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Synthetic and natural iron chelators: therapeutic potential and clinical use

Heather C Hatcher¹, Ravi N Singh¹, Frank M Torti^{1,3}, and Suzy V Torti^{1,2,3,†}

¹Department of Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, NC, USA

²Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, NC, USA

³Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC, USA

Abstract

Iron-chelation therapy has its origins in the treatment of iron-overload syndromes. For many years, the standard for this purpose has been deferoxamine. Recently, considerable progress has been made in identifying synthetic chelators with improved pharmacologic properties relative to deferoxamine. Most notable are deferasirox (Exjade®) and deferiprone (Ferriprox®), which are now available clinically. In addition to treatment of iron overload, there is an emerging role for iron chelators in the treatment of diseases characterized by oxidative stress, including cardiovascular disease, atherosclerosis, neurodegenerative diseases and cancer. While iron is not regarded as the underlying cause of these diseases, it does play an important role in disease progression, either through promotion of cellular growth and proliferation or through participation in redox reactions that catalyze the formation of reactive oxygen species and increase oxidative stress. Thus, iron chelators may be of therapeutic benefit in many of these conditions. Phytochemicals, many of which bind iron, may also owe some of their beneficial properties to iron chelation. This review will focus on the advances in iron-chelation therapy for the treatment of iron-overload disease and cancer, as well as neurodegenerative and chronic inflammatory diseases. Established and novel iron chelators will be discussed, as well as the emerging role of dietary plant polyphenols that effectively modulate iron biochemistry.

Iron in mammalian systems

Iron is an essential element involved in many cellular processes that are necessary for life, including oxygen transport, oxygen sensing, electron transfer, energy metabolism and DNA synthesis [1–6]. The absolute requirement for iron in mammals has resulted in the evolution of complex mechanisms to efficiently acquire, transport and store this poorly soluble transition metal [7–9]. These mechanisms also shepherd iron safely, since unliganded or incompletely liganded iron ions can participate in ‘Fenton-type’ redox chemistry, reacting with hydrogen peroxide (H₂O₂) or lipid peroxides to generate the highly reactive hydroxyl radical (OH•) or lipid radicals such as LO• and LOO•. These reactive oxygen species (ROS)

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[†]Author for correspondence storti@wfubmc.edu.

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can damage lipid membranes, proteins and nucleic acids. Thus, excess iron can be toxic and patients with **iron overload** must be treated.

Medicinal interest in iron chelators originated with the treatment of such patients with acute or chronic iron overload [5,10–12]. However, as discussed in this review, this represents a limited subset of the potential medical benefits of iron chelators, which are currently being explored for their cardioprotective, neuroprotective, anti-cancer, anti-inflammatory and other properties. In this review, we focus on the potential medicinal benefits of iron chelators. We first provide a brief overview of systemic iron homeostasis (for more extensive reviews of this complex topic readers are referred elsewhere [5,13]). We then describe natural and synthetic iron chelators and discuss their current and potential therapeutic uses.

Systemic iron homeostasis

Absorption of dietary iron occurs in the proximal small intestine and is carefully regulated to maintain equilibrium between absorption and loss of body iron [14]. Figure 1 provides an overview of iron homeostasis. Most dietary nonheme iron is in the ferric (Fe^{3+}) form, which must be reduced to ferrous (Fe^{2+}) iron for efficient uptake. The activity of luminal ferrireductases such as duodenal cytochrome B (*CYBRD1*, also known as DCYTB) likely facilitates this reduction [13]. Absorptive enterocytes obtain Fe^{2+} through divalent metal transporter 1 (DMT1), the same iron transporter used for endosomal transfer in the transferrin cycle [13]. Upon entry into the intestinal epithelial cell, some iron remains in the cell for use or storage in ferritin, the cytosolic protein in which iron is stored. This iron will not be absorbed by the body; rather, it is lost as enterocytes are sloughed into the gut lumen [13].

The majority of iron is delivered to the circulating plasma protein transferrin following efflux from the enterocyte through the basolateral iron transporter ferroportin (also known as FPN-1, IREG1, MTP1 and *Slc40a1* [solute carrier family 4, member 1])[15–17]. Oxidation of iron by hephaestin or ceruloplasmin, both of which have ferroxidase activity ($\text{Fe}^{2+} \rightarrow \text{Fe}^{3+}$) precedes its loading onto transferrin [18]. Extracellular iron circulates in the plasma in a nonreactive form bound to transferrin (Tf), which can be taken up by cells following binding to transferrin receptor 1 (Tfr1), present on cell surfaces [13]. Tf–Tfr1 complexes are taken into the cell by receptor-mediated endocytosis. Endosomes become acidified through proton influx, leading to conformational changes in both Tf and Tfr1 and promoting iron release [8,9,13]. Liberated inorganic iron is subsequently reduced by the ferrireductase six-transmembrane epithelial antigen of prostate (STEAP)3 to Fe^{2+} [19] and transported out of the endosome by DMT1 or (solute carrier family 11, member 2 (SLC11A2) [13,20–22]. Apo-Tf (iron-free) and Tfr1 are recycled to the cell surface to be used in further cycles of iron binding and uptake [5]. A second Tfr-like molecule, transferrin receptor 2 (Tfr2), can mediate cellular iron uptake and is expressed in liver cells, erythroid cell lines and duodenal crypt cells [23]. The affinity of Tfr2 for transferrin is substantially lower than that of Tfr1 and Tfr2 has been suggested to play an as yet poorly understood role as a systemic iron sensor [24]. Although virtually all circulating iron is bound to transferrin under physiological conditions, nontransferrin-bound iron (NTBI) can increase in iron overload and is proposed to contribute to the pathology of iron overload [25,26].

The major site of iron utilization is the bone marrow, where it is used in the synthesis of hemoglobin by red blood cell precursors. Due to the constant degradation of erythrocytes, conservation and recycling of iron is essential to replenish the iron contained within hemoglobin [27,28]. This recycling process occurs primarily within the macrophage, which

is capable of phagocytosing erythrocytes, with subsequent liberation of iron in heme by heme oxygenase-1 (HO-1) [28–31].

Systemic iron homeostasis depends on the coordinate control of intestinal iron absorption, iron recycling and iron storage [13]. Hepcidin, a recently discovered peptide hormone, produced in the liver, has been shown to play a major role in this regulatory circuit. Hepcidin acts as a negative regulator of iron efflux by causing the degradation of ferroportin [32,33]. Ferroportin, the iron efflux pump involved in delivery of iron from enterocytes to the circulation, is also expressed at high levels in placenta, hepatocytes and macrophages and is an essential component of systemic iron homeostasis [16,34].

Synthesis of hepcidin is increased by iron loading and decreased by anemia and hypoxia [34]. The bone morphogenetic protein (BMP)/SMAD pathway is critical in the activation of hepcidin transcription: loss of hepatic SMAD4 results in severe iron overload due to failure of hepcidin-mediated degradation of ferroportin [35]. In addition to its role as an iron-regulatory hormone, hepcidin is induced by infection and inflammation. This results in hypoferrremia, which contributes to defense against microbial infections [34]. A consensus signal transactivator of transcription 3 (*STAT3*)-binding site in the hepcidin gene has been shown to mediate hepcidin induction in inflammation through a signaling pathway triggered by the cytokine IL-6 [33,36,37]. ROS inhibit this effect [38], suggesting a link between ROS and iron metabolism [27].

