Perspective

Role of Iron in Aging Related Diseases

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Abstract: Iron progressively accumulates with age and can be further exacerbated by dietary iron intake, genetic factors, and repeated blood transfusions. While iron plays a vital role in various physiological processes within the human body, its accumulation contributes to cellular aging in several species. In its free form, iron can initiate the formation of free radicals at a cellular level and contribute to systemic disorders. This is most evident in high iron conditions such as hereditary hemochromatosis, when accumulation of iron contributes to the development of arthritis, cirrhosis, or cardiomyopathy. A growing body of research has further identified iron's contributory effects in neurodegenerative diseases, ocular disorders, cancer, diabetes, endocrine dysfunction, and cardiovascular diseases. Reducing iron levels by repeated phlebotomy, iron chelation, and dietary restriction are the common therapeutic considerations to prevent iron toxicity. Chelators such as deferoxamine, deferiprone, and deferasirox have become the standard of care in managing iron overload conditions with other potential applications in cancer and cardiotoxicity. In certain animal models, drugs with iron chelating ability have been found to promote health and even extend lifespan. As we further explore the role of iron in the aging process, iron chelators will likely play an increasingly important role in our health.

Keywords: iron; aging; oxidative stress; chronic diseases; iron chelator

1. Introduction

Iron is vital for the transport of oxygen in the hemoglobin of red blood cells and in the myoglobin of muscles. It is also a quintessential component of cytochromes and other proteins and cofactors involved in critical systemic biochemical reactions. Diet is the main source of iron for the body and with a lack of specialized mechanism for excretion of excess iron, most organisms including *Caenorhabditis elegans* [1], *Drosophila melanogaster* [2], *Saccharomyces cerevisiae* [3], *Rattus norvegicus* [4], *Mus musculus* [5], and *Homo sapiens* [6] have been found to accumulate iron as they age. Several studies indicate that iron accumulation further contributes to cellular aging in a multitude of these species [7–11]. Iron supplementation is found to accelerate the aging process by increasing oxidative stress whereas iron restriction slows the aging [12,13]. A recent report on multivariate genome scanning suggests that high levels of iron in the blood are associated with reduced healthy lifespan [14]. Lower iron levels in women before menopause may also be a contributing factor to the increased longevity in women compared to men. Collectively, the evidence indicates a strong positive correlation between iron accumulation and aging.

2. Iron Overload and Oxidative Stress

Iron has an inherent ability to exchange electrons with other molecules serving as electron donor and acceptor in the form of ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron respectively. Hence iron plays an important role in oxygen binding, electron transport, and as a cofactor for the function of many enzymes [15]. However, this highly transitional state of iron renders it toxic when present in its free form. Excess iron can catalyze the conversion of H_2O_2

to hydroxyl radical by undergoing Fenton reaction. Hydroxyl radicals, the most reactive oxygen species, cause lipid peroxidation and DNA strand breaks, thereby promoting the oxidative damage in tissues leading to cellular aging and death termed ferroptosis [16].

Iron homeostasis in the body is regulated primarily at the level of intestinal absorption of dietary heme or non-heme iron [17]. Although a minor amount of iron is lost every day from the body through sloughing of intestinal mucosal cells, urinary excretion and menstruation in women, there is no active mechanism for iron excretion [17]. Aging is associated with increase in non-heme iron such as ferritin or hemosiderin iron in different tissues [18–20]. As iron progressively accumulates with age, cellular iron retention is further exacerbated by dietary iron intake, genetic factors, repeated blood transfusions, and in certain pathological conditions. The mammalian target of rapamycin (mTOR), a serine/threonine kinase that plays a crucial role in aging, is inhibited by rapamycin through iron chelation mediated by hepcidin [21]. In addition, age-associated persistent accumulation of senescent cells in tissues exhibit proinflammatory cell fate and aberrant iron homeostasis [22]. In fact, the abundance of senescent cells has been found to influence the iron levels in aging tissue by impairing ferritinophagy, a lysosomal process that promotes ferritin degradation and ferroptosis [23]. Conversely, excess iron stimulates senescence in cells [24] causing organ dysfunction by producing reactive oxygen species leading to liver injury, diabetes, cardiac disorders, endocrine dysfunction, neurodegeneration, and ocular diseases.

