 cases of visceral leishmaniasis, and about 50 000 deaths per year. The increase in leishmaniasis worldwide is mainly attributed to the rise of several anthropogenic risk factors, such as high migration, urbanization, deforestation, and immunosuppression. Leishmaniasis is still one of the most neglected diseases in the world, which mainly affects poor and developing countries[26]. The studies have evaluated the treatment effects of various compounds with different cell death mechanisms, such as inhibiting cell division, destroying the cell wall, inducing apoptosis, and other mechanisms against the *Leishmania* parasite[27]. Metal chelators such as DFO have been shown to attenuate growth *in vitro*. Poor lipophilic properties of

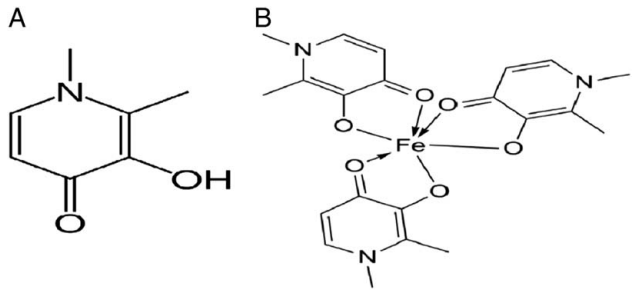

Figure 4. Chemical structure of deferiprone (A) and its iron complex (B).

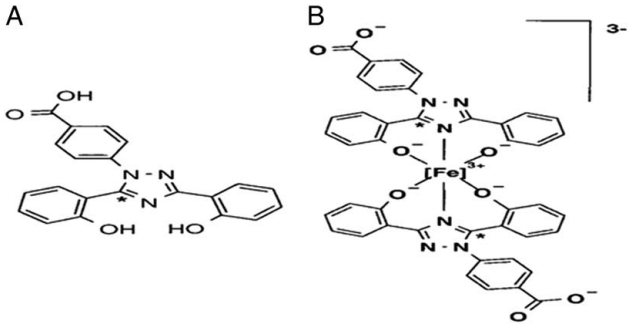

Figure 5. Chemical structure of deferasirox (A) and its iron complex (B).

these iron chelators are the leading cause of low penetration to the cell membranes[28].

A study examined the effects of quercetin (Qr) as an iron chelator on the *Leishmania* parasite. By targeting it, Qr can reduce the amount of ribonucleotide reductase (RR). The latter enzyme is a tetrameric protein with R1 as a regulatory site and R2 as a diiron (Fe^{2+}) unit for producing stable tyrosyl free radicals, essential for enzyme activity. The insufficient presence of iron disrupts the production of tyrosyl radicals in the R2 subunit, which can suppress the rate of DNA synthesis and inhibit parasite replication[27]. So, RR can be considered an essential intracellular target for Qr (an iron-chelating agent) and a good target for identifying and developing new anti-leishmaniasis compounds with Qr-like functions. Another study in 2019 reported that the sesquiterpene lactone part of artemisinin contains an unusual peroxide bridge, which is generally unstable in basic or acidic conditions. Also, reducing agents such as Fe^{2+}, heme, and Cu^{2+} can lead the peroxide bridge to generate cytotoxic center-oxygen radicals. Artemisinin disrupts the normal function of the *Leishmania* parasite by several mechanisms: (1) toxic radicals formation, (2) mitochondrial membrane depolarization, and (3) decrease of adenosine triphosphate production, which are three main mechanisms. In unstable iron ions, the endoperoxide bridge in the artemisinin will turn to free toxic radicals and disintegrate the parasite through oxidative stress and subsequent destruction of the cell wall[29].

In 2012, da Silva *et al.*[30] published a paper on the anti-leishmaniasis effect of flavonol compounds, which can be related to the reaction between L-arginine and flavonol. These flavonols exhibit docking activity with Asp_{129}, which, in the active site of arginase, is responsible for forming metal bridges for the cofactor Mn^{2+}. Arginine is converted into ornithine and urea by arginase, a metallohydrolase enzyme. In addition to its role in cell proliferation, ornithine is essential for detoxifying reactive oxygen species (ROS)[30].

Thalassemia

Thalassemia is a common hemoglobinopathy disorder called alpha-thalassemia or beta-thalassemia, depending on whether the defect is in the alpha or beta chain[31]. In thalassemia major, the homozygous form of beta-thalassemia, no beta chains are produced, but in thalassemia intermedia, there is a decrease in the production of beta chains. Beta-thalassemia major is diagnosed in around 23 000 newborn cases annually, and there are 80 million beta-thalassemia carriers worldwide. Every year, roughly 56 000 babies are born with severe alpha or beta-thalassemia, and more than half of them necessitate frequent blood transfusions. Alpha-thalassemia major is responsible for approximately 5500 annual prenatal deaths due to fetal hydrops[32]. These patients' lives depend on blood transfusions, and the result of these frequent transfusions is iron deposition in various body organs. Following repeated blood transfusions in transfusion-dependent thalassemia patients, large amounts of iron enter the body that cannot be excreted physiologically[33,34]. Without the use of iron chelator drugs, iron deposition in various organs can lead to heart failure, liver failure, endocrine dysfunction, and even kidney failure. The majority of transfusion-dependent thalassemia patients develop splenic hypertension in the second or third decade of their life, necessitating splenectomy. Bone marrow transplantation is the only definitive method for treating these patients[35]. Iron accumulates from three distinct sources in patients with hemoglobinopathies at varied rates depending on the condition and therapies:

(1) Iron-bound hemoglobin is released during hemolysis and is picked up by macrophages. Iron required for Hb biosynthesis is typically transported to the bone marrow by transferrin to form new red cells. Non-Transferrin Bound Iron (NTBI) accumulates in a harmful manner in the parenchyma, especially the heart and the endocrine glands, when hemolysis is excessive[36].
(2) In thalassemia, hematopoiesis is compromised since hepcidin synthesis is inhibited and iron absorption increases[37,38].
(3) One milligram of packed red blood cells contains 1.08 mg of iron. Blood transfusions produce iron that accumulates first in macrophages and then in the liver. A 60 kg thalassemic patient receives 9 g of iron yearly through frequent transfusions. Iron accumulation in the heart and cardiomyopathy are the leading causes of mortality in thalassemia patients who have several blood transfusions[34].

Iron overload assessment methods in thalassemia

(1) Measuring serum ferritin, which reflects tissue iron stores, is the most common way to detect iron overload. Ferritin also increases during infections, such as tissue inflammation, liver disease, hepatitis, and vitamin C deficiency. It is hypothesized that individuals with transfusion-dependent thalassemia who have serum concentrations of ferritin below 1000 ng/ml would have a decreased death risk[39–41]. The advantages of this test are its cheapness, availability, and the possibility of repeated and serial measurements[40]. Measuring the liver iron concentration (LIC), which is proportional to the quantity of iron stored in the whole body, is another method for estimating the body's iron content. The most accurate measurement of LIC is a liver biopsy. LIC levels higher than 7 mg/g DW (milligram per gram of dry weight) demonstrate an elevated risk of iron overload-related consequences in transfusion-dependent thalassemia (TDT). It has been shown that liver fibrosis values over 15 mg/g DW predict mortality and cardiac disease in TDT patients[40].
(2) Using magnetic resonance imaging (MRI) T2* among thalassemic patients has been recommended as a reliable and noninvasive technique for diagnosing iron overload in organs. Several institutions have defined iron overload by T2* values of <6.3, <20, and <21 ms in the liver, heart, and pancreas, respectively. Numerous studies have shown that early diagnosis of iron deposits in mentioned tissues may

prevent organ damage from compromising their function. Despite substantial studies on MRI T2* of hepatic and cardiac iron overload, there is insufficient data on pancreatic MRI in individuals with beta-thalassemia major[42–44].

The effect of iron-depleting drugs on TDT patients

Three iron chelators are now available for treating iron overload in thalassemia: DFO, oral deferiprone, and oral DFX are administered subcutaneously or intravenously, in tablet or solution form, and coated tablet form, respectively[45,46]. Since the advancement of MRI technology, several large randomized trials have demonstrated the efficacy and safety of oral iron chelation therapy in attempting to remove iron from the liver and heart[47,48]. This represents an improvement in medication care due to the improved simplicity of oral iron chelation therapy, especially compared to parenteral DFO. Nevertheless, parenteral DFO remains the preferred therapy for individuals with decompensated heart disease and may be the sole economical alternative in resource-poor societies[47] (Table 1).