Ferritin is an iron storage protein that is found both intracellularly and circulating in plasma. Cellular ferritin is composed of 24 subunits of heavy or heart (H-) and light or liver (L-) types, the ratios of which are tissue-specific and can be modified by disease and other stimuli [39]. The protein shell can hold up to 4500 iron ions in a redox-inactive ferrihydrite mineral form with phosphate and oxohydroxide anions. The primary function of ferritin is the sequestration of iron in a nontoxic form, which minimizes the ability of iron to catalyze the formation of ROS. Transcriptional and post-transcriptional controls increase cellular ferritin in response to environmental cues, as well as high iron levels [40]. While most ferritin is used to store iron within cells, a small amount is released into the serum and is measured clinically as a semiquantitative indicator of iron stores [28]. Serum ferritin has been reported to be rich in the L-subunit and glycosylated, although this characterization is based on ferritin isolated from non-normal (hemochromatitic) individuals [41]. The biological role of serum ferritin is unclear, although our laboratory has speculated that it may play a role in regulation of angiogenesis [42].

The expression of genes involved in angiogenesis, erythropoiesis and iron metabolism, including *Tf* and *Tfr*, is upregulated in response to hypoxia [43]. These pathways are tightly connected via regulation by hypoxia-inducible factor (HIF)-1, a transcription factor that binds to the hypoxia-response elements (HREs) of target genes [43]. The HIF-1 heterodimer consists of a regulatory subunit, HIF-1 α , which is the oxygen-responsive component, and a constitutively expressed HIF-1 β subunit, also known as the aryl hydrocarbon receptor nuclear translocator (ARNT) [43]. When oxygen is present, the regulatory subunit is hydroxylated on two prolines by iron-dependent prolyl-hydroxylases (PHDs). This recruits the von Hippel-Lindau (vHL) tumor-suppressor protein and triggers its degradation through the ubiquitin–proteasome pathway [43]. Under hypoxic conditions, prolyl hydroxylase activity is inhibited. This results in accumulation of HIF-1 α and its translocation to the nucleus, where it binds ARNT/HIF-1 β , and permits the transcription of HIF-dependent genes [43]. Iron chelators, such as deferoxamine (DFO) [44] and the flavonoid quercetin [45,46] inhibit the hydroxylation of HIF-1 α , presumably by removing iron from PHD, which increases levels of HIF-1 α ; thus, activation of HIF-1 may contribute to the biological effects of iron chelators [8,9].

Iron chelators & iron-chelation therapy: overview

While iron chelators are chemically quite diverse, they typically contain oxygen, nitrogen or sulfur-donor atoms that form coordinate bonds with bound iron. The donor atoms of the ligand affect the preference of the chelator for either the Fe(II) or Fe(III) oxidation states [7]. Chelators that prefer Fe(II) contain ‘soft’ donor atoms, such as nitrogen and sulfur, and, consequently, retain a relatively high affinity for other biologically important divalent metals such as Cu^{2+} and Zn^{2+} [47]. Iron can coordinate six ligands in an octahedral arrangement; thus, iron chelators with the highest affinity will normally be hexadentate, binding iron in a 1:1 ratio (chelator:iron), one example being DFO. By contrast, bidentate (3:1 ratio) or tridentate (2:1 ratio) chelators, which bind to only two or three of the available iron chelation sites, can potentially redox cycle and thereby promote free radical generation [26]. Effective iron chelators must efficiently compete with the biological ligands that normally bind iron; therefore, the affinity of chelators for iron and their stoichiometry of iron binding will greatly impact their activity as therapeutic agents [8,9]. Chemical structures of the most important iron chelators with medicinal applications are shown in Table 1.

Iron-chelation therapy has largely focused on the treatment of iron overload in patients who receive multiple blood transfusions as supportive therapy for treatment of conditions such as α -thalassaemia, sickle cell disease and myelodysplasia [47,48]. As discussed below, however, the potential spectrum of activity of iron chelators is much broader than this. For example, due to their ability to sequester metals essential to tumor growth or to foster redox cycling of bound iron, chelators have been suggested to be useful as anticancer agents [8,9,49]. Indeed, numerous preclinical and clinical studies have suggested a role for iron chelators in the treatment of cancer [8,9,50]. In addition, iron chelators may play a role in diseases mediated by oxidative stress, including ischemia–reperfusion injury [51], liver [52], infectious [53] and neurologic [54] diseases, diabetes [55], inflammation [56] and atherosclerosis [57].

Chelators in current medicinal use include natural compounds derived from microorganisms (siderophores) and synthetic chelators. Additionally, there is a growing appreciation of the role of natural iron chelators that inhibit oxidative stress and are found in foods and plants. Below, we discuss recent advances in the medicinal applications of these three major classes of chelators: siderophores, synthetic chelators and food- and plant-derived chelators. Table 1 presents the structures of these chelators and some of the biological contexts in which they have been studied.

Siderophores

Iron-dependent microorganisms have evolved a strategy to solve the problems of bioavailability and toxicity of iron through the synthesis of siderophores (low-molecular mass Fe^{3+} -specific chelators) employed for iron uptake and storage [58]. The iron-binding constant of siderophores can reach at least 10^{30} M, permitting microbial extraction of iron even from stainless steel [59].

Deferoxamine—Deferoxamine mesylate (Desferal®, desferrioxamine) is the best-known example of a medicinal siderophore and the most common one in medical use [8,9,27]. DFO has been used for decades to treat iron-overload diseases and remains the current standard for iron-chelation therapy [60–62]. Toxicity of iron overload is due largely to NTBI, as this pool of iron has both redox activity and the ability to access highly vascular tissues, especially hepatic, cardiac and endocrine tissue [25,26]. DFO has been shown to be a multifunctional therapeutic agent that can detoxify NTBI by chelation and heme proteins by ferryl reduction and radical scavenging [63]. DFO also acts as a reducing agent, preventing

oxidation of membrane lipids by removing high-oxidation states of heme iron, such as ferryl myoglobin (Mb) or Hb [64–66].

Hematologic diseases for which iron-chelation therapy with DFO has shown clinical effectiveness include thalassemia major, sickle cell disorders and myelodysplasia [67]. - thalassemia major is a rare recessively inherited disorder of hemoglobin synthesis resulting in transfusion-dependent anemia; consequently, chronic transfusion therapy results in a toxic accumulation of iron in the liver, spleen, endocrine organs and the myocardium [68]. Iron-chelation therapy benefits thalassemia major patients both by reducing the iron-loading burden and ameliorating iron-induced dysfunction within the heart [68–71]. Sickle cell disease (SCD) is an inherited disorder of hemoglobin synthesis characterized by lifelong hemolytic anemia [72]. Iron overload develops in 10–20% of SCD patients who receive repeated blood transfusions; these patients show similar rates of liver iron loading as patients with transfusion-dependent thalassemia, and are treated similarly [25,73]. Myelodysplastic syndromes (MDSs) are a common heterogeneous group of bone marrow disorders characterized by ineffective hematopoiesis and an increased risk of the development of acute myeloid leukemia [25,74]. Patients with MDSs may develop long-term dependence on blood transfusions, which generates higher levels of NTBI, requiring iron-chelation therapy [75,76]. The goal of chelation therapy in patients with MDS is primarily prevention of iron overload to preserve organ function, with the potential to improve patient survival [77]. Although there are few studies of efficacy for treatment of MDS, a retrospective study in patients with MDS indicated that iron chelation therapy using DFO was significantly associated with improved survival [74]. Few relevant clinical trials have been performed to evaluate the impact of iron chelation therapy in SCD and MDS or whether particular chelators could be more effective than others; however, documentation to date supports the use of DFO treatment in these diseases [67].

Iron chelation also may aid in reducing injury due to oxidant-related inflammation. Pro-oxidants play a significant role in the inflammation and tissue injury observed in many renal and hepatic diseases, including acute and chronic kidney disease, diabetic nephropathy, renal and hepatic ischemia–reperfusion injury (IRI) and nonalcoholic fatty liver disease (NAFLD) [78–81]. Since iron contributes to oxidative stress, siderophores such as DFO may play a role in the therapy of these diseases. While DFO was shown to ameliorate IRI in animal models, treatment using iron scavengers in ischemic syndromes is not in current clinical use [82].