3. Iron Overload in Aging Associated Diseases

The detrimental effects of iron in the aging process are attributed to abnormal cellular iron absorption, trafficking, or storage, affecting different systems of the body as shown in Figure 1.
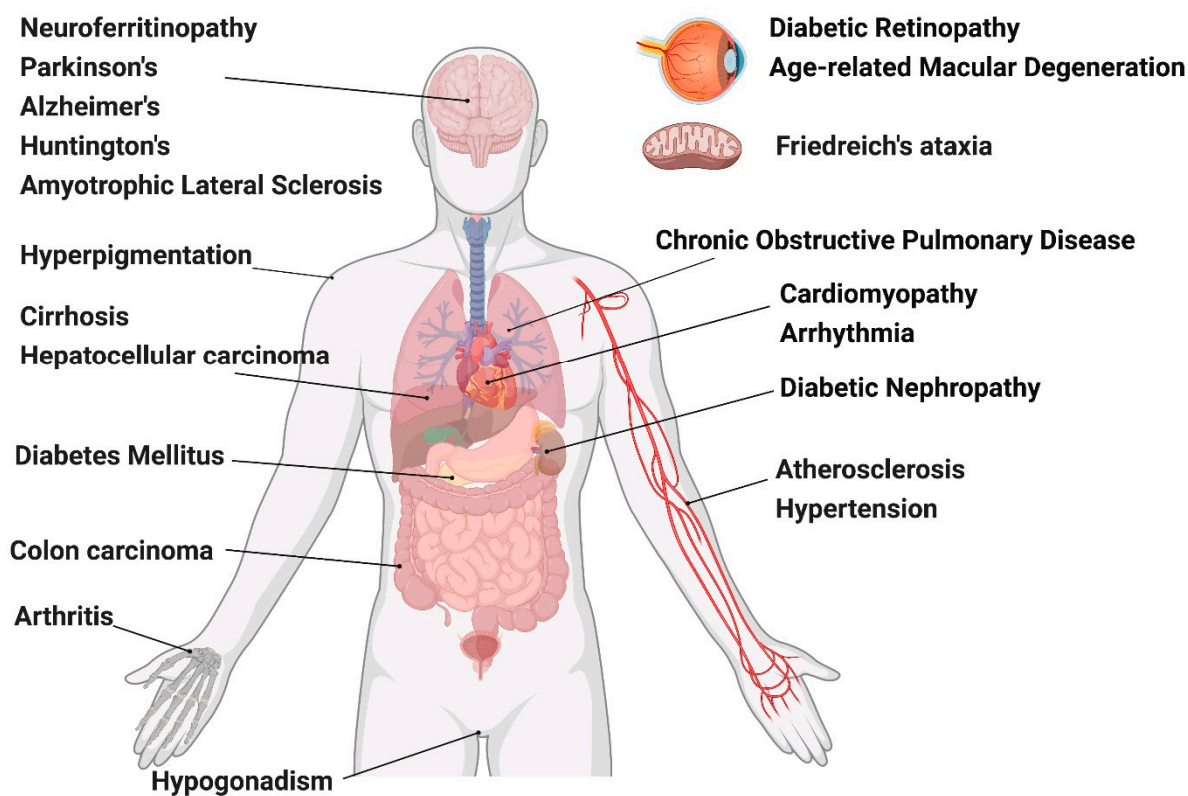

Figure 1. Illustration of iron overload associated diseases. Created with BioRender.com (accessed date: 15 April 2022).

Mutation in any of the genes involved in iron homeostasis, namely HFE (High Fe), hemojuvelin, hepcidin, ferroportin, or transferrin receptor, leads to a genetic disorder called hereditary hemochromatosis (HH) [25]. Hemochromatosis patients and mouse models accumulate iron drastically with age in various organs as indicated in Table 1.

Table 1. Iron values in normal and hemochromatosis human and mouse samples.

Iron	Normal	Hemochromatosis
Human Serum	0–14 year old: 16–128 µg/dL [26]	HFE-hemochromatosis 212.65 ± 30.82 mg/dL [27]
	14–19 year old: 31–168 µg/dL (Male), 20–162 µg/dL (Female) [26]	Hemojuvelin-hemochromatosis 225–315 µg/dL [28]
	Adults: 50–150 µg/dL or 9–27 µmol/L [29]	Hepcidin/Ferroportin-hemochromatosis 284 µg/dL [30]
Human Liver	0.2–2 mg/g or 3.6–36 µmol/kg [31]	HFE-hemochromatosis 20 mg/g [31]
		Hemojuvelin-hemochromatosis 411–429 µmol/g [28]
		Hepcidin/Ferroportin-hemochromatosis 200–500 µmol/g [32]
Human Brain	Quantitative susceptibility mapping (parts per million, PPM) [33] Caudate: 0.108 ± 0.002 Putamen: 0.095 ± 0.002 Pallidum: 0.190 ± 0.003 Cortex: 0.041 ± 0.001	HFE-hemochromatosis Quantitative susceptibility mapping (parts per million, PPM) [33] Caudate: 0.108 ± 0.002 Putamen: 0.104 ± 0.003 * Pallidum: 0.187 ± 0.004 Cortex: 0.042 ± 0.001
	Putamen: [34] 50–59 years: 777 ± 267 µg/g 80–89 years: 1155 ± 363 µg/g	
	Globus pallidus: [34] 50–59 years: 577 ± 266 µg/g 80–89 years: 1062 ± 526 µg/g	
	Caudate nucleus: [34] 50–59 years: 533 ± 268 µg/g 80–89 years: 743 ± 360 µg/g	
Human Retina	0–35 years: 76.5 ± 9.15 µg/g [35] >65 years: 116 ± 9.73 µg/g [35]	
Mouse Serum	10 week old: 291 ± 9 µg/dl [36]	HFE-hemochromatosis 323 ± 24 µg/dL [36]
	14 week old: 26.20 ± 1.597 µmol/L [37]	Hemojuvelin-hemochromatosis 48.50 ± 1.682 µmol/L [37]
	24 week old: 34.9 ± 8.7 µmol/L [38]	Hepcidin/Ferroportin-hemochromatosis 39 ± 10 µmol/L [39]