Deferoxamine (DFO): Deferoxamine (DFO) is the first iron chelator to treat iron toxicity. DFO exhibits limited absorption through the gastrointestinal tract when ingested orally. Therefore, it requires administration through intramuscular, subcutaneous, or intravenous routes. As indicated, local responses to subcutaneous DFO are prevalent in thalassemia patients and represent a risk factor for chelation treatment discontinuation. It does not seem that injection-site pain and erythema are allergic[63]. Ototoxicity, which is often permanent, may develop when the ratio of DFO (mg/kg) to serum ferritin (μg/l) is more than 0.025.

Table 1

The clinical applications of iron chelators.

Disease	Type of iron chelator	Reference
Leishmaniasis	Deferoxamine	[49]
	Quercetin	[28]
	Artemisinin	[30]
Thalassemia	Deferoxamine	[45]
	Deferiprone	[50]
	Deferasirox	[51]
NBIA:	Tetrabenazine	[52]
NBIA1/PKAN	Baclofen	[53]
NBIA2/PLAN	Anticholinergic antidopaminergic	
NBIA4/MPAN	drugs	
NBIA5/BPAN	Iron chelators and supplement	
CoPAN	docosahexaenoic acid	
FAHN syndrome	Lactoferrin	
aceruloplasminemia	PBT2	
Neuroferritinopathy		
Kufor–Rakeb		
Woodhouse–Sakati syndrome		
Jabels syndrome		
Friedreich's ataxia		
Alzheimer's Disease		
Cancer	Deferoxamine	[54,55]
	Deferasirox	[56–58]
	Dp44mT	[59,60]
		[61,62]

CoPAN, a rare form of NBIA; Dp44mT, Di-2-pyridyl ketone-4,4-dimethyl-3-thiosemicarbazone; FAHN syndrome, hydroxylase-associated neurodegeneration; Kufor–Rakeb, an uncommon type of atypical Parkinson's disease; NBIA, Neurodegeneration with Brain Iron Accumulation; PBT2, (5,7-dichloro-2-((dimethylamino)methyl)-8-hydroxyquinoline).

Cataracts, night blindness, hazy vision, diminished visual acuity, poor color vision, retinopathy, and reduced visual acuity may be symptoms of ocular poisoning. Doses more than 60 mg/kg are related to retarded development and skeletal abnormalities, infections such as *Yersinia enterocolitica* and other pathogens, and respiratory and neurological illness. The kidneys may be impacted. Consequently, creatinine/blood urea nitrogen levels and liver function should be evaluated every 3 months[44,64].

Deferiprone (L1): Deferiprone (L1) was the initial oral iron chelator released in the 1980s. It creates stable complexes with plasma iron eliminated in urine[64]. Decades of clinical experience have shown that L1 helps increase iron excretion. Nonetheless, DFO is somewhat more practical. This has been related to DFO-induced fecal iron excretion[65]. Like DFO, L1 has a short half-life, requiring numerous daily doses[66]. The suggested dosage is 75–100 mg/kg/day, given in three split doses. Reversible agranulocytosis (1%) and neutropenia (5%) are the most severe adverse effects of L1[67]. Gastric intolerance, joint aches, and Zn^{2+} shortage are among the less toxic severe side effects. In clinical trials involving many of these patient categories, the possible medical utilization of L1 as a widespread antioxidant in non-iron-overloading diseases, including neurodegenerative, cardiovascular, renal, and infectious diseases, in addition to various conditions, including cancer and aging disorders, has been evaluated[67]. In most instances, joint and musculoskeletal discomfort associated with L1 is minor and manageable[68].

Deferasirox (Exjade, ICL670): Deferasirox (DFX) is an oral iron chelator with a long half-life and 24-h chelation. Thus, it may be used once daily. Multiple phase II studies and a critical phase III study have shown that, in transfusion-dependent individuals with beta-thalassemia major, DFX is as effective as the hitherto used DFO. At a dosage of DFX of 20 mg/kg/day, serum ferritin and hepatic iron content are stabilized. In contrast, 30 mg/kg daily decreases serum ferritin and liver iron content and establishes a negative iron balance[51].

Oral suspension DFX should be taken with an empty stomach at least 30 min before eating, ideally at the same time each day. Doses should be estimated to the closest whole tablet, with pills distributed in an appropriate amount of water, orange juice, or apple juice (by stirring). The new oral suspension version of DFX tablets is available in doses of 125, 250, and 500 mg[69]. In contrast to Exjade, which is a dispersible tablet that must be combined with fluids and given on an empty stomach, Jadenu may be taken in a single step, with or without a small meal, hence simplifying administration for the treatment of patients with chronic iron overload. This might meaningfully improve the compliance to treatment of beta-thalassemia major (BMT) patients. This medicine is available in 90, 180, and 360 mg tablets[70]. DFX can lead to decreased counts of specific blood cells, increasing vulnerability to bleeding and infections. To mitigate these risks, avoiding contact with sick individuals, maintaining regular hand hygiene, and avoiding engaging in rough sports or activities that may cause injury are advised. If experiencing diarrhea or vomiting, consuming ample water or other fluids is essential to maintain proper hydration levels[71]. However, it is crucial to note that each medication has its benefits and drawbacks, and the most effective treatment should be personalized to suit each patient[72].

The use of iron chelation for cardiac siderosis has not been extensively studied in randomized controlled trials (RCTs). The robustness of the presented data is also variable due to the paucity

of data. Our focus is on describing and reviewing the published trials. Iron overload-induced cardiac complications are the leading cause of death in beta-thalassemia major (TM). There may be distinct effects on myocardial siderosis owing to the use of different chelators. A randomized controlled trial was conducted on 61 patients previously administered subcutaneous DFO. The primary objective was to evaluate the progression of myocardial siderosis (myocardial T2*) over a period of one year in patients who were either maintained on subcutaneous DFO or switched to oral L1 monotherapy. L1 was 92 mg/kg/day, and DFO was 43 mg/kg for 5/7 days/week. The L1 treatment showed a significantly more improvement in myocardial T2* compared to DFO.

Additionally, the group treated with L1 experienced a significant increase in left ventricular ejection fraction. However, no significant differences were observed between the two groups regarding changes in liver iron and serum ferritin levels. These findings indicate that L1 monotherapy was significantly more effective than DFO over one year in improving asymptomatic myocardial siderosis in individuals with beta-thalassemia major[73].

In severe cardiac siderosis caused by TM, continuous parenteral DFO can be used to treat it, but there is a risk of poor compliance, complications, and deaths. The combination of L1 and DFO is a promising treatment for moderate myocardial siderosis, but it has not been evaluated in severe myocardial siderosis. In the Tanner *et al*. study, 167 patients with thalasssemia major received standard subcutaneous DFO monotherapy. Among the patients, 22 individuals had severe myocardial siderosis (T2* < 8 ms) with left ventricular (LV) dysfunction. Subcutaneous DFO and oral L1 were combined in treating 15 of these patients, and CMR follow-up was performed. Initially, DFO was given at 38 ± 10.2 mg/kg for 5.3 days/week, and L1 was given at 73.9 ± 4.0 mg/kg, for 12 months. Each patient continued taking both L1 and DFO. No new cardiovascular events or deaths occurred. Combined chelation therapy with subcutaneous DFO and oral L1 is effective in reducing myocardial iron and improving cardiac function in patients with severe myocardial siderosis and impaired LV function. The patient may consider this treatment an alternative as it is much less onerous than conventional high-dose continuous subcutaneous or intravenous DFO monotherapy[74].

Alpendurada *et al*. evaluated in 2012 to examine the correct ventricular function of patients with major thalassemia who received L1 and DFO. In the RCT of mild to moderate cardiac iron loading, combination treatment improved the right ventricle (RV) function significantly more than DFO alone. Combination treatment also improved RV function in severe cardiac siderosis. Therefore, adding L1 to DFO benefits both RV and LV function in TM patients with cardiac siderosis[75].