Iron-chelation therapy with DFO has been studied in other diseases characterized by chronic inflammation, such as atherosclerosis and diabetes. Some epidemiological and many experimental studies suggest that development of atherosclerosis is associated with the amount of iron stored in the body [83]. Iron and oxidized lipids are both found in atherosclerotic lesions [84]. Iron depletion by DFO was shown to delay formation of atherosclerotic lesions [84–86], indicating that chelation therapy may aid in the treatment or prevention of atherosclerosis.

Deferoxamine also may have therapeutic value in the treatment of diabetes. Excess iron appears to be associated with insulin resistance and Type II diabetes, as well as increased risk of diabetic complications [55]. Use of DFO to lower elevated serum ferritin levels in Type II diabetic patients improved fasting glucose, triglyceride and HbA_{1c} levels and correlated well with diabetes control [87]. Coronary metabolic vasodilation is impaired in diabetes, and administration of DFO to patients with Type II diabetes was shown to substantially improve coronary microvasculature function [88]. A recent study showed that treatment with DFO not only induced iron depletion in HepG2 hepatocytes and in rat liver, but also increased glucose uptake and upregulated insulin receptor activity and signaling

[89]. The results of this study suggest that iron status may affect progression to hyperglycemia and may help to explain the pathogenesis of hepatic iron-overload insulin-resistance syndrome [89]. Thalassaemic patients with iron overload have a high incidence of insulin resistance and diabetes; combination treatment of some of these patients with DFO and deferiprone (see ‘Synthetic chelators’ section) improved their diabetes and glucose tolerance [90,91] and decreased ferritin levels [92–94]. Further studies are required to confirm a beneficial role of iron chelators in other diabetic populations.

Iron chelators have also been explored as cancer chemopreventive and chemotherapeutic agents [8,9]. DFO was among the first to be explored in this context, largely due to its well-documented history of clinical safety and efficacy in the treatment of iron-overload disease [8,9,95]. DFO was observed to inhibit DNA synthesis and cell proliferation and induce apoptosis in multiple cancer cell lines. However, the ability of DFO to inhibit tumor growth in animal studies and clinical trials was limited [8,9,50,96–99]. The incomplete success of DFO as an anti-tumor agent has led to an emphasis on designing more effective iron chelators, with particular focus on chelator lipophilicity, membrane permeability and selective anti-tumor activity [50,99].

Synthetic alternatives to DFO have also been sought for the treatment of iron overload. While the long-term efficacy of DFO therapy in the treatment of iron overload has been demonstrated, its poor oral bioavailability requires an inconvenient regimen of parenteral administration. This has motivated the search for alternative, preferably oral, tridentate and bidentate chelators [26,60,62]. Efforts to substitute synthetic chelators for DFO in both the treatment of iron overload and cancer have met with substantial success, as discussed later (see ‘Synthetic chelators’ section).

Desferrithiocin—Desferrithiocin (DFT), a tridentate siderophore, is an orally effective iron chelator [100]. DFT was found to have potent antineoplastic activity against hepatocellular carcinoma cells *in vitro* with low levels of cytotoxicity for normal hepatocytes; studies with DFT and synthetic analogues that may be more selective for cancer cells are ongoing [101,102]. Although DFT showed much promise as a chelating agent, it exhibited severe nephrotoxicity [103]. The high oral activity of DFT made this chemical backbone a promising scaffold and structure–activity relationship studies have been performed to develop less-toxic derivatives of this pharmacophore [7].

Synthetic chelators

Although DFO is safe and effective in the treatment of iron overload, the requirement for prolonged subcutaneous infusions 5–7 days per week frequently results in patient non-compliance. This has led to the search for alternative chelators with superior pharmacological properties. The major synthetic focus has been on the design of Fe³⁺-selective chelators, which feature ‘hard’ oxygen donor atoms that are generally more selective for trivalent metal cations over divalent cations [7].

Deferiprone—Deferiprone (Ferriprox®), one of hundreds of oral chelators that have been tested, is a bidentate ligand that has shown comparable efficacy to DFO and is more effective than DFO in the removal of excess iron from the heart [60,70]; however, major toxic side effects include agranulocytosis, musculoskeletal and joint pains, gastric intolerance and zinc deficiency [60,63]. An advantage of this compound is that the Fe(III) chelate of deferiprone carries no net charge and, therefore, can penetrate membranes easily, allowing removal of potentially toxic iron from tissues. In addition, the combination of DFO/deferiprone is increasingly used and no new toxic side effects have been reported for the combination [26,60,104]. Clinical data documenting the use of deferiprone in

thalassemia major are limited; however, its use is associated with agranulocytosis and arthropathy [68]. A recent clinical study showed that deferiprone was well tolerated and effective in lowering serum ferritin levels in patients with thalassemia major, with few adverse effects [105]. The combination of deferiprone with DFO showed a greater efficacy in promoting iron excretion than either chelator alone, as well as rapid reduction of iron overload in the heart and liver and reversal of cardiac dysfunction in thalassemic patients [92–94]. Deferiprone was effective in only a small number of MDS patients [74]. Overall, the compliance with oral deferiprone therapy is greatly improved compared with that typical with DFO therapy [62].

Based on *in vitro* studies suggesting a neuroprotective effect of deferiprone, analogues of deferiprone are currently under investigation for treating neurodegeneration [106]. Neurodegeneration in Parkinson's disease (PD) and Alzheimer's diseases (AD) or other **neurodegenerative diseases**, such as Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), are multifactorial. A complex set of toxic reactions, including induced expression of proapoptotic proteins and increase of iron and nitric oxide levels, lead to oxidative stress damage, inflammation, reduced expression of trophic factors and accumulation of protein aggregates, culminating in the death of neurons [107,108]. Metal ions such as iron and copper, have been cited as having key roles in the protein aggregation associated with many neurodegenerative diseases, including HD, AD, PD and Friedreich's ataxia (FA) [54]. The accumulation of iron at sites of neuronal degeneration in HD, AD, PD and at significant levels within the mitochondria of FA patients supports a role for iron in the pathology of these diseases [109] and provides a rationale for the development of chelators as viable new therapeutic strategies [109].

8-hydroxyquinoline derivatives—To date, a range of 8-hydroxyquinoline analogues have demonstrated substantial potential for the treatment of neurodegeneration, and one compound, clioquinol (CQ), has entered clinical trials [54]. CQ is a small lipophilic bioavailable metal chelator that has shown great promise in both AD and PD animal models [110,111]. Although issues relating to the transport of iron chelators across the blood–brain barrier remain a significant problem, one recent study has shown a promising therapeutic role for nanoparticle-mediated delivery of iron chelators [112]. 8-hydroxyquinoline derivatives exhibited substantial cytotoxic activity against *in vitro* models of cancer and this could be related to blockade of voltage-activated K^+ channels in the lipid membrane of the cancer cells [113]. Viability was significantly decreased in the rat hepatoma cell line FAO [114] and the human hepatoma cell line HepG2 [115] following treatment with the hexadentate hydroxyquinoline iron chelator O-trensox (*tris-N*-(2-aminoethyl)-[8-hydroxyquinoline-5-sulfonato-7-carboxamido] amine). These studies offer insight into the protective efficiency of iron chelators against hepatocellular carcinoma, which is correlated with iron overload [116,117].