Table 1. *Cont.*

Iron	Normal	Hemochromatosis
Mouse Liver	10 week old: 255 ± 23 μg/dL [36]	HFE-hemochromatosis 2071 ± 450 μg/dL [36]
	≤6 months: 50.6 ± 1.66 μg/g [40]	Hemojuvelin-hemochromatosis 6070 ± 411.3 μg/g [37]
	≥16 months: 65.6 ± 2.35 μg/g [40]	Hepcidin/Ferroportin-hemochromatosis 1119 ± 176 μg/mg [38]
Mouse Lung	36 week old: ~0.6 μmolg [41]	HFE-hemochromatosis ~0.9 μmol/g [41]
	25–35 week old: 90–100 μg/g [42]	Hepcidin-hemochromatosis ~400 μg/g [42]
	36 week old: ~250 μg/g [43]	Ferroportin-hemochromatosis ~2300 μg/g [43]
Mouse Heart	1 month old: ~30 μg/g [44]	HFE-hemochromatosis ~75 μg/g [44]
	2.5 month old: ~5 μmol/g [45]	Hemojuvelin-hemochromatosis ~20 μmol/g [45]
	12 months old: ~50 μg/g [44]	Ferroportin-hemochromatosis ~9 ng/mg [38]

* indicates $p < 0.05$.

Iron overload in hemochromatosis manifests as arthritis [46], cirrhosis [47], hepatocellular carcinoma [48], diabetes [49], hypogonadism [50], or cardiomyopathy [51]. Similarly, mutation in the iron storage protein L-ferritin contributes to neuroferritinopathy (NF), which belongs to a heterogenous group of disorders called neurodegeneration with brain iron accumulation (NBIA) and presents an accelerated aging process with signs of early neurodegeneration and motor coordination deficits [52]. This disorder is characterized by accumulation of iron in the basal ganglia, cerebellum, and motor cortex of the brain with symptoms of chorea, dystonia, and cognitive impairments that worsen with age [53]. In aceruloplasminemia and Friedreich's ataxia, mutation in ferroxidase ceruloplasmin or in mitochondrial iron storage protein frataxin respectively can lead to iron overload in a multitude of organs [54].

Apart from genetic factors, there is growing evidence that neuronal iron accumulation due to aging or dietary exposure has a substantial role in degenerative diseases including Parkinson's [55], Alzheimer's [56], Huntington's [57], and amyotrophic lateral sclerosis [58]. The misfolding and aggregation of neuronal proteins like α-synuclein, amyloid beta (Aβ), and Tau is a common hallmark of many neurodegenerative disorders. Iron has been found to enhance aggregation of α-synuclein [59], Aβ [60], or Tau [61] either directly by iron binding to the amyloidogenic proteins or indirectly by iron-mediated aggregation through reactive oxygen species production. In addition, several clinical studies indicate that iron overload condition with high levels of serum ferritin at admission during stroke is associated with increased brain damage and worse outcome induced by ischemic stroke [62,63]. Iron is also involved in the pathogenesis of age-related macular degeneration (AMD) with strong experimental evidence indicating that retinas of AMD patients contain more iron than retinas of healthy subjects [64]; however, further studies are warranted to determine if iron is a cause or a consequence of AMD.

Patients with hypertension along with iron overload display sympathetic activation characterizing high blood pressure [65]. Similarly, increased serum ferritin is found to be a significant predictor for developing hypertension in middle-aged men [66]. We have reported that iron overload in mouse induces renin angiotensin system, a critical signaling pathway that regulates blood pressure [67]. Iron deposition in the heart often causes arrhythmias, progressive systolic dysfunction, cardiac hypertrophy, and cardiomyopathy [68].

Intraplaque hemorrhage in atherosclerosis may contribute to further free iron releasealtering the inflammatory and lipid metabolism, which in turn may accelerate atherogenesis leading to myocardial infarction. Thus, iron chelation plays as a potential therapeutic role in managing cardiovascular diseases [69,70].

Type 2 diabetes is a common complication in hemochromatosis patients with excess iron [71]. In fact, moderately elevated iron and ferritin levels, and a lower ratio of transferrin receptors to ferritin are associated with an increased risk of type 2 diabetes independent of other known diabetes risk factors [72]. Iron-catalyzed hydroxyl radical formation is considered to contribute to insulin resistance initially and reduced insulin secretion subsequently resulting in the development of type 2 diabetes [73]. Iron also accelerates end organ damage during diabetes by augmenting the progression of diabetic retinopathy and nephropathy in mouse models of diabetes with iron overload [67,74]. However, further research is needed to corroborate the causative role of iron in diabetic retinopathy and nephropathy progression in human patients.