Iron chelation is crucial to caring for patients with sickle cell disease (SCD) or other rare anemias requiring chronic blood transfusions. The primary objective of iron chelation therapy is to prevent the adverse effects of iron overload. The only approved chelators for these specific patient populations are DFO and DFX. The effectiveness of L1 in managing iron overload in patients with SCD or other rare anemias is comparable to that of DFO, as determined by the alterations in liver iron concentration. The non-inferiority was demonstrated through the examination of cardiac iron load and serum ferritin. The safety profile of L1 was deemed satisfactory and resembled the previously observed outcomes in thalassemia patients, with no occurrence of unforeseen adverse events. These findings provide evidence for using L1 as a treatment option for iron overload in patients with SCD or other rare anemias requiring transfusions[76]. Specific forms of thalassemia, precisely various thalassemia intermedia (TI), do not require blood transfusions. However, these individuals still experience iron overload due to ineffective erythropoiesis, which leads to a chronic increase in iron absorption.

Compared to patients with TM, the rate of iron overloading in TI is much slower. To address this issue, personalized chelation therapy protocols can be developed using substances like DFO, L1, or a combination of both. These protocols effectively and safely remove the excess toxic iron and help prevent heart, liver, and other organ damage. Additionally, both L1 and DFO can inhibit iron absorption. A new oral chelator called DFX has been found to increase iron excretion and reduce liver iron levels in both TM and TI patients. However, there are limitations associated with using DFX in TI, including dose restrictions, potential toxicity issues, high cost, patient's iron load status, and inadequate removal of excess iron from the heart[67].

A group of 48 individuals diagnosed with early myelodysplastic syndrome (MDS) without excess blasts were chosen as participants in a research study. These individuals had an average initial serum ferritin level of 2739.5 μg/l, ranging from 825 to 11 287 μg/l. The treatment involved the administration of L1 at a daily dosage ranging from 40 to 90 mg/kg. The median duration of the chelation treatment was 10.9 months, ranging from 4 to 24 months. The results showed that chelation therapy effectively maintained or reduced iron stores in 1622 patients (73%) with serum ferritin levels below 2000 μg/l. In addition, when L1 was combined with recombinant human erythropoietin (rHuEPO) at a dosage of 30–40 kU/week, it resulted in effective chelation therapy for an additional five patients who had serum ferritin levels exceeding 3000 μg/l. However, it is essential to note that some adverse effects were observed during the study. Specifically, five patients (13%) experienced decreased granulocytes, while two (4%) developed agranulocytosis. Fortunately, granulocyte counts were restored after discontinuing L1 treatment and administration of granulocyte colony-stimulating factor (G-CSF), except for one patient. Based on these findings, it can be suggested that administering L1 at a daily dosage of at least 75 mg/kg may serve as an alternative approach for treating mild to moderate iron overload in MDS patients who cannot undergo treatment with DFX or DFO[77].

Iron chelators and neurodegeneration with brain iron accumulation (NBIA)

Neurodegeneration with brain iron accumulation (NBIA) is a collection of rare genetic neurological disorders characterized by abnormal iron buildup in the basal ganglia. The basal ganglia, located deep within the brain, play a crucial role in regulating movements[67]. The precise relationship between iron accumulation and the symptoms of NBIA remains incompletely understood. While iron is ordinarily present in this region, individuals with NBIA experience an excess of iron that can visualized through magnetic resonance imaging (MRI). Specifically, particular MRI views, such as T1-weighted and T2-weighted images, reveal dark regions in the brain corresponding to the accumulated iron. The globus pallidus, a component of the basal ganglia, is

frequently affected by high levels of iron, as is the substantia nigra[51,68]. A movement disorder, painful dystonia, parkinsonism, mental disability, and early death usually characterize various forms of NBIA. Currently, only limited data exist on the epidemiology of NBIA disorders. For all NBIA forms, a combined prevalence of 1–3 per million individuals has been estimated based on reported cases[78,79]. NBIA is a progressive condition for which no cure currently exists. However, scientists are looking for a way to reduce the accumulated iron in the brains of patients with NBIA. For this purpose, they investigated the use of iron chelators as a treatment for NBIA[69,70]. Different NBIA is shown in Fig. 6[51].

NBIA1/PKAN (pantothenate kinase-associated neurodegeneration)

The hallmarks of Hallervorden–Spatz disease (HSD) include extrapyramidal stiffness, dystonia, retinal degeneration, and dementia. Iron deposition occurs pathologically in the globus pallidus and zona reticularis of the substantia nigra, as well as in the axonal spheroids of these and other brain regions[80]. Currently known as PKAN, pantothenate kinase-associated neurodegeneration is a rare metabolic inborn defect and the most prevalent NBIA variant, accounting for around 50% of cases[81]. PANK2 enzyme, a coenzyme A (CoA) sensor, is located in mitochondria's intermembrane space (IMS). In a normal cell, the enzyme PANK2 is suppressed in the presence of sufficient amounts of CoA in the matrix. Therefore, in the absence of the PANK2 enzyme, a false signal is sent to the cell that the level of CoA is sufficient, and the CoA-dependent pathways in the cell, such as fatty acid oxidation and synthesis, are disrupted.

The PANK2 enzyme catalyzes the ATP-dependent conversion of pantothenate (vitamin B5) to 4′-phosphopantothenate, the first limiting step in mitochondrial CoA biosynthesis. The cause of iron buildup in PKAN is unknown. Although it was hypothesized that elevated cysteine levels in PKAN patients might cause iron–cysteine aggregates that result in neurotoxic oxidative stress, this has not been confirmed. Different hypotheses based on the relationship between iron, CoA, and lipid metabolism in mitochondria have emerged in light of identifying alternative NBIA variants without elevated cysteine levels[81] (Fig. 7).

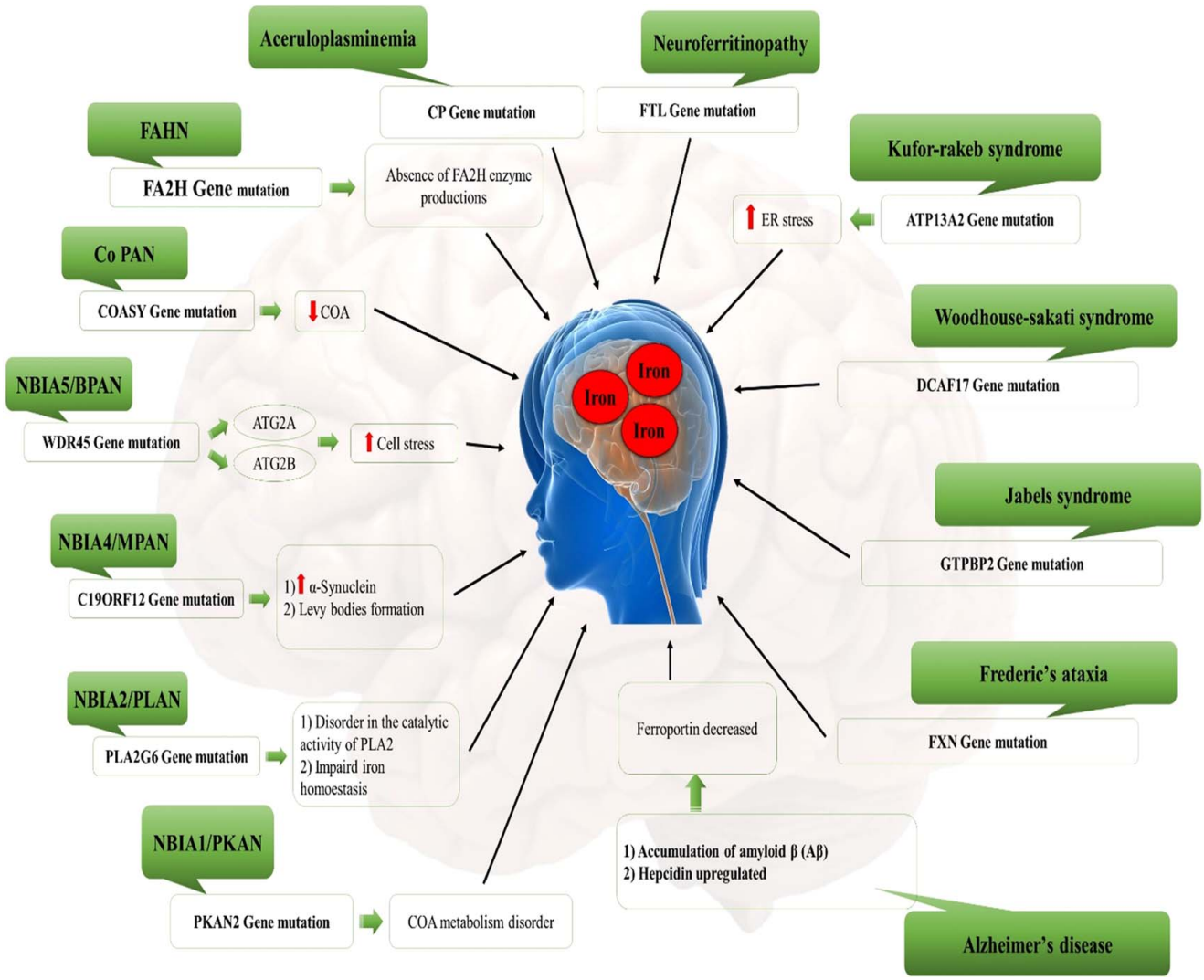

Figure 6. The gene mutations in NBIA disorders and their association with iron accumulation and neurodegeneration are shown.