Deferasirox—Deferasirox (ICL670; Exjade®) is a tridentate oral chelator that has recently been approved by the US FDA for use in the treatment of chronic iron overload due to blood transfusions (transfusional iron overload). Deferasirox has proven effective in removing excess iron from the liver and shown acceptable tolerance, although special attention should be given to monitoring renal function [118–121]. Clinical studies using deferasirox in the treatment of some hematologic diseases suggest that it is as effective as DFO in maintaining iron balance. Adverse events with deferasirox included transient rash, gastrointestinal disturbances and mild nonprogressive increase in serum creatinine, as well as cases of renal failure and cytopenias [67,68]. Both deferiprone and deferasirox have shown efficacy in controlling body iron burden in SCD patients and no agranulocytosis was described [67]. A single study indicated that deferasirox may aid in controlling iron burden in MDS [76]. Combinations of DFO/deferasirox or the two orally active chelators deferiprone and

deferasirox have been suggested as a treatment option for transfusional iron overload; however, the former would require slow subcutaneous or intravenous infusion of DFO and the latter may result in the formation of mixed (deferiprone–Fe–deferasirox) complexes that could raise new safety concerns [61].

Deferasirox also has been used in the treatment of rare anemias associated with iron overload. For example, serious complications of iron overload have been reported among patients with aplastic anemia and inherited bone marrow failure syndromes such as Diamond–Blackfan anemia (DBA) and Fanconi’s anemia. Recently, a 1-year prospective study showed that treatment with deferasirox was effective as a monotherapy in maintaining or decreasing iron loading in patients with DBA and other rare anemias, including aplastic anemia, α -thalassemia and sideroblastic anemia, myelofibrosis, pure red cell aplasia, pyruvate kinase deficiency, autoimmune hemolytic anemia, Fanconi’s anemia, hereditary sideroblastic anemia, erythropenia and β -thalassemia [122].

Tachpyridine—Tachpyridine (*N,N,N'*-tris(2-pyridylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane) is a hexadentate metal chelator that chelates divalent metal ions and is toxic to cultured cancer cells, exhibiting an enhanced potency, relative to DFO [123–125]. Importantly, ferritin synthesis was depressed following tachpyridine treatment of cells, indicating that tachpyridine can effectively reduce levels of intracellular iron [123]. Additionally, tachpyridine sensitized cancer cells to ionizing radiation, suggesting that chelators may function in anticancer therapy, both as radio-enhancing agents and as cytotoxic agents [126]. Analysis of chelators based on the *cis,cis*-1,3,5-triaminocyclohexane (tach) backbone revealed that the most rapid cytotoxic response was achieved with chelators whose Fe(II) complexes underwent rapid oxidation, suggesting a path to further optimization of these chelators as anticancer agents [127].

Dexrazone—Dexrazone (ICRF-197; DZR), which belongs to a class of *bis*(2,6-dioxopiperazines), is a prodrug that is hydrolyzed to an iron-chelating EDTA-type structure (ADR-925) designed as an anti-tumor agent [128]. DZR is clinically approved as a cardioprotective agent to reduce doxorubicin-induced cardiotoxicity and it is supported by extensive animal studies [129] and clinical trials [130], showing it to be highly effective in reducing doxorubicin-induced cardiotoxicity, without affecting the anti-tumor activity of doxorubicin [128]. Additional studies have shown DZR can reduce or prevent the following: mitoxantrone toxicity, daunorubicin toxicity, bleomycin pulmonary toxicity, isoproterenol-induced cardiotoxicity, acetaminophen-induced hepatotoxicity, alloxan-induced diabetes and hyperoxia-induced pulmonary damage [131]. ADR-925 prevents formation of damaging ROS by removing Fe^{3+} from the Fe^{3+} –anthracycline complex or by binding free iron in the cell [132,133].

Thiosemicarbazones—Thiosemicarbazones possess iron chelator activity and inhibit ribonucleotide reductase (RR), an iron-dependent enzyme that catalyzes the rate-limiting step in DNA synthesis [134]. Since RR is a validated drug target in cancer chemotherapy, effort has been devoted to the development of thiosemicarbazones in anticancer therapy [135]. Because RR participates in DNA repair, the effect of Triapine® (3-aminopyridine-2-carboxaldehyde thiosemicarbazone [3-AP]) on tumor cell radiosensitivity was investigated. Triapine significantly increased radiation-induced tumor growth delay in tumor-bearing mice [136]. Triapine is currently in clinical trials as an anticancer drug [50]. Considering the promising results observed from studies combining Triapine with gemcitabine [137] and cytarabine [138], Triapine may become the first iron chelator to be widely used as an anticancer drug [50].

Pyridoxal isonicotinoyl hydrazone analogs—Pyridoxal isonicotinoyl hydrazone (PIH) and its analogs are tridentate ligands, which bind iron via a carbonyl oxygen, an imine nitrogen and a phenolic oxygen and possess a high affinity and specificity for Fe³⁺ [139]. They are relatively lipophilic, compared with other chelators, resulting in rapid membrane permeability, and they exhibit excellent antioxidant properties [140].

Extensive structure–function studies on PIH analogs have been carried out. Interest in the anti-tumor activity of this group of compounds identified 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone (311) as among the most toxic to tumor cells [141]. This compound continues to be investigated; recent work has suggested that it may have potential anti-HIV activity [142]. Further studies on the chemistry of PIH-related compounds led to the development of the di-2-pyridylketone isonicotinoyl hydrazone (PKIH) analogs, which prevent iron uptake from Fe–Tf and are potent inhibitors of cell growth, in part due to free radical generation through the Fenton reaction [143,144]. For example, di-2-pyridylketone isonicotinoyl hydrazone (HPKIH) possesses significant antiproliferative activity against cancer cells that is influenced by the redox properties of the iron complexes [145].

Condensation of the di-2-pyridyl structure with thiosemicarbazides yielded a group of iron chelators, the DpT family, which shows selective toxicity for cancer cells [99,146–149]. Thiosemicarbazones are themselves chelators that inhibit RR activity (see earlier); thus, the strategic goal in the design of the DpT family was to incorporate this moiety into a ‘hybrid’ series. The most active compound in the DpT series is Dp44mT, with an average IC₅₀ of 30 nM in 28 cancer cell types and good efficacy at inhibiting tumor growth in xenografts [149]. These novel iron chelators not only have potent and broad anti-tumor activity, but can overcome resistance to established chemotherapeutics and appear very promising as antineoplastic agents [99,148,149].

Phytochemicals

Evidence supporting the therapeutic efficacy of **phytochemicals** in conditions ranging from cancer to neurodegenerative disease has been steadily accumulating in recent years (Table 1). Although studies are, in many cases incomplete, data suggest that foods containing plant polyphenols and flavonoid compounds may have benefits not only as potent antioxidants, but also as iron chelators [27,150–152].

Proanthocyanidins, epicatechins, flavanols and anthocyanin contain an iron-binding motif similar to the catechol moiety that is a known iron-binding element of microbial siderophores [27,153–159]. Subclasses of flavonoids are based on chemical structure: flavanols (examples of rich sources: teas and red wine), flavanones (citrus foods), flavones (fruit skins, peppers and leafy vegetables), isoflavones (soy foods), flavonols (leeks, onions, leafy vegetables and tomatoes), anthocyanidins (berries) and proanthocyanidins (apples, chocolate and nuts) [160]. The activities of flavonoids are dependent on their chemical structures and the position and degree of hydroxylation appear particularly important for their biochemical and pharmacological actions [161]. The most well-absorbed flavonoids by humans are isoflavones, gallic acid, catechins, flavanones and quercetin glucosides, each with different kinetics [162,163]. The various terms applied to these polymeric flavon-3-ols have contributed to the confusing and often erroneous nomenclature used to describe these compounds [164]. The terms ‘proanthocyanidins’ and ‘condensed tannins’ are most frequently used in the literature (for a comprehensive description of proanthocyanidin nomenclature, see elsewhere [165]).