Carcinogenicity of iron due to its prooxidant activity leading to oxidative damage has been shown in animal models [75] as well as in human patients [76]. Hence majority of hemochromatosis patients with iron overload present with cirrhosis and hepatocarcinoma. Iron is suggested as a risk factor for many types of cancer [77] including liver [78], colorectal [79], breast [80], and lung cancer [81]. Heme iron derived mainly from intake of red meat can induce cancer by acting as a nitrosating agent forming carcinogenic N-nitroso compounds [82]. In addition to solid tumors, recent evidence indicates iron overload in myelodysplastic syndrome (MDS) and in acute myeloid leukemia (AML), contributed by factors inherently associated with these diseases and due to multiple blood transfusions [83]. The status of iron overload has been shown to have a prognostic impact both in MDS and AML patients making iron and iron regulatory proteins an essential therapeutic target which can be explored further for chelation as well as for targeted delivery of anti-cancer drugs.

Iron present in cigarette smoke is an environmental factor with a strong causative link to pulmonary damage [84]. Iron-responsive element-binding protein 2 (IRP2) has been implicated in the development and progression of chronic obstructive pulmonary disease (COPD) [85], making IRP2 a powerful therapeutic target. The primary rheumatic manifestations of iron overload in hemochromatosis are arthropathy and osteoporosis [86]. Synovial iron accumulation is also found in patients with hemochromatosis and rheumatoid arthritis [87]. Iron deposition and defects in cartilage and immune function have been found to contribute to the development of arthritis in hemochromatosis patients.

A direct relationship between aging, and susceptibility and severity to infectious diseases is well known [88]. Iron is one such factor that accumulates with aging and also contributes to developing infections as elevated iron levels promote microbial growth, and impede inflammatory responses with consequent defects in bacterial clearance [89]. Peripheral blood monocytes during iron overload also secrete reduced amounts of tumor necrosis factor TNFα in response to lipopolysaccharide (LPS) [90]. Innate immunity effectively restricts iron availability to invading microbes by iron sequestration and improving the ability of phagocytes to kill microbes. Iron overload leads to dysfunctional bacterial phagocytosis due to destabilization of the secondary lysosomes in macrophages and decreased phagolysosomal fusion in peripheral blood monocytes [91]. The host's iron status thus has a potential impact on the susceptibility and severity to infectious diseases, and conversely, infections also alter host iron homeostasis [92].

4. Ironing out the Aging

Since iron plays an important role in the aging process, reducing iron levels can be a significant therapeutic option to prevent the incidence and progression of chronic diseases. The most common treatment to reduce iron levels in hemochromatosis patients is repeated phlebotomy and patients continue having normal life expectancy as long as their iron levels are adequately managed before developing cirrhosis or diabetes [93]. Iron chelators in

current clinical use are siderophores derived from micro-organisms, synthetic chelators and natural chelators. Desferrioxamine, also referred as Deferoxamine mesylate or Desferal®, is the most common siderophore to treat patients with iron overload. Although long term use of deferoxamine therapy has been demonstrated to be safe, it requires parenteral administration due to poor oral bioavailability [94].

Deferiprone or Ferriprox® is a widely used synthetic iron chelator with comparable efficacy to deferoxamine. Deferiprone is used orally and can penetrate membranes easily allowing iron removal from tissues [95]. Deferasirox or Exjade® is an oral chelator that has been approved for treating chronic iron overload due to blood transfusion [96]. Salicylaldehyde isonicotinoyl hydrazone (SIH) is a small molecule lipophilic iron chelating agent from the group of pyridoxal isonicotinoyl hydrazone (PIH) analogues that firmly binds ferric ions from the cellular labile iron pool and possesses a better ratio of chelation efficiency to toxicity among various iron chelators including deferoxamine, deferiprone, and deferasirox [97]. Thiosemicarbazones possess iron chelating activity and inhibit ribonucleotide reductase (RR), an iron-dependent enzyme that catalyzes the rate-limiting step in DNA synthesis [98]. Triapine® (3-aminopyridine-2-carboxaldehyde thiosemicarbazone [3-AP]), Dp44mT (di-2-pyridylketone-4,4,-dimethyl-3-thiosemicarbazone) and DpC (di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone) are some of the thiosemicarbazones that act as iron chelators and are widely used as anticancer drugs [99–101]. Dexrazone is an iron chelator belonging to the class of bis(2,6-dioxopiperazines) and clinically approved as a cardioprotective agent to treat doxorubicin-induced cardiotoxicity [102]. Clioquinol, an 8-hydroxyquinoline analogue, is a small lipophilic chelator of iron, copper and zinc showing substantial potential for the treatment of neurodegenerative diseases [103]. In addition, clioquinol is found to inhibit the aging-associated mitochondrial protein Clock-1, CLK-1 (human homologue Coenzyme Q7 or CoQ7) [104]. Long term aspirin use has been observed to lower serum ferritin in patients [105] and is reported to extend the lifespan in *C. elegans* [106]. Ibuprofen [107], doxycycline [108], metformin [109,110], clofibrate [111–113], fenofibrate [114,115], and enalapril [116,117] have all been found to have iron chelating activity and can increase longevity by protecting against oxidant-induced damage.