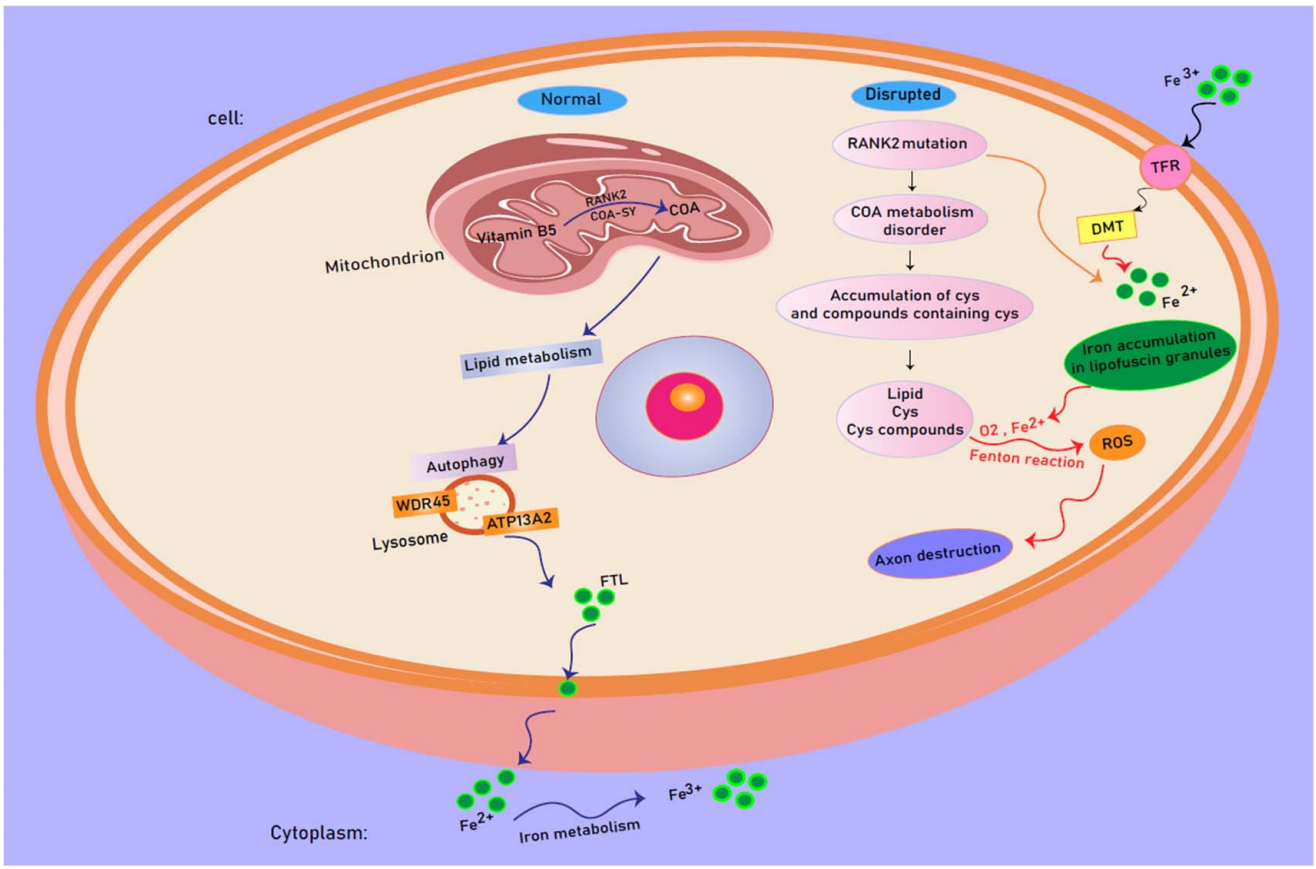

Figure 7. The biochemical pathway and the cellular processes involved in pantothenate kinase-associated neurodegeneration (PKAN). In a normal cell, the PANK2 enzyme catalyzes the ATP-dependent conversion of pantothenate (vitamin B5) to 4′-phosphopantothenate, which is the first limiting step in mitochondrial CoA biosynthesis. The excess amount of iron is exported out of the cell through the process of autophagy. In the absence of the PANK2 enzyme, a false signal is sent to the cell, indicating that the level of CoA is sufficient, leading to disruption of CoA-dependent pathways in the cell, such as fatty acid oxidation and synthesis. As a result, there is an accumulation of iron, cysteine, and compounds containing cysteine in the cell. In the presence of iron, these compounds undergo oxidation, resulting in the formation of reactive oxygen species (ROS). Ultimately, the accumulation of iron in the brain leads to the destruction of axons.

NBIA2/PLAN (PLA2G6-associated neurodegeneration)

PLAN includes various clinical symptoms, from early psychological analysis to parkinsonism-dystonia in adulthood. The PLAN covers about 20% of NBIA cases. In this disease, the central and peripheral nervous systems are disturbed[81,82]. In PLAN, mutations in the PLA2G6 gene occur. Hence, the name PLA2G6-associated neurodegeneration. The PLA2G6 gene encodes a phospholipase that releases free fatty acids from phospholipids. This gene is essential for phospholipid homeostasis, and inhibiting its enzyme activity may increase phospholipid and acetyl CoA levels. Alteration in the lipid composition of plasma membranes, vesicles, or endosomes may alter membrane permeability, fluidity, and iron homeostasis when phospholipid homeostasis is disrupted[83,84].

NBIA4/MPAN (mitochondria protein-associated neurodegeneration)

NBIA4/MPAN is a particular and relatively new form of NBIA. After PKAN and PLAN, MPAN is the most prevalent type of NBIA. Symptoms of this disease often occur in childhood or early adulthood and include movement disorders, behavioral disorders, and dementia. Dystonia, spasticity, parkinsonism, and psychological problems, including anxiety, depression, hallucinations, fatigue, inattention, and hyperactivity, are other features of this disease. Other symptoms include swallowing disorders, speech disorders, optic nerve atrophy, and axonal neuropathy[82,85]. A mutation in the C19orf12 gene causes this disease. This gene encodes a small protein located in the mitochondrial membrane. Post-mortem studies of the patients with MPAN and the main features of NBIA resulting from the accumulation of iron and axonal spheroids have shown the abundance of α-synuclein and the formation of Levy bodies. Post-mortem studies in the brains of patients with MPAN have shown the main features of NBIA (due to the accumulation of iron and axonal spheroids), the abundance of α-synuclein, and the formation of Levy bodies[85,86].

NBIA5/BPAN (beta-propeller protein-associated neurodegeneration)

Symptoms of NBIA5/BPAN include delayed neural development in infancy and childhood, mental retardation, seizures, and sleep problems. These patients have limited language skills, and speech may never take shape. Other clinical manifestations of

BPAN include ataxia, dystonia, and adolescent or adult-onset Parkinson's disease. The condition is caused by a mutation in the WDR45 gene, which encodes an autophagy protein called beta-propeller[87]. There is evidence of autophagic defects in this disease. WDR45 protein is a member of a protein family that enables the creation of protein complex structures and is a critical component in several biological processes, including cell cycle progression, signal transduction, apoptosis, and gene expression regulation. Its capacity to bind to two autophagy-dependent proteins is responsible for WDR45's direct interaction with the autophagy process (ATG2A and ATG2B)[88–90]. Iron accumulation in the Globus pallidus and Substantia nigra is one of the pathogenic characteristics of BPAN in the brain[88].