The most common group of flavonoids in the US diet, the flavan-3-ols and their polymeric condensation products, the proanthocyanidins, have been reported to exhibit antioxidant, anti-carcinogenic, cardioprotective, antimicrobial, antiviral and neuroprotective properties

[165]. The general chemical structure (Table 1) includes a C₁₅ (C₆-C₃-C₆) skeleton joined to a chroman ring (benzopyran moiety) that in turn bears an aromatic ring at C2, C3 or C4. The ability of flavan-3-ol to chelate iron and other essential minerals limits growth of invasive microorganisms by causing severe mineral depletion and is vital to plant defense against pathogens [165]. Flavan-3-ols exhibit antioxidant activity via several mechanisms, including the scavenging of free radicals, chelation of transition metals and inhibition of enzymes (for a detailed review of antioxidant activity of flavon-3-ols, see elsewhere [166]). The flavan-3-ols and their microbial phenolic acid metabolites are particularly good antioxidants; they are considered better than vitamins C and E, due to the greater stability and less harmful nature of the derived radical compared with the initial radical species [165,167].

Flavonoids have been studied for their chemopreventive and anticancer effects, particularly through three mechanisms: prevention of carcinogenic metabolite formation, prevention of tumor cell proliferation and induction of tumor cell apoptosis [168]. Within the last decade, numerous studies have focused on the use of natural iron chelators as therapeutic agents; however, it is important to note that detrimental effects have also been noted for flavan-3-ol. Depending on the source, type, quantity and existence of other dietary factors, flavan-3-ol-related detrimental effects include activation of procarcinogens, ROS formation (pro-oxidant activity), hemorrhage formation, mutagenicity, initiation of hepatotoxicity, alteration of pharmacokinetics of therapeutic drugs, increased estrogenic plasma biochemistry, development of gastroenteritis, anti-nutritive activity and weight loss [165,169].

The following studies elucidate a role for phytochemicals as iron chelators and their therapeutic applications. They are summarized and presented according to flavon-3-ol-source: herbal remedy, grape or wine and other fruits and nuts, green tea, black tea and soy protein. Table 1 lists some of the phytochemicals with iron-binding properties discussed in this review and their sources.

Although many results reported with phytochemicals are encouraging, caution is required when interpreting some of these studies. In particular, herbal remedies are occasionally used as extracts or powders of poorly defined composition. Limitations of such studies are therefore that, first, effects are not always attributable to a chemically defined component and, second, may be the result of a mixture.

Herbal remedies

Curcumin, the active ingredient in the traditional herbal remedy and dietary spice turmeric, is a free radical scavenger and hydrogen donor and exhibits both pro- and anti-oxidant activity [150]. It is remarkably nontoxic and exhibits limited bioavailability. Curcumin exhibits great promise as a therapeutic agent and is currently in human clinical trials for a variety of conditions, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis and AD [150]. Cancer development and progression is inhibited by curcumin via its ability to target multiple steps in the pathway to malignancy (for a comprehensive review of curcumin, see elsewhere [150]).

Iron chelation may contribute to the anti-cancer activity of curcumin [170]. The chemical properties of curcumin are consistent with iron-chelator activity [171], and our laboratory recently observed that liver cells treated with curcumin exhibited hallmarks of iron depletion, which included decreases in the iron-storage protein ferritin, increases in TfR1 and activation of iron-regulatory proteins [172]. Curcumin also acts as an iron chelator *in vivo*, particularly in the setting of mild iron deficiency [170,172]. Under these conditions, dietary curcumin exerted profound effects on systemic iron, inducing a decline in hematocrit, hemoglobin, serum iron and Tf saturation, the appearance of hypochromic red blood cells and decreases in spleen and liver iron content [170]. Curcumin also repressed

synthesis of hepcidin, a peptide that plays a central role in regulation of systemic iron balance [170]. Consistent with these reports, curcumin reduced NTBI in a mouse model of α -thalassemia [173].

Some naturally occurring chelators cross the blood–brain barrier and can exert their antioxidant and iron-chelating properties in the brain [174,175]. Neuroprotective effects have been evaluated for curcumin [176], as well as apocynin, which is derived from the rhizome of *Picrorhiza kurroa*, a well-known herb in traditional Ayurvedic medicine [177–179]. While these studies provide experimental evidence in rodents that curcumin and apocynin act as neuroprotective agents for cerebrovascular diseases, further studies are necessary to determine the mechanism involved. Apocynin not only exhibited potent antioxidative properties by scavenging free radicals, but also acted on specific signaling pathways that regulate inflammatory responses in cultured human eosinophils and neutrophils [180]. *Mucuna pruriens*, another naturally occurring antioxidant used in traditional Ayurvedic Indian medicine, has also been shown to slow the progression of PD symptoms and to have none of the side effects of the current pharmaceutical L-dopa [174]. *Mucuna pruriens* inhibited the oxidation of lipids and deoxyribose sugars and exhibited divalent iron-chelating activity [174].

Kolaviron, a natural biflavonoid from *Garcinia kola* seeds that have been used in African herbal medicine, was shown to protect against oxidation of lipoproteins in rats through the chelating activity of kolaviron on Fe^{2+} , suggesting kolaviron may offer protective effects against atherosclerosis [181]. The antioxidant activity of floranol (a new flavonoid isolated from the roots of *Dioclea grandiflora*, a vine that grows in Brazil) was shown to be related to its ability to efficiently bind Cu^{2+} and/or Fe^{3+} . By preventing the reduction of these metals in heparanized blood collected from healthy, normolipidemic volunteers, floranol prevented the formation of free radicals that can oxidize low-density lipoprotein (LDL) [182]. This sequestering of metals makes floranol a beneficial candidate in reducing atherosclerosis [182], although the degree and duration of iron reduction required to normalize atherosclerotic plaque iron concentrations to that of healthy arterial tissue is not known and this will be a key question for future studies [57].

Pycnogenol™ (PYC), a standardized extract composed of a mixture of flavonoids, mainly procyanidins and phenolic acids obtained from a French maritime pine, may be shown to provide cardioprotective activity, which has been attributed to the strong free radical scavenging activity of its oligomeric procyanidin components [183]. Procyanidins extracted from *Vitis vinifera*, which have a composition similar to that of PYC, were observed to form a complex with ferric iron with a procyanidin–iron ratio of 1:2 [184]. Furthermore, the stability constant of the procyanidin–iron complex was comparable to another strong iron-chelating agent, nitrilotriacetate (NTA) [184]. Electron spin resonance observations indicate that PYC may act as an efficient metal chelator; thus, PYC may act as a preventive antioxidant via formation of redox-inert iron complexes and may inhibit the peroxidative process [183,185]. The mechanism of this complex interaction between radical species requires further investigation; furthermore, *in vivo* studies are necessary to evaluate the precise compounds that eventually exert biological activity.

Baicalein and its glycoside baicalin, the major bioactive compounds found in the Chinese herb *Scutellaria baicalensis* Georgi, have been found to strongly inhibit iron-promoted Fenton chemistry via a combination of chelation and radical scavenging mechanisms [186]. Baicalein also was shown to induce apoptosis in human breast cancer cells and human lung squamous carcinoma cells via alteration of the Bcl-2 family of mitochondrial proteins and activation of caspase-3 [187,188]. Baicalin and quercetin (see later) were shown to increase antioxidant status and decrease iron content and lipid peroxidation in the liver of mice with

iron-overload-induced liver oxidative injury [189,190]. In addition, when added to rodent chow (1% w/w final) both flavonoids significantly reduced hydroxyproline content in liver homogenates, indicating that these flavonoids can protect liver from fibrosis, a complication of iron-overload disease that can lead to liver cirrhosis [189]. Although these flavonoids are generally regarded as poorly bioavailable, a study of an orally administered formulation that contained *S. baicalensis* reported an apparent 8-h elimination half-life for baicalein; thus, baicalein can remain in the body long enough to affect iron homeostasis and reduce oxidative stress [186]. These studies suggest that phenolic compounds with an 'iron-binding motif' are strong iron-chelating agents that may modulate the bioactivity and bioavailability of iron in the body [191].