Natural chelators derived from spices and plants have also been investigated for their therapeutic properties. Curcumin from the dietary spice turmeric or *Curcuma longa* [118], and floranol from the roots of *Dioclea grandiflora* in Brazil [119] are found to efficiently chelate iron. Phytic acid in soy protein is an inhibitor of nonheme iron absorption and incorporating soy in the diet can reduce iron stores [120]. In addition, soy isoflavone genistein also can chelate iron and is indicated to have a therapeutic role in obesity and Type II diabetes [121]. Quercetin, a plant flavonoid found in red wine, green tea, apples and berries, binds Fe^{2+} more strongly than the well-known ferrous chelator ferrozine [122]. Epigallocatechin-3-gallate (EGCG) in green tea [123], Baicalein and its glycoside baicalin found in the Chinese herb *Scutellaria baicalensis* Georgi [124], Apocynin derived from the Ayurvedic Indian medicinal herb *Picrorhiza kurroa* [125], *Mucuna pruiens* [126], Kolaviron from African seeds *Garcinia kola* [127], and tannic acid found in gallnut, wine, and tea [128] have all been found to have iron-chelating properties. However, caution is required in using herbal remedies as iron chelators since the effect is not attributable to a specific chemical component and further research on the safe effective dosage and organ toxicity is warranted. Careful dosing of iron chelator is important to prevent the opposite concern of iron deficiency anemia which can lead to a wide range of other symptoms. Apart from siderophores, synthetic and natural iron chelators listed in Table 2, reduced intake of iron-rich food like red meat [129] and calorie restriction in general [130] have been found to reduce body iron levels and increase healthspan and lifespan [4,131].

Table 2. List of Iron Chelators.

Siderophores	Synthetic Chelators	Natural Chelators
Deferoxamine mesylate	Deferiprone Deferasirox Salicylaldehyde isonicotinoyl hydrazone (SIH) Thiosemicarbazones (triapine, Dp44mT, DpC) Dexrazoxane Clioquinol Aspirin Ibuprofen Doxycycline Metformin Clofibrate Fenofibrate Enalapril	Curcumin Floranol Phytic acid Soy isoflavone genistein Quercetin Epigallocatechin-3-gallate (EGCG) Baicalein/Baicalin Apocynin Mucuna pruiens Kolaviron Tannic acid

5. Conclusions

There is astounding growing evidence between iron accumulation and aging. As iron naturally accumulates through life, various factors including excessive dietary intake, genetic factors, blood transfusions, and pathologic conditions exacerbate its progression. Interestingly, iron accumulation has been linked to sympathetic activation, signaling pathways that regulate blood pressure, autophagy, and senescence, thereby contributing to cardiovascular, neurodegenerative, metabolic, and cancer pathogenesis. In addition to the prooxidant signaling, the effects of iron independent of the oxidative stress pathway should also be considered. The degree of iron overload evaluated by measuring serum ferritin and transferrin saturation are inexpensive and helpful but are non-specific. Liver iron concentration determined from biopsy is invasive and has high sampling variability. Superconducting quantum interference device (SQUID) to estimate the magnetic susceptibility of the liver is generally accurate but the equipment is not commonly available yet. Magnetic resonance imaging (MRI) assessment of tissue iron has become the de facto method of evaluation in chronically iron overload patients. Clinical studies aimed at analyzing reliable biomarkers to detect pathological tissue iron overload could be a promising diagnostic tool in the future.

Due to devastating effects of iron accumulation, repeated phlebotomy, iron chelation, and diet restriction are mainstay therapeutic opportunities to prevent the iron toxicity. In addition to siderophores derived from micro-organisms and synthetic iron chelators, several natural iron chelators derived from herbs have been identified as therapeutic targets and continue to be heavily investigated. Iron chelators are also able to cross the blood brain barrier and remove excess iron from various regions of the brain [132]. Clinical trials exemplified the benefit of deferiprone in significantly attenuating neuronal loss in patients with Parkinson's disease and Friedrich ataxia [133,134]. Type and severity of iron overload, dosage, treatment duration, and cost are critical factors that must be taken into consideration in selecting a chelator. Iron is chelated from different organs at different rates with hepatic iron overload usually improving more rapidly than other organs depending on the intensity of chelation. Therefore, the major challenges are to develop a safe and feasible drug that can reduce iron in organ-specific manner while maintaining systemic iron balance. In addition to chelation therapy, alternative approaches like targeting the regulation of proteins involved in iron metabolism and novel methods to induce ferroptosis demands further investigation. Preclinical studies in mouse models of iron overload have shown that long acting hepcidin analogs, also referred to as minihepcidins [135,136], and antisense oligonucleotides targeting TMPRSS6, a metalloprotease that inhibits endogenous hepcidin production [137], effectively decrease iron load, improve erythropoiesis, and increase hemoglobin concentrations, thus showing merit for further clinical investigation. Future

studies on senescence, autophagy and ferroptosis to determine the temporal sequence of the molecular and cellular signaling events during chronic iron accumulation are necessary to develop effective therapies that prevent iron toxicity, and promote health and longevity.