CoPAN (COASY protein-associated neurodegeneration)

CoPAN is a rare form of NBIA. The condition is defined by its characteristic NBIA symptoms. Signs of the disease include progressive movement disorder, dystonia (in childhood), spasticity, and cognitive impairment. This disorder, known as COASY protein-associated neurodegeneration, is caused by a mutation in the COASY gene, which codes for the enzyme CoA-synthase[89]. Deficiency in this gene reduces the level of CoA and acetyl CoA. Acetyl CoA participates in regulating autophagic processes, and its reduction leads to the induction of autophagy, and its increase leads to the suppression of autophagic processes. CoPAN studies show a strong association between lipid metabolism, CoA synthesis, and autophagy in NBIA[89,91,92].

FAHN (fatty acid hydroxylase-associated neurodegeneration)

Another uncommon variety is FAHN syndrome, which is caused by mutations in FA2H and is allelic to type 35 hereditary spastic paraplegia (SPG35). The presence of spasticity, ataxia, and dystonia in children characterizes FAHN. There may be seizures and divergent strabismus. Nonetheless, the iron buildup is limited to a subset of situations. This protein catalyzes the hydroxylation of ceramide moiety[93]. FA2H mutations lower levels of the FA2H enzyme, resulting in a deficiency of 2-hydroxylated sphingolipids and associated impairment in myelin sheath maintenance and degeneration[89,94].

Aceruloplasminemia

Aceruloplasminemia is a kind of NBIA documented globally and is closely connected to iron homeostasis. After middle age, aceruloplasminemia patients suffer from retinal pigment degeneration, diabetes mellitus, and extrapyramidal system dysfunction. Aceruloplasminemia is a rare disorder in which a mutation in the ceruloplasmin (CP) gene causes a deficiency or malfunction of CP[95]. CP carries iron from the cell's cytoplasm to the capillaries, where it binds to ferritin and enters circulation[96,97]. CP is the sole protein that transfers iron inside cells; without appropriate CP activity, iron accumulates in cells, and serum ferritin levels rise. Iron accumulates mainly in the eye, brain, pancreas, and liver in people with aceruloplasminemia[98]. Therefore, the distinctive trifecta of aceruloplasminemia consists of retinal degeneration, diabetes, and adult-onset extrapyramidal disease. However, this disease's phenotype is often varied, and early diagnosis utilizing the triad is challenging[99]. Bioactive Cp is a holo form of Cp (holo-Cp), and its biosynthesis incorporates six copper atoms. Failure to integrate copper into Cp causes the release of an unstable apo form of Cp (apo-Cp) that lacks oxidase function and quickly degrades in the serum. Cp is found on the surface of astrocytes in the brain, and the glycosylphosphatidylinositol (GPI)-linked Cp (Cp-GPI) is crucial for the mobilization of iron in the central nervous system[100,101].

Neuroferritinopathy

Neuroferritinopathy, an autosomal dominant neurodegenerative disease marked by tremors, cerebellar ataxia, parkinsonism, pyramidal symptoms, behavioral abnormalities, and cognitive impairment, is connected with an aberrant buildup of ferritin. These symptoms may manifest in succession for four decades. Glia and subsets of neurons in the central nervous system and extraneural tissue include pathological intranuclear and intracytoplasmic entities. The biochemical analysis of these entities separated from the striatum and cerebellar cortex indicates that ferritin light polypeptide (FTL) and ferritin heavy polypeptide (FTH1) are the predominant components[102]. The iron storage protein ferritin comprises 24 polypeptides organized into a hollow shell. Each of these polypeptides might be FTL or FTH1[103]. The FTL subunit lacks enzymatic activity, but its surface cavity contains acidic residues that enable iron nucleation. The ferroxidase center is located inside the FTH1 subunit, the central regulator of ferritin activity. The ferroxidase activity is necessary for the incorporation of iron into ferritin. However, it may also play a role in controlling the redox state of cells by eliminating the possibly more hazardous Fe (II)[104]. Iron regulatory proteins ACO1 (or IRP1) and IREB2 control the expression of the two ferritin polypeptides (or IRP2). The mutation in the coding area of the FTL gene is related to neuroferritinopathy, an autosomal dominant neurodegenerative disease. This condition is distinguished by extrapyramidal symptoms, aberrant iron deposition and ferritin in the basal ganglia, and low blood ferritin concentrations[105]. FTL's most prevalent gene mutation (460InsA and 498InsTC) modifies ferritin's structure, leading to ferritin and iron buildup in central neurons, neuronal inflammation, oxidative stress, and neuronal degeneration[106].

Kufor–Rakeb

Young-onset Kufor–Rakeb is an uncommon type of atypical Parkinson's disease. This disease is known as Kuf–Rakab in Jordan, as it was first reported in this region[107]. Kufor–Rakeb disease (KRD, PARK9) is an extrapyramidal-pyramidal illness with global brain atrophy caused by mutations in the ATP13A2 gene. The ATP13A2 gene encodes putative lysosomal P-type transmembrane cation transporting ATPase. Evidence of molecular linkages to synuclein pathways suggests that KRD should be categorized as a Parkinsonian condition[108]. Clinical information and investigative findings concentrate on radiological evidence of a genetically confirmed case of KRD. Early onset levodopa-responsive dystonia-parkinsonism with pyramidal symptoms and aberrant eye movement was seen clinically. The brain MRI indicated bilateral putaminal and caudate iron buildup and widespread atrophy. The results add KRD to the list of NBIA syndromes. This condition should be addressed in individuals with dystonia-parkinsonism and iron on brain imaging; classification as NBIA type 3 is indicated[108].

Woodhouse–Sakati syndrome

Hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome, further recognized as Woodhouse–Sakati syndrome [WSS (MIM 241080)], is an infrequent autosomal recessive disorder that was initially presented in many consanguineous Saudi families and has since been confirmed in other ethnic groups[109]. Sensorineural deafness, reduced signal intensity in the basal ganglia, T-wave abnormalities, and decreased insulin-like growth factor 1 (IGF-1) levels are other signs. Brain imaging reveals iron accumulation in the Globus pallidus and Substantia nigra in specific individuals with this condition. The severity of the disease's symptoms increases with age. This disease is caused by a mutation in the DCAF17 (C2orf37) gene, which encodes an uncharacterized membrane-bound nuclear protein[110,111].

Jabels syndrome

Jabels syndrome is an autosomal recessive condition marked by intellectual impairment and developmental delay. Other variable characteristics include ataxic gait and aberrant motions, vision impairment, microcephaly, abnormal foot or hand posture, kyphoscoliosis, dysmorphic facial features, and seizures. Imaging of the brain often reveals atrophy of the cerebellum and hypoplasia of the corpus callosum. Brain MRI showed atrophy of the cerebellar vermis and aberrant T2-signal hypointensity in the globus pallidus and substantia nigra, resembling iron accumulation diseases[112]. In this disorder, the GTPBP2 gene's function is disrupted. The exact role of the GTP-binding protein encoded by this gene is unknown[113].

Friedreich's ataxia

Friedreich's ataxia is a hereditary disorder characterized by cardiomyopathy, dysarthria, an increase in diabetes, and progressive ataxia[114]. The loss of frataxin expression impairs the synthesis of iron-sulfur clusters and, therefore, mitochondrial energy generation. An increase in iron transport into the mitochondrial compartment, resulting in a toxic buildup of reactive iron, is one of the pathogenic effects. However, the mechanism causing this abnormal accumulation of mitochondrial iron remains unexplained[115]. In frataxin homolog mutants, iron accumulation in the nervous system increases the production of sphingolipids, therefore activating 3-phosphoinositide-dependent protein kinase-1 (Pdk1) and myocyte enhancer factor-2 (Mef2) and causing neurodegeneration of adult photoreceptors[116].