Tetramethylpyrazine and ferulic acid, two active ingredients in the Chinese herbal medicine *Ligusticum wallichii* Francha (ligustrazine), can chelate ferrous iron and decrease the formation of hydroxyl radicals [192]. Ligustrazine may be useful in preventing neuronal diseases associated with oxidative stress as pretreatment of cultured neuronal cells with the active compounds found in this herb attenuated iron-induced oxidative neuronal damage [192]; however, pharmaceutical-grade tetramethylpyrazine and ferulic acid were used in this cell culture study and it is unclear if the levels of these active ingredients would be similar in an orally administered supplement of the herbal medicine ligustrazine. In additional studies, pretreatment with pharmaceutical-grade ligustrazine administered by intraperitoneal injection provided functional protection after renal IRI in mice by decreasing generation of ROS, inhibiting apoptosis, decreasing neutrophil infiltration and interfering with cell adhesion [193,194]. This study did not report whether any adverse systemic effects were observed following administration of ligustrazine.

Grape, wine, fruits & nuts—The iron-binding properties of the flavonol quercetin, the major phenolic phytochemical present in cranberries and other selected phenolic compounds (chrysin, 3-hydroxyflavone, 3,4-dihydroxy flavone, rutin and flavones), were investigated in aqueous media using UV/vis, NMR and electron paramagnetic resonance (EPR) spectroscopies and ESI-MS [191]. Quercetin was found to bind Fe^{2+} more strongly than the well-known Fe^{2+} chelator ferrozine. Quercetin can also bind Fe^{3+} , Ga^{3+} and Zn^{2+} . Interestingly, quercetin completely suppressed iron-promoted Fenton chemistry at micromolar levels, even in the presence of the major cellular iron chelators ATP or citrate. Data from this study indicate that the radical scavenging activity of quercetin provides only partial protection against Fenton chemistry-mediated damage. On the other hand, iron chelation by quercetin can completely inhibit the Fenton chemistry. Thus, quercetin's antioxidant activity may be attributed to its iron-chelation activity [191]. Furthermore, superoxide radical-scavenging activity of flavonoid iron complexes was found to be more effective than the uncomplexed parent flavonoid [195].

Flavonols, including quercetin, are rapidly absorbed and reach maximum plasma concentration within a few hours, while the elimination of flavonols (e.g., quercetin metabolites) is quite slow, with reported elimination half-lives ranging from 11 to 28 h. Circulating flavonoids (and their metabolites) are further delivered into various organs, including liver, skin and brain [196]. Cranberry extracts rich in these compounds reportedly inhibit oxidative processes, including oxidation of LDL [197,198], oxidative damage to rat neurons during simulated ischemia [199] and oxidative and inflammatory damage to the vascular endothelium [200].

The potential of flavonols to act as anticancer agents was suggested by the ability of water-soluble cranberry phenolic extracts prepared from commercial cranberry powder to inhibit proliferation of several human tumor cell lines [201]. A total polyphenol extract containing a variety of flavonoids inhibited proliferation of two oral cancer cell lines (CAL27 and KB),

four colon cancer cell lines (HT-29, HCT-116, SW480 and SW620) and three prostate cancer cell lines (RWPE-1, RWPE-2 and 22Rv1) [201]. Enhanced antiproliferative activity was obtained when cranberry extract was enriched in polyphenolic content [201]. The authors of these studies indicated that there were additive or synergistic antiproliferative effects, resulting from the combination of anthocyanidins, proanthocyanidins and flavonol glycosides compared with individual purified phytochemicals [201]. Further studies are needed to determine if the anti-tumor activity of these compounds is linked to their iron-chelation properties and to determine their bioavailability in cranberry juices and whole cranberry fruit.

Grape seed extract (GSE) contains various polyphenols, including gallic acid, catechin, epigallocatechin gallate (EGCG) and proanthocyanidins. GSE possesses antioxidant activity [202–205], which derives from the ability of these constituents to scavenge free radicals and to chelate metals such as iron [204]. Interestingly, GSE and EGCG inhibited nonheme iron absorption in human intestinal Caco-2 cells by reducing basolateral iron exit via FPN-1 rather than by decreasing apical iron import [204]. A study of brain cell iron chelation suggested that EGCG and GSE are membrane permeable and may enter cells as complex forms with Fe^{2+} [206]. The iron-chelating activity of EGCG was comparable with that of DFO [206]. In most of these studies, GSE or EGCG was commercially prepared and characterized for use in cell culture or animal diets. Comparisons between purified products and dietary sources of GSE or EGCG were not presented and will be an interesting direction for future research. The effect of these compounds on uptake of dietary iron as well as the uptake of iron–polyphenol complexes also needs to be assessed [204].

Green tea catechins & black tea theaflavins—Flavonoids extracted from tea leaves (catechins present in green teas and theaflavins present in black teas) act directly as radical scavengers and exert indirect antioxidant effects through activation of transcription factors and antioxidant enzymes [175,207]. The most abundant polyphenolic compound of green tea is EGCG [175]. In addition to their radical scavenging action, green tea catechins possess well-established metal-chelating properties, with the structurally important features defining their chelating potential being the 3,4-dihydroxyl group in the B ring as well as the gallate group [151,208–210]. Furthermore, tea polyphenols that were dried and purified from black and green teas have been shown to have a profound protective effect on red blood cells challenged with exogenous oxidants via formation of a redox-inactive complex with iron [210].

Green tea catechins and black tea theaflavins were evaluated for their ability to induce cell death in several human cancer cells including human breast (MCF-7), colon (HT-29), hepatoma (liver; HepG2) and prostate (PC-3) and compared with normal human liver and lung (HEL299) cells [211]. It was observed that water tea extracts generally exhibited lower effects than the ethanol extracts and the authors of the study suggest that aqueous ethanol should be used in the preparation of concentrated black and green tea extracts for sale as dietary supplements [211]. The tea extracts were also cytotoxic to normal liver but not to lung; therefore, it will be important to determine the ratio of effective preventive or therapeutic to toxic dose [211]. Further studies demonstrated that apoptotic effects of black tea theaflavins were mediated by p53 in a transcription-dependent manner through the mitochondrial death cascade [212]. Regulator of G-binding protein signaling 10 (RGS10), which was induced within 4 h of theaflavin treatment in human colon cancer cells, was identified as a target gene [213]. This finding may be significant, since dysregulation of G-protein signaling, including G proteins and RGS proteins, has been implicated in tumorigenesis [213–215].

In addition to their potential as chemotherapeutic agents, green and black tea extracts also demonstrated chemopreventive activity in rodent models of breast carcinogenesis [216–219]. Green tea catechins and black tea theaflavins administered in the drinking water to transgenic multiple mammary adenocarcinoma (TAg) mice were shown to delay mammary carcinogenesis accompanied by an antioxidant effect in the target organ. The delay of carcinogenesis was reflected by a slight prolongation of mouse survival and significant decrease in tumor volumes [216]. Further evidence of the chemopreventive efficacy of theaflavins and EGCG was provided by a study that showed these compounds could inhibit or delay benzo(a)pyrene-induced lung carcinogenesis in mice [220]. Mice exposed to theaflavins and EGCG exhibited reduced expression of the proliferation-associated gene cyclooxygenase 2 (*COX-2*) as well as upregulation and increased activation of the apoptosis-inducing genes caspase-3 and caspase-7 [220]. Additionally, black tea theaflavins were shown to be potent inducers of apoptosis in human mammary epithelial carcinoma cells.

Once considered primarily radical scavengers, green tea catechin polyphenols are now understood to be multimodal acting molecules that direct numerous cellular neuroprotection/neurorescue mechanisms involving iron chelation, scavenging of oxygen and nitrogen radical species and activation of protein kinase C signaling pathway and prosurvival genes. Their nontoxic, lipophilic (and thus, brain-permeable) nature is advocated for iron removal from those brain areas where it preferentially accumulates in neurodegenerative diseases [221]. Metal ions, and iron in particular, are critical to catalyzing redox cycling; thus, iron-chelation therapy should be considered as a valuable strategy for the treatment of neurodegenerative diseases [222].