Conflicts of Interest: The authors declare that they have no competing interest.

References

1. James, S.A.; Roberts, B.R.; Hare, D.J.; de Jonge, M.D.; Birchall, I.E.; Jenkins, N.L.; Cherny, R.A.; Bush, A.I.; McColl, G. Direct in vivo imaging of ferrous iron dyshomeostasis in ageing Caenorhabditis elegans. *Chem. Sci.* **2015**, *6*, 2952–2962. [CrossRef] [PubMed]
2. Massie, H.R.; Aiello, V.R.; Williams, T.R. Iron accumulation during development and ageing of Drosophila. *Mech. Ageing Dev.* **1985**, *29*, 215–220. [CrossRef]
3. Reverter-Branchat, G.; Cabiscol, E.; Tamarit, J.; Ros, J. Oxidative damage to specific proteins in replicative and chronological-aged *Saccharomyces cerevisiae*: Common targets and prevention by calorie restriction. *J. Biol. Chem.* **2004**, *279*, 31983–31989. [CrossRef] [PubMed]
4. Cook, C.I.; Yu, B.P. Iron accumulation in aging: Modulation by dietary restriction. *Mech. Ageing Dev.* **1998**, *102*, 1–13. [CrossRef]
5. Massie, H.R.; Aiello, V.R.; Banziger, V. Iron accumulation and lipid peroxidation in aging C57BL/6J mice. *Exp. Gerontol.* **1983**, *18*, 277–285. [CrossRef]
6. Fairweather-Tait, S.J.; Wawer, A.A.; Gillings, R.; Jennings, A.; Myint, P.K. Iron status in the elderly. *Mech. Ageing Dev.* **2014**, *136–137*, 22–28. [CrossRef]
7. Klang, I.M.; Schilling, B.; Sorensen, D.J.; Sahu, A.K.; Kapahi, P.; Andersen, J.; Swoboda, P.; Killilea, D.W.; Gibson, B.W.; Lithgow, G.J. Iron promotes protein insolubility and aging in *C. elegans*. *Aging* **2014**, *6*, 975–991. [CrossRef]
8. Jacomin, A.-C.; Geraki, K.; Brooks, J.; Tjendana-Tjhin, V.; Collingwood, J.F.; Nezis, I.P. Impact of Autophagy and Aging on Iron Load and Ferritin in Drosophila Brain. *Front. Cell Dev. Biol.* **2019**, *7*, 142. [CrossRef]
9. Montella-Manuel, S.; Pujol-Carrion, N.; Mechoud, M.A.; de la Torre-Ruiz, M.A. Bulk autophagy induction and life extension is achieved when iron is the only limited nutrient in *Saccharomyces cerevisiae*. *Biochem. J.* **2021**, *478*, 811–837. [CrossRef]
10. Droge, W.; Schipper, H.M. Oxidative stress and aberrant signaling in aging and cognitive decline. *Aging Cell* **2007**, *6*, 361–370. [CrossRef]
11. Xu, J.; Knutson, M.D.; Carter, C.S.; Leeuwenburgh, C. Iron Accumulation with Age, Oxidative Stress and Functional Decline. *PLoS ONE* **2008**, *3*, e2865. [CrossRef] [PubMed]
12. Xu, J.; Marzetti, E.; Seo, A.Y.; Kim, J.S.; Prolla, T.A.; Leeuwenburgh, C. The emerging role of iron dyshomeostasis in the mitochondrial decay of aging. *Mech. Ageing Dev.* **2010**, *131*, 487–493. [CrossRef] [PubMed]
13. Polla, A.S.; Polla, L.L.; Polla, B.S. Iron as the malignant spirit in successful ageing. *Ageing Res. Rev.* **2003**, *2*, 25–37. [CrossRef]
14. Timmers, P.R.H.J.; Wilson, J.F.; Joshi, P.K.; Deelen, J. Multivariate genomic scan implicates novel loci and haem metabolism in human ageing. *Nat. Commun.* **2020**, *11*, 3570. [CrossRef]
15. Crielaard, B.J.; Lammers, T.; Rivella, S. Targeting iron metabolism in drug discovery and delivery. *Nat. Rev. Drug Discov.* **2017**, *16*, 400–423. [CrossRef]
16. Halliwell, B.; Gutteridge, J.M. Oxygen toxicity, oxygen radicals, transition metals and disease. *Biochem. J.* **1984**, *219*, 1–14. [CrossRef]
17. Kohgo, Y.; Ikuta, K.; Ohtake, T.; Torimoto, Y.; Kato, J. Body iron metabolism and pathophysiology of iron overload. *Int. J. Hematol.* **2008**, *88*, 7–15. [CrossRef]
18. Bloomer, S.A.; Moyer, E.D. Hepatic macrophage accumulation with aging: Cause for concern? *Am. J. Physiol. Liver Physiol.* **2021**, *320*, G496–G505. [CrossRef]
19. Ugarte, M.; Geraki, K.; Jeffery, G. Aging results in iron accumulations in the non-human primate choroid of the eye without an associated increase in zinc, copper or sulphur. *BioMetals* **2018**, *31*, 1061–1073. [CrossRef]
20. Saito, H. Metabolism of iron stores. *Nagoya J. Med. Sci.* **2014**, *76*, 235–254.
21. Mleczko-Sanecka, K.; Roche, F.; da Silva, A.R.; Call, D.; D'Alessio, F.; Ragab, A.; Lapinski, P.E.; Ummanni, R.; Korf, U.; Oakes, C.; et al. Unbiased RNAi screen for hepcidin regulators links hepcidin suppression to proliferative Ras/RAF and nutrient-dependent mTOR signaling. *Blood* **2014**, *123*, 1574–1585. [CrossRef] [PubMed]
22. Killilea, D.W.; Wong, S.L.; Cahaya, H.S.; Atamna, H.; Ames, B.N. Iron accumulation during cellular senescence. *Ann. N. Y. Acad. Sci.* **2004**, *1019*, 365–367. [CrossRef] [PubMed]