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the loss of memory and cognitive functions. The leading causes of neurotoxicity in AD are the accumulation of amyloid β (Aβ) protein and neurofibrillary tangles (NFTs) composed of tau protein. It is predicted that the number of patients with AD will reach 152 million people worldwide by the middle of the century, with the most significant increase expected in low- and middle-income countries. Alzheimer's Disease 2020 predicts that by 2050, the number of people over 65 with AD will rise from 5.8 million to 13.8 million in the United States. In addition, the number of deaths due to AD has increased by 146.2% from 2000 to 2018, and AD has become the fifth leading cause of death in older Americans. Significantly, caregivers experience more psychological stress and adverse emotional effects. As a result, the social and family responsibilities of caring for the AD population will be high and unsustainable[117].

Inflammation, oxidative stress, and iron dyshomeostasis are prominent features of AD pathology[118,119]. Additionally, inflammation, oxidative stress, and iron accumulation contribute to the disease's progression[120,121]. Iron accumulation in the brain has been debated, but recent evidence suggests that the upregulation of a peptide hormone called hepcidin may be responsible[122]. Hepcidin regulates iron levels in the body by controlling the expression of an iron export protein called ferroportin[123]. When iron levels are high, hepcidin is upregulated, leading to the internalization and degradation of ferroportin, thus reducing circulating iron.

Conversely, hepcidin is downregulated when low iron levels, allowing for increased iron uptake and release from stores[124]. The brain and the eye have barriers that protect them from changes in iron levels in the blood. However, specific cells in the brain, retina (part of the eye), and front part of the eye produce a protein called hepcidin, which suggests additional iron regulation within these tissues. Hepcidin is found in various brain areas, including the cortex, hippocampus, cerebellum, thalamus, and medulla oblongata[125–127]. In the eye, hepcidin is synthesized and expressed in different cell types in the retina and front part of the eye[128–130]. Although hepcidin helps maintain strict control over iron levels, it can be increased by inflammatory signals such as IL-6, IL-1β, and transforming growth factors β1 and β2. These signals override the iron signal and contribute to anemia in chronic inflammation. Iron is trapped in liver cells in this condition, and further uptake is blocked despite low circulating iron levels[131]. This suggests that in cases of Alzheimer's disease, where chronic inflammation is present, local hepcidin may be upregulated in the brain and retina. This upregulation decreases ferroportin (Fpn) production, a protein involved in iron export, increasing intracellular iron levels. This elevated iron can create a harmful environment by increasing the production of ROS[125]. In AD, glaucomatous degeneration and AMD are accompanied by inflammation.

Activated microglia release various cytokines that likely increase hepcidin levels, leading to iron buildup. Glaucoma is characterized by prominent oxidative stress, worsened by the release of TGFβ1 and IL-6, cytokines known to trigger hepcidin upregulation[132–134]. A recent study found that TGFβ2 induces a positive feedback loop between TGFβ2, hepcidin, and iron, fueled by ROS, in TM cells[128,135]. Disrupting this loop with hepcidin antagonists and antioxidants reduced iron accumulation and ROS, indicating the significant role of ROS in primary open-angle glaucoma. Chelating iron provides considerable protection for RGCs, further supporting the toxic part of iron in glaucomatous degeneration[136].

In summary, Alzheimer's disease and other neurodegenerative disorders are associated with the accumulation of iron and oxidative stress. Hepcidin, a key regulator of iron homeostasis, may promote iron accumulation in the brain and the eye, contributing to disease progression. Understanding these mechanisms could lead to new therapeutic approaches targeting iron dysregulation in neurodegenerative diseases[137].

Treatment of neurodegenerative diseases using iron chelators

Until now, there is no definitive treatment for NBIA disease, and the treatment of patients is primarily symptom-oriented. The use of drugs such as tetrabenazine, baclofen, anticholinergic and antidopaminergic drugs, iron chelators and supplements, and docosahexaenoic acid have been reported in some cases[138]. In 2015, Ward and colleagues reviewed iron-chelating therapies to treat neurodegenerative diseases. They observed that iron-chelating in Parkinson's disease reduced iron levels in the substantia nigra and dentate nuclei. Nevertheless, it does not change the concentration of iron in the red nucleus, and eventually, the motor signs improve[139]. Shuang-Feng Xua *et al.* examined the effect of lactoferrin (an iron-chelating agent) on iron concentration in Parkinson's disease (using animal research and the Prussian blue staining method). Lactoferrin inhibits the destruction of dopaminergic neurons, treats behavioral disorders in Parkinson's patients, inhibits inflammatory reactions in glial cells, blocks cell death pathways, and, by binding to Fe^{3+}, reduces iron concentrations in brain nuclei. Lactoferrin acts as an antioxidant, anti-inflammatory, and anti-apoptotic and can trap iron, thus facilitating the treatment of Parkinson's[53]. Alzheimer's disease is exacerbated by the imbalance of iron, copper, and zinc ions in the disease's amyloid. PBT2 (5,7-dichloro-2-((dimethylamino)methyl)-8-hydroxyquinoline) absorbs these metals and reduces their concentration[53]. In Friedrich's ataxia, iron accumulation occurs in the thalamus, cerebellum, and pallidal nuclei, and L1 is effective in detoxification (Table 1)[139].

Cancer and iron chelators

Cancer is the most significant cause of mortality and disability on a worldwide scale, accounting for around 7.6 million deaths annually. The prevalence of cancer is expected to increase as 10 million patients died worldwide in 2020, and 19 million patients were newly diagnosed with cancer[140]. The reality is that only 5–10% of all cases of cancer are caused by genetic defects and the remaining 90–95% are caused by lifestyle modifications (including smoking, nutrition, diet, alcohol, lack of physical activity, obesity, and sun exposure), infectious diseases, and environmental pollutants offer significant possibilities for cancer prevention[141]. It has been shown that, between many lifestyle variables, diet and associated factors play a crucial role in the development of cancer. Observational research shows that between 30 and 40% of cancer occurrences may be prevented by modifying dietary variables and food consumption habits[141]. ROS may be produced by increased iron consumption from meals or nutritional supplements. Iron combines with hydrogen peroxide and catalyzes the production of highly reactive hydroxyl radicals, raising oxidative stress, which increases free iron levels through the Fenton and Haber–Weiss reaction[142,143]. The oxidative stress caused by iron ingestion may be modulated by endogenous oxidant and antioxidant capacities that work together to form a coordinated defense network against ROS buildup and oxidative damage[142,144]. ROS generated inside cells may function as second messengers in intracellular signaling cascade that initiate and sustain the oncogenic phenotype of cancer cells[142,143,145]. Free radicals lead to gene mutations, which may hasten tumor development. DNA mutation is a vital stage in carcinogenesis, and an increase in the amount of oxidative DNA lesions has been observed in a variety of tumor types[146].

One of the most effective ways to treat intracellular iron depletion cancer is to inhibit the expression of iron-regulating proteins and impair redox homeostasis. DFO and L1 are iron chelators that tend to be iron and treat excess iron. As an iron chelator, Di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone (Dp44mT) is an effective compound in treating cancer. Iron chelators are effective in treating cancer with two mechanisms. First, they hinder the production of essential proteins and enzymes needed for cell growth by depleting the iron present inside the cells. Secondly, they enhance the production of harmful ROS within cancer cells by creating an active iron complex with potent redox properties, leading to cell death[54].

In some studies, Fe deprivation by DFO blocked differentiation and induced S-phase arrest and apoptosis[147,148]. Some research has shown that DFO has anti-tumor effects on neuroblastoma, leukemia, and esophageal cancers, inhibiting cell proliferation and differentiation[149–151]. Several significant reports have also indicated that tumor cells might lack the ability to regulate the amount of iron within their cells, known as homeostasis. Specifically, studies have demonstrated that esophageal cancer[55] and colorectal cancer[152] can alter the expression of iron-related proteins within cells. These proteins include transferrin receptor 1 (TFR1), ferritin, and ferroportin 1, which are involved in the storage and movement of iron within a cell. The exact mechanism responsible for these changes in esophageal cancer is not yet fully understood. However, recent research has revealed that in colorectal adenocarcinoma, cells appear to lose their ability to sense the levels of iron inside the cell accurately.