EGCG has been shown to improve age-related cognitive decline and to protect against cerebral IRIs [223,224], brain inflammation and neuronal damage in experimental autoimmune encephalomyelitis [225]. Long-term administration of green tea catechins or EGCG improved spatial cognition and learning ability in rats and reduced cerebral amyloidosis in Alzheimer's transgenic mice, respectively [226,227]. A recent study of the molecular mechanism of the neurorescue effect of EGCG demonstrated decreased protein levels and mRNA expression of the enzyme prolyl 4-hydroxylase, which belongs to the family of iron-oxygen sensors of HIF prolyl hydroxylases that regulate cell survival and differentiation in cultured human neuroblastoma cells [228]. While the source of EGCG was not identified in this study, proteins and genes related to various specific neuroprotective/neurorescue effects of EGCG were identified. These interactions should be investigated further in animal models of neurodegenerative diseases.

Soy protein—Several studies have highlighted the beneficial effects of soy protein on CVD risk factors [229–231]. Age-related increase in iron stores is observed in both men and women and parallels the rise in CVD [232]. Consumption of commercially prepared powders of soy protein with native phytate after only 6 weeks was shown to reduce iron stores, as assessed by serum ferritin concentrations, in postmenopausal women [230]. Declines in serum iron and Tf saturation were also observed [230]. Phytic acid in soy protein isolates is a major inhibitor of nonheme iron absorption in humans [233,234]; thus, postmenopausal women who are at risk of excess iron may benefit by incorporating soy into their diets to reduce iron stores and lower CVD risk [230]. While consumption of soy protein in perimenopausal women did not reduce the rate of menopause-associated increases in iron stores, a beneficial effect on total antioxidant status was observed at 12 weeks in these women [235].

Lipoxygenase-mediated pathways play a major role in chronic inflammatory diseases. Results from a recent study reveal that soy isoflavones (purified from defatted soy flour and

having an isoflavone content >95%) reduce the catalytically active ferric lipoxygenase to its resting ferrous form, indicating that soy isoflavones are natural redox inhibitors [236]. In a study of the signaling pathways underlying dietary tumor protection in rats, lifetime consumption of the soy isoflavone genistein and soy protein revealed that both dietary factors altered expression of mammary epithelial cell genes and identified a diverse subset of genes that may serve as potential biomarkers in other target tissues [237].

Additionally, soy proteins with isoflavones have been shown to impact the pathogenesis of insulin resistance and metabolic syndrome in obese male Zucker Diabetic Fatty (ZDF/Lepr^{fa}) rats [238]. In this study, both low and high isoflavone soy protein improved dyslipidemia and renal function in rats, compared with those on a casein-based diet; isoflavone-enriched soy protein had even greater antiadipogenic and hepatoprotective effects [238]. This study, along with previous investigations by this same group [238–242], indicates a potential therapeutic role for isoflavones in obesity and Type II diabetes and warrants further research to elucidate the mechanisms of soy phytochemicals on the development of insulin resistance and diabetes.

Future perspective

The spectrum of conditions that may be successfully treated with iron chelators has increased, as has the palette of chelators available to treat them. In particular, the development of deferiprone and deferasirox, new synthetic chelators with improved pharmacologic properties relative to deferoxamine, represent landmark accomplishments of the past few years. Although these chelators are not without their toxicities [120,243] and will continue to be evaluated, attention can now be more intensively focused on the application of iron chelators to a broad array of conditions related to oxidant stress, ranging from cardiovascular to neurodegenerative to inflammatory to malignant disease. Indeed, iron chelators appear very promising in many of these arenas, although investigations are largely still in preclinical and early clinical stages. The combined action of multiple chelators also offers fruitful ground for further investigation. Particularly encouraging has been the demonstration that smaller bidentate chelators can acquire iron from transferrin and shuttle it onto DFO [244] and the successful use of this combination in increasing cardiac function in patients with severe iron overload [245,246]. This strategy may find application not only in the treatment of iron overload, but in the treatment of neurodegenerative diseases and other conditions that represent known and potential targets for chelator therapy.

Perhaps most encouraging has been the recent recognition that a number of natural products contain endogenous substances that function as iron chelators. A caveat in interpretation of studies using natural products is that they are sometimes used as partially purified extracts, which can complicate the interpretation of results. Nevertheless, it is not unlikely that the chelating activity of naturally occurring dietary substances, such as the polyphenols, curcumin and others, may partially contribute to the widely acknowledged health benefit of dietary fruits and vegetables [247]. The recognition that dietary constituents long known to have beneficial health effects contain constituents with strong binding affinities for iron that can suppress Fenton chemistry [191] opens the prospect of extending the use of iron chelators beyond treatment for the prevention of disease. Optimization of the use of such agents in prevention will ultimately require studies of the potential of dietary iron and iron supplements to block their iron-chelation activity, as well as careful balancing of overall nutritional demands. Nevertheless, prospects for the use of iron chelators in the treatment and prevention of human disease appear greater than ever.

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Glossary

Iron-overload disease	Characterized by excessive deposition with consequent injury or dysfunction of the heart, liver, anterior pituitary, pancreas or joints
Neurodegenerative disease	Degenerative nerve diseases, including Alzheimer's disease and Parkinson's disease, that affect functions such as balance, movement, memory, talking, breathing and heart function
Phytochemicals	Non-nutritive plant chemicals that have protective or disease-preventive properties

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Executive summary

Iron is the most abundant trace metal in the body

Iron is an essential element involved in oxygen transport and oxygen sensing, electron transfer, energy metabolism and DNA synthesis. Excess free iron that is not properly stored or chelated can catalyze the formation of tissue-damaging radicals and induce oxidative stress.

Iron chelators have been used to treat iron toxicity

Iron-chelation therapy originated in the treatment of iron-overload syndromes.

Preclinical and clinical studies suggest a role for iron chelators in the treatment of cancer and other diseases mediated by oxidative stress including ischemia–reperfusion injury, neurodegenerative and chronic inflammatory diseases.

Three major classes of iron chelators are chemically diverse

Siderophores are synthesized by microorganisms to manage iron uptake and storage. Deferoxamine mesylate is a medicinal siderophore and remains the current standard for iron-chelation therapy.

New orally effective synthetic iron chelators have shown promising clinical results in treating a broad spectrum of iron-dependent disorders.

A variety of phytochemicals with iron-binding properties are currently being investigated as potentially therapeutic iron chelators.

Conclusion

Iron-chelation therapy is an effective therapy for treating iron-overload disorders.

Iron chelators may have additional utility in the treatment of a broad array of conditions related to oxidant stress, ranging from cardiovascular to neurodegenerative to inflammatory to malignant disease.

Combinations of multiple chelators have shown promise and continue to be investigated.

The iron-chelating ability of many dietary substances likely contributes to the widely acknowledged health benefits of fruits and vegetables.