23. Masaldan, S.; Clatworthy, S.A.S.; Gamell, C.; Meggyesy, P.M.; Rigopoulos, A.T.; Haupt, S.; Haupt, Y.; Denoyer, D.; Adlard, P.A.; Bush, A.I.; et al. Iron accumulation in senescent cells is coupled with impaired ferritinophagy and inhibition of ferroptosis. *Redox Biol.* **2018**, *14*, 100–115. [CrossRef] [PubMed]

24. Cozzi, A.; Orellana, D.I.; Santambrogio, P.; Rubio, A.; Cancellieri, C.; Giannelli, S.G.; Ripamonti, M.; Taverna, S.; Di Lullo, G.; Rovida, E.; et al. Stem Cell Modeling of Neuroferritinopathy Reveals Iron as a Determinant of Senescence and Ferroptosis during Neuronal Aging. *Stem Cell Rep.* **2019**, *13*, 832–846. [CrossRef] [PubMed]

25. Santos, P.C.J.L.; Krieger, J.E.; Pereira, A.C. Molecular Diagnostic and Pathogenesis of Hereditary Hemochromatosis. *Int. J. Mol. Sci.* **2012**, *13*, 1497–1511. [CrossRef] [PubMed]

26. Soghier, L.M.; Fratantoni, K.; Reyes, C.; Mullins, K. *Reference Range Values for Pediatric Care*, 2nd ed.; American Academy of Pediatrics: Itasca, IL, USA, 2019. [CrossRef]

27. Evangelista, A.S.; Nakhle, M.C.; de Araujo, T.F.; Abrantes-Lemos, C.P.; Deguti, M.M.; Carrilho, F.J.; Cançado, E.L.R. HFE Genotyping in Patients with Elevated Serum Iron Indices and Liver Diseases. *BioMed Res. Int.* **2015**, *2015*, 164671. [CrossRef]

28. Pietrangelo, A.; Caleffi, A.; Henrion, J.; Ferrara, F.; Corradini, E.; Kulaksiz, H.; Stremmel, W.; Andreone, P.; Garuti, C. Juvenile hemochromatosis associated with pathogenic mutations of adult hemochromatosis genes. *Gastroenterology* **2005**, *128*, 470–479. [CrossRef]

29. Kratz, A.; Sluss, P.M. Laboratory Reference Values. *N. Engl. J. Med.* **2004**, *351*, 1548–1563. [CrossRef]

30. Nishina, S.; Tomiyama, Y.; Ikuta, K.; Tatsumi, Y.; Toki, Y.; Kato, A.; Kato, K.; Yoshioka, N.; Sasaki, K.; Hara, Y.; et al. Long-term phlebotomy successfully alleviated hepatic iron accumulation in a ferroportin disease patient with a mutation in SLC40A1: A case report. *BMC Gastroenterol.* **2021**, *21*, 111. [CrossRef]

31. Sirlin, C.B.; Reeder, S.B. Magnetic Resonance Imaging Quantification of Liver Iron. *Magn. Reson. Imaging Clin. N. Am.* **2010**, *18*, 359–381. [CrossRef]

32. Mayr, R.; Janecke, A.R.; Schranz, M.; Griffiths, W.J.; Vogel, W.; Pietrangelo, A.; Zoller, H. Ferroportin disease: A systematic meta-analysis of clinical and molecular findings. *J. Hepatol.* **2010**, *53*, 941–949. [CrossRef]

33. Kalpouzos, G.; Mangialasche, F.; Falahati, F.; Laukka, E.J.; Papenberg, G. Contributions of HFE polymorphisms to brain and blood iron load, and their links to cognitive and motor function in healthy adults. *Neuropsychopharmacol. Rep.* **2021**, *41*, 393–404. [CrossRef] [PubMed]