The abnormally high cellular iron levels in colorectal adenocarcinoma seem to be influenced by oncogenic products (c-myc) produced by the primary carcinogenic pathway, Wnt signaling[56,152]. A recent study explored the impact of DFO on TRAIL-induced apoptosis in colon cancer cells. DFO treatment hindered cancer cell apoptosis by increasing Akt activation and reducing caspase activation. Additionally, DFO-induced autophagy flux, which was blocked by chloroquine. These findings suggest that DFO is an inhibitor against TRAIL-mediated tumor cell death through the autophagy pathway, making it a potential anticancer agent for TRAIL protein therapies[57].

Iron and ferritin are crucial in developing and multiplying human NB (neuroblastoma). Hann and colleagues found that patients with advanced NB often have higher levels of ferritin in their blood, which is believed to originate from the neuroblastoma cells themselves[58,153]. The exact relationship between ferritin, NB cells, and the host is not yet understood, but previous research suggests that ferritin indirectly hampers the host's immune response, thereby promoting tumor growth[153]. More recently, it has been shown that ferritin directly impacts tumor growth. This is evidenced by experiments demonstrating that the iron chelator DFO has an anti-neuroblastoma effect on the human NB cell lines CHP126 and CHP100 when tested in a laboratory setting[154,155].

The findings indicated that DFO had a significant inhibitory effect on the viability of K562 cells and triggered cell apoptosis in a manner that depended on the dosage. Additionally, it was observed that the levels of specific proteins (Bax, p53, and Fas) at both the protein and mRNA levels increased proportionally with the dose of DFO in K562 cells. Conversely, the level of Bcl-2 decreased notably in a dose-dependent manner. Furthermore, the

results demonstrated that the effects of DFO treatment on K562 cells were reversed by adding ferric chloride[59].

DFX is one of the oral iron chelators with a longer half-life than DFO. This drug has anti-tumor properties for esophageal, gastric, and lung cancers[156,157]. A recent study demonstrated that DFX exhibits a significant reduction in the viability of three AML cell lines, HL60, THP1, and WEHI3, as well as two primary leukemic cells obtained from AML patients. The mechanism of action of DFX involves inducing cell cycle arrest at the G1 phase, promoting apoptosis, and inhibiting the phosphorylation of ERK (extracellular signal-regulated kinase)[60]. DFO has been found to profoundly impact the survival of T-cell acute lymphoblastic leukemia/lymphoma cells by inducing apoptosis.

Additionally, it has demonstrated synergistic effects when combined with three ALL (acute lymphoid leukemia)--specific drugs: dexamethasone, doxorubicin, and L-asparaginase. This combination therapy has enhanced efficacy in treating T-cell acute lymphoblastic leukemia/lymphoma[158]. DFO has been widely utilized as an iron chelator for treating iron overload diseases. Additionally, it has displayed potential anti-tumor activity. Extensive in-vitro and clinical studies have demonstrated that DFO can impede the growth of tumor cells by binding with intracellular iron, thereby exhibiting a notable inhibitory effect on tumor cell proliferation[61,159–164].

Many studies show that Dp44mT is better than DFO in treating cancer[62,165]. Other studies have shown that DFO tends to trap Fe^{3+}, which has been shown to improve cancer treatment by depleting iron[166,167]. DFO and triapine are iron chelators that have recently been shown to be effective in suppressing cancer[168]. Iron chelators have been used concomitantly with anticancer drugs, including cisplatin, thiotepa, cyclophosphamide, and carboplatin[150,169]. Enterobactin has been studied as an iron chelator with a high tendency to absorb and reduce excess iron in cancer cells[170]. Enterobactin also disrupts the mitochondrial activity of tumor cells and facilitates cellular apoptosis[171]. Therefore, enterobactin is more effective in cancer treatment due to its hydrophobic properties better membrane permeability, and it has three times the effect of DFO (Table1)[172].

The applications of different iron chelators in Trojan Horse

Siderophores are substances bacteria produce to collect iron (III) from their surroundings. They have a specific pathway for absorbing iron, which can be exploited for Trojan Horse strategy purposes. Trojan Horse antibacterials, also known as antibacterial siderophore conjugates, have received more attention in recent years due to the rise of antimicrobial resistance. Trojan Horse antibacterials have the potential to utilize the specific pathways in bacteria for active iron uptake, allowing them to bypass membrane-associated resistance mechanisms. The Trojan Horse approach can potentially redesign outdated antibiotics and develop antibacterials that target specific pathogens[173].

In Laurent *et al*. study, DFO was modified at its primary amine with carboxylic acids carrying different ligands. This modification resulted in the formation of complexes with ruthenium, including both mono- and bidentate complexes, as well as a RAPTA-like complex ([Ru(η6-arene)X2(PTA)], PTA = 1,3,5-triaza-7-phosphaadamantane) where DFO is attached to the coordinated arene ring. To evaluate their antibacterial activity, the researchers tested these compounds against important ESKAPE pathogens (*Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*). Additionally, they conducted experiments to assess the compounds' effects on the growth of healthy human cells (HEK-293) and cancer cells (A2780). Interestingly, some of the complexes exhibited both anticancer and antibacterial properties simultaneously. This combination of properties is advantageous because cancer patients often have compromised immune systems and may struggle to fight off infections[174].

Recently, researchers have identified novel, non-toxic nanoparticles made of chitosan and Fe (III) that possess strong antibacterial properties. These nanoparticles incorporate a unique ligand called DFO, which acts as a Trojan Horse to deliver therapeutic agents. In this study, researchers developed chitosan/Fe (III)/DFO nanoparticles with a uniform size (~250 nm) and positive surface charge. These nanoparticles demonstrated exceptional antibacterial activity in lab and animal tests, surpassing the effectiveness of well-known antibiotics like ampicillin and gentamicin. Notably, the nanoparticles were found to be non-toxic. Adding iron ions to the chitosan structure enhanced their ability to disrupt microbial membranes compared to pure chitosan. Furthermore, incorporating DFO into the nanoparticles significantly increased their effectiveness in destroying bacterial membranes. These findings suggest that the antibacterial nanoparticles hold promise for further preclinical investigations[175].

Mattos *et al*. reported the synthesis of a derivative compound consisting of cadmium and DFO, a bacterial siderophore. The new mix was characterized by elemental analysis, vibrational (infrared and Raman) spectroscopy, mass-coupled thermal analyses, and X-ray diffraction methods. Studies on the in-vitro toxicity toward a fungus and two bacterial strains indicated that the coordination compound is more active against microorganisms than cadmium chloride on a Cd-concentration basis, showing that desferrioxamine can work as a 'Trojan horse' in the delivery of toxic metal[176]. Mycobacterium tuberculosis, the microorganism responsible for causing tuberculosis, is a type of pathogen that must reside inside the phagosome of macrophage immune cells. McQueen and Groves found that mycobactin J, produced by *Mycobacterium paratuberculosis*, has toxic effects on murine macrophage cells. Its toxicity is higher than that of iron chelators desferrioxamine B and TrenCAM. Their experiments indicated that the toxicity was likely due to iron starvation, which triggered a hypoxia-like response. They also discovered that mycobactin J is a more potent iron chelator than previously thought and can penetrate cell membranes and hydrophobic organelles. Overall, mycobactin J exhibits toxicity and induces a hypoxia-like response under physiological conditions[177].

Bacteria and fungi use siderophores to acquire iron but can develop antibiotic resistance. The Trojan Horse Effect offers a solution by loading toxic metals into siderophores and disguising them. A study synthesized and characterized aluminum or gallium complexes with desferrioxamine (DFO) and desferrioxamine-caffeine (DFO-caff). The complexes Me (DFO) and Me (DFO-caff) showed higher toxicity against microorganisms than free Me^{3+}. This demonstrates the effectiveness of the Trojan Horse effect in achieving broad-spectrum antimicrobial action by loading non-essential or toxic metal ions into microbes using siderophore carriers[178].