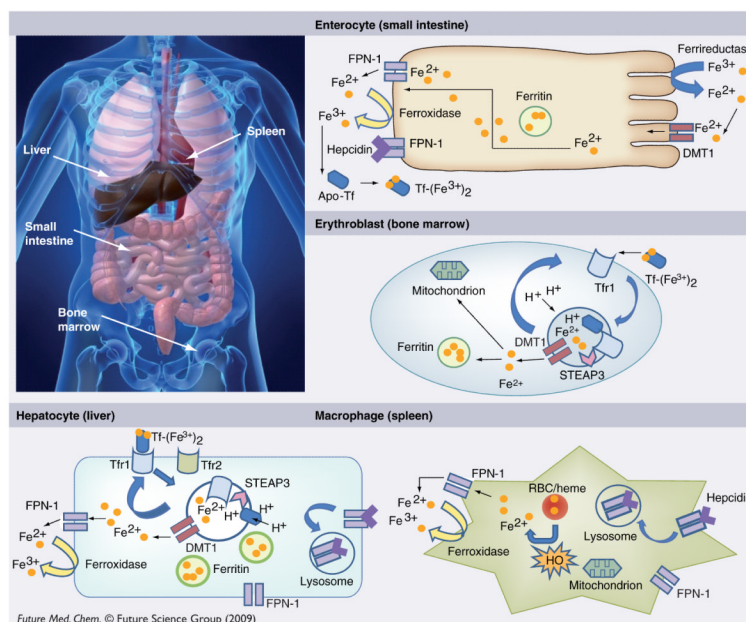
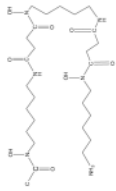
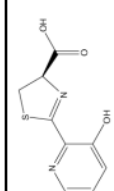
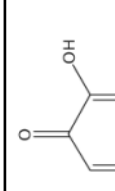
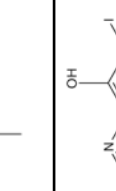


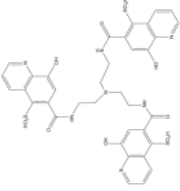
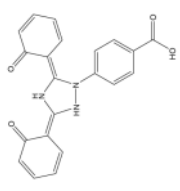
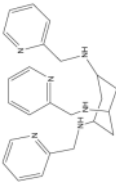
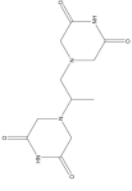
Figure 1. Overview of iron homeostasis

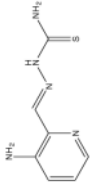
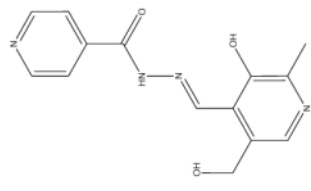
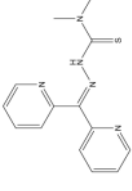
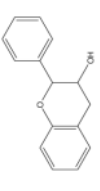
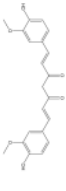
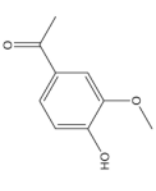
DMT1: Divalent metal transporter 1; FPN-1: Ferroportin-1; HO: Heme oxygenase; RBC: Red blood cell; STEAP3: Six-transmembrane epithelial antigen of prostate 3; Tf: Transferrin; Tfr1: Transferrin receptor 1; Tfr2: Transferrin receptor 2.

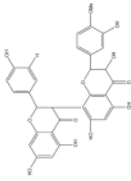
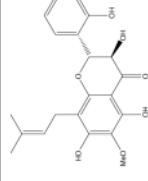
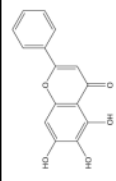
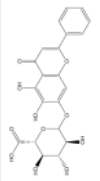
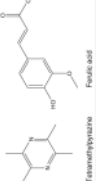
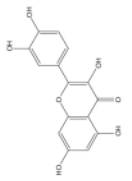
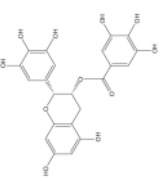
Table 1

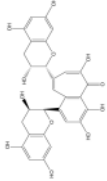
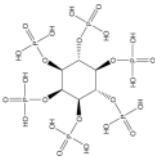
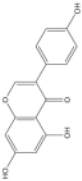
Iron chelators and their therapeutic uses.

Name	Structure	Therapeutic use
	Cell culture	Animal study
	Human study	
Siderophores		
Deferoxamine		Ischemia-reperfusion injuries [82], atherosclerosis [84–86], type II diabetes [87–94], cancer chemotherapy [8,9,50, 95–99]
Desferriothicin [2-(3-hydroxypyridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxylic acid		Type II diabetes [87–94], cancer chemotherapy [8,9,50, 95–99]
Synthetic chelators		
Deferiprone (Ferriprox®)		Potent antineoplastic activity [101,102]
Clioquinol		Treatment of iron overload disease [100]
	Analogues of deferiprone used to treat neuro-degeneration [106]	Treatment of iron overload disease [60,63,70] and in combination with DFO [26,60,104], thalassemia major [68,93–95, 105], myelodysplastic syndromes (MDS) [74], sickle-cell disease[67], type II diabetes [90–94]
	Alzheimer's disease and Parkinson's disease [110,111]	Treatment of neuro-degeneration [54]

Name	Structure	Cell culture	Therapeutic use	Animal study	Human study
O-trensox (Tris-N-(2-aminoethyl)-18-hydroxyquinoline-5-sulfonato-7-carboxamido]amine)		Cytotoxic to cancer cells [114,115]			
Deferasirox (ICL670, Exjade®)			Treatment of chronic iron overload due to blood transfusions [67,68,118–121], myelodysplastic syndromes [76], Blackfan–Diamond syndrome and other rare anemias [122]		
Tachypyr (N,N',N''-tris(2-pyridylmethyl)- <i>cis,cis</i> -1,3,5-triamino-cyclohexane)		Cytotoxic to cancer cells [123–125,127], sensitized cancer cells to ionizing radiation [126]			
Dexrazoxane (ICRF-197)			Cardioprotective agent to reduce doxorubicin-induced cardiotoxicity [128–130] and reduce or prevent the following: mitoxantrone toxicity, daunorubicin toxicity, bleomycin pulmonary toxicity, isoproterenol-induced cardiotoxicity, acetaminophen-induced hepatotoxicity, alloxan-induced diabetes, and hyperoxia-induced pulmonary damage [131–133]	Cardioprotective agent to reduce doxorubicin-induced cardiotoxicity [128–130]	

Name	Structure	Therapeutic use	
		Cell culture	Animal study
Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone)		Anticancer therapy [50,134–138]	Anticancer therapy [50,134–138]
Pyridoxal isonicotinoyl hydrazone		Cytotoxic to cancer cells [141,143–145], anti-retroviral therapy (anti-HIV) [142]	
Di-2-pyridylketone thiosemicarbazone series		Cytotoxic to cancer cells [99,146–149]	
Phytochemicals			
Flavan-3-ol		Chemo-preventive and cytotoxic to cancer cells [168]	
Curcumin		Cancer chemotherapy and iron chelation [170,172]	Cancer chemotherapy and iron chelation [170,172], -thalassemia [173], neuroprotection [176,180]
Apocynin		Neuroprotection [177–180]	Neuroprotection [177–180]

Name	Structure	Therapeutic use	
		Animal study	Human study
Kolaviron		Atherosclerosis [181]	
Floranol			Atherosclerosis [182]
Baicalein		Cytotoxic to cancer cells [187,188]	
Baicalin			Iron-overload disease [189,190]
<i>Ligusticum wallichii</i> Francha (ligustrazine)			Ischemia-reperfusion injuries [193,194]
Quercetin		Inhibit tumor cell growth [197,201], vascular and neuroprotective [199,200]	Vascular and neuroprotective [199,200]; iron overload [189,190]
Epigallocatechin gallate		Cytotoxic to cancer cells [211], neuroprotective [223–228]	Chemo-preventive [216–218], neuroprotective [223–228]

Name	Structure	Therapeutic use	
		Cell culture	Human study
Theaflavin		Cytotoxic to cancer cells [211–213]	Chemo-preventive [216–220]
Phytic acid			Cardiovascular disease [229–235]
Genistein (5,7,4'-tri-hydroxyisoflavone)		Insulin resistance and metabolic syndrome [238–241]	Insulin resistance and metabolic syndrome [238–241], cancer prevention [237] Atherosclerosis and other inflammatory diseases [236]