The applications of iron chelators in PET/CT (positron emission tomography/X-ray computed tomography)

Jang *et al.* developed copper-64 (^{64}Cu)-incorporated iron oxide (IO) nanoparticles (NPs) without the need for a chelating agent. These dual-functional NPs possess magnetic and radioactive properties, making them suitable for PET-MRI. IO nanoparticles with ^{64}Cu were found to act as a contrast agent for PET imaging and function effectively as a T2 MRI nanoprobe due to their favorable r2/r1 ratio. Incorporating ^{64}Cu at the core of core-shell-structured IO NPs demonstrated excellent in-vivo stability, offering valuable insights for designing PET-MRI contrast agents[179]. The initial version of a chelator called THPMe, which is made up of tris(1,6-dimethyl-3-hydroxypyridin-4-one) and designed explicitly for gallium-68 (^{68}Ga), has demonstrated significant potential in quickly and effectively labeling PET radiopharmaceuticals through kit-based methods. Peptide variations of THPMe have been employed in preclinical and clinical research to visualize the activation of their intended receptors within living organisms. Imberti *et al.* developed new synthetic pathways to expand the THP platform by replacing the N1–CH3 group of THPMe with either an oxygen atom (THPO) or a hydrogen atom (THPH). The modifications were studied for their effects on properties like solubility, binding affinity to gallium, and selectivity for metal ions. THPH demonstrated the ability to bind ^{68}Ga under mild conditions (5 min, room temperature, pH 6, ligand concentration: 1 μM) *in vitro* and *in vivo* in a mouse model. Spectrophotometric analysis revealed that THPMe and THPH preferred binding Ga^{3+} over Fe^{3+}, enabling selective labeling with $^{68}Ga^{3+}$ even in excess Fe^{3+}. Compared to THPMe, THPH had reduced affinity for Fe^{3+}, increased affinity for Ga^{3+}, and improved radiolabeling efficiency. THPO had lower labeling efficiency, but its benzylated precursor Bn-THPO provides a potential framework for synthesizing various THP compounds with customizable chemical properties and preferences for different metal ions[180].

It is feasible to substitute iron with ^{68}Ga while maintaining the same level of bioactivity, enabling the use of PET for molecular imaging. According to Petrik *et al*., a preclinical assessment of the ^{68}Ga-radiolabeled siderophore DFO-B, commonly used in clinical settings, was conducted to image bacterial infections. DFO-B was successfully labeled using ^{68}Ga, resulting in a high level of radiochemical purity. Furthermore, it exhibited hydrophilic characteristics, minimal binding to proteins, and demonstrated remarkable stability when exposed to human serum and PBS. The in-vitro and in-vivo experiments confirmed the significant and targeted uptake of [^{68}Ga]Ga-DFO-B by *Pseudomonas aeruginosa* and *Staphylococcus aureus* bacteria. This provides strong evidence for the potential use of [^{68}Ga]Ga-DFO-B in accurately imaging bacterial infections. Considering that DFO-B has been used in clinical settings for many years and the estimated radiation dose of [^{68}Ga]Ga-DFO-B is lower compared to other radiopharmaceuticals labeled with ^{68}Ga, it is believed that [^{68}Ga]Ga-DFO-B holds great promise for clinical applications[181]. In addition, the research carried out by Misslinger *et al.* demonstrated that [^{68}Ga]Ga-DFO-B can be effectively employed in preclinical molecular imaging to identify pulmonary infection caused by the fungal pathogen *Aspergillus fumigatus* in a rat model of aspergillosis[182]

The novel and advanced application of iron chelators

Chelation therapy is a valuable therapeutic approach for treating neurological disorders. In 2023, Kupershmidt and Youdim conducted research on compounds that possess iron-chelating and anti-apoptotic properties, focusing on their potential use in neurological conditions like Parkinson's disease (PD), Alzheimer's disease (AD), age-related dementia, and amyotrophic lateral sclerosis (ALS). Their study utilized the two most effective substances, M30 and HLA20, which were selected based on the multimodal drug design paradigm. These innovative iron chelators demonstrate neuroprotective effects by reducing neurodegenerative pathology, fostering positive behavioral changes, and boosting neuroprotective signaling pathways[183].

Non-melanoma skin cancers are the most common form of cancer globally. They were using topical dermatological Photodynamic therapy (PDT) with protoporphyrin IX (PpIX) as the active photosensitizing agent, which has proven to be an effective treatment for these cancers, mainly when they are in the early stages. Researchers are currently studying new iron-chelating agents to improve and broaden the applications of this treatment method. By reducing free iron, these agents enhance the accumulation of PpIX, making it more accessible for light activation and consequently increasing the effectiveness of cell destruction. In the study, Anayo *et al.* used two iron-chelating agents, CP94 and AP2-18, compared to PpIX precursors, namely aminolevulinic acid (ALA) and methyl-aminolevulinate (MAL). Their findings revealed that the administration of CP94 or AP2-18 increased PpIX fluorescence. The addition of either iron-chelating agent consistently boosted PpIX accumulation. However, when a higher dose of ALA, which was already highly effective, was used, the iron-chelating agents did not always provide an additional beneficial effect on PpIX-PDT cell kill. Compared to ALA or MAL administration, these adjuncts showed significant advantages in skin cancer cells. Throughout the study, AP2-18 was found to be at least as effective as CP94 + ALA/MAL co-administration and significantly superior to CP94 supplementation in enhancing PpIX fluorescence in human lung fibroblasts (MRC-5)[184].

A recent study used iron-chelating polymer micelles for concurrent doxorubicin delivery and cardiotoxicity reduction. The amphiphilic polymer comprised a copolymer with methoxy poly (ethylene glycol) and poly(glutamic acid) as the backbone and a side chain comprising an L1 analogue. According to their findings, these polymeric micelles effectively inhibit ferroptosis in cardiomyocytes, a form of iron-dependently regulated cell death (Fe^{2+}). This inhibition is achieved through efficient iron chelation and leads to a reduction in cardiotoxicity. Including both doxorubicin and coenzyme Q10 (CoQ10) within micelles also provides additional relief from cardiotoxicity. This is because of the ability of the reduced CoQ10 to function as a radical trapping agent, effectively limiting lipid peroxidation and cardiomyocyte ferroptosis[185].

Ghassemi-Rad *et al.* demonstrated the impact of the recently created iron-binding polymer known as DIBI on the production of inflammatory mediators by RAW 264.7 macrophages and bone marrow-derived macrophages (BMDMs) when exposed to lipopolysaccharide (LPS) stimulation. The presence of DIBI during macrophage culture reduced iron levels and proinflammatory cytokines (interferon-β, IL-1β, and IL-6) upon LPS exposure.

It also decreased ROS, nitric oxide, and cytokine-induced activation of STAT 1 and 3, which enhance LPS-induced inflammation[186].

Future trends

Iron chelators are compounds that bind to excess iron in the body and help remove it from the system. Their role in conditions of increased iron, such as hemochromatosis or thalassemia, is well-established. However, their potential therapeutic role in other conditions, including infectious diseases like COVID-19, is an area of ongoing research. Given that iron plays a role in the immune response and that excessive iron levels can exacerbate inflammatory processes, the role of iron in the pathogenesis of COVID-19 and the potential treatment with iron chelators is indeed an important area for future investigation.

Research into the interplay between iron metabolism, inflammation, and viral infections, including COVID-19, could provide valuable insights into potential therapeutic interventions. Understanding how iron levels affect the body's response to viral infections and whether iron chelators could play a beneficial role has the potential to open up new avenues for treatment. As research in this area progresses, it will be important to carefully evaluate the potential benefits and risks of using iron chelators in the context of COVID-19 and other infectious diseases.

Conclusions

Iron chelate compounds prevent iron from acting as a catalyst for oxidation and reduction processes. In addition to this, they also provide the possibility of transferring and excreting iron through urine or feces. Consequently, iron chelators decrease tissue iron levels by preventing excess iron accumulation in organs. Infectious disorders, inflammation, cardiovascular diseases, atherosclerosis, neurological diseases, and cancer may be influenced by oxidative stress. Iron is crucial for the multiplication of cancer cells.

Consequently, the development of cancerous cells will be challenging in the absence of this essential component. The three commercially available iron chelators, DFO, L1, and DFX, have distinct characteristics. Nevertheless, each medicine has benefits and downsides, and the appropriate therapy for each patient must be determined individually. Correctly administered iron chelation treatment may significantly minimize the difficulties caused by iron overload and enhance the patient's quality of life.

Limitations

Despite the therapeutic effectiveness, iron chelates also show adverse effects and require precautions during use, which should also be discussed in future studies. Also, this review did not discuss the information or procedure for iron chelator administrations. The type of iron chelators and their dosage have different therapeutic effects. The other applications of a combination of varying iron chelators in nuclear/heavy metal detoxification in classified cancers and COVID-19covid 19 diseases can be investigated.

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Author contribution

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