34. Ramos, P.; Santos, A.; Pinto, N.R.; Mendes, R.; Magalhães, T.; Almeida, A. Iron levels in the human brain: A post-mortem study of anatomical region differences and age-related changes. *J. Trace Elem. Med. Biol.* **2013**, *28*, 13–17. [CrossRef] [PubMed]

35. Hahn, P.; Ying, G.-S.; Beard, J.; Dunaief, J.L. Iron levels in human retina: Sex difference and increase with age. *NeuroReport* **2006**, *17*, 1803–1806. [CrossRef] [PubMed]

36. Zhou, X.Y.; Tomatsu, S.; Fleming, R.E.; Parkkila, S.; Waheed, A.; Jiang, J.; Fei, Y.; Brunt, E.M.; Ruddy, D.A.; Prass, C.E.; et al. HFE gene knockout produces mouse model of hereditary hemochromatosis. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 2492–2497. [CrossRef] [PubMed]

37. Gkouvatsos, K.; Fillebeen, C.; Daba, A.; Wagner, J.; Sebastiani, G.; Pantopoulos, K. Iron-dependent regulation of hepcidin in Hjv-/- mice: Evidence that hemojuvelin is dispensable for sensing body iron levels. *PLoS ONE* **2014**, *9*, e85530. [CrossRef] [PubMed]

38. Lakhal-Littleton, S.; Wolna, M.; Carr, C.A.; Miller, J.J.; Christian, H.C.; Ball, V.; Santos, A.; Diaz, R.; Biggs, D.; Stillion, R.; et al. Cardiac ferroportin regulates cellular iron homeostasis and is important for cardiac function. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 3164–3169. [CrossRef] [PubMed]

39. Lunova, M.; Goehring, C.; Kuscuoglu, D.; Mueller, K.; Chen, Y.; Walther, P.; Deschemin, J.-C.; Vaulont, S.; Haybaeck, J.; Lackner, C.; et al. Hepcidin knockout mice fed with iron-rich diet develop chronic liver injury and liver fibrosis due to lysosomal iron overload. *J. Hepatol.* **2014**, *61*, 633–641. [CrossRef]

40. Hahn, P.; Song, Y.; Ying, G.-S.; He, X.; Beard, J.; Dunaief, J.L. Age-dependent and gender-specific changes in mouse tissue iron by strain. *Exp. Gerontol.* **2009**, *44*, 594–600. [CrossRef]

41. Ali, M.K.; Kim, R.Y.; Brown, A.C.; Mayall, J.R.; Karim, R.; Pinkerton, J.W.; Liu, G.; Martin, K.L.; Starkey, M.R.; Pillar, A.L.; et al. Crucial role for lung iron level and regulation in the pathogenesis and severity of asthma. *Eur. Respir. J.* **2020**, *55*, 1901340. [CrossRef]

42. Deschemin, J.-C.; Mathieu, J.R.R.; Zumerle, S.; Peyssonnaux, C.; Vaulont, S. Pulmonary Iron Homeostasis in Hepcidin Knockout Mice. *Front. Physiol.* **2017**, *8*, 804. [CrossRef] [PubMed]

43. Neves, J.; Leitz, D.; Kraut, S.; Brandenberger, C.; Agrawal, R.; Weissmann, N.; Mühlfeld, C.; Mall, M.A.; Altamura, S.; Muckenthaler, M.U. Disruption of the Hepcidin/Ferroportin Regulatory System Causes Pulmonary Iron Overload and Restrictive Lung Disease. *eBioMedicine* **2017**, *20*, 230–239. [CrossRef] [PubMed]

44. Sukumaran, A.; Chang, J.; Jonghan, K.; Mintri, S.; Khaw, B.-A.; Kim, J. Iron overload exacerbates age-associated cardiac hypertrophy in a mouse model of hemochromatosis. *Sci. Rep.* **2017**, *7*, 5756. [CrossRef] [PubMed]

45. Niederkofler, V.; Salie, R.; Arber, S. Hemojuvelin is essential for dietary iron sensing, and its mutation leads to severe iron overload. *J. Clin. Investig.* **2005**, *115*, 2180–2186. [CrossRef] [PubMed]

46. FFaraawi, R.; Harth, M.; Kertesz, A.; Bell, D. Arthritis in hemochromatosis. *J. Rheumatol.* **1993**, *20*, 448–452.

47. Olynyk, J.K.; Pierre, T.G.S.; Britton, R.S.; Brunt, E.M.; Bacon, B.R. Duration of Hepatic Iron Exposure Increases the Risk of Significant Fibrosis in Hereditary Hemochromatosis: A New Role for Magnetic Resonance Imaging. *Am. J. Gastroenterol.* **2005**, *100*, 837–841. [CrossRef]

48. Harrison, S.A.; Bacon, B.R. Relation of hemochromatosis with hepatocellular carcinoma: Epidemiology, natural history, pathophysiology, screening, treatment, and prevention. *Med. Clin. N. Am.* **2005**, *89*, 391–409. [CrossRef]

49. Utzschneider, K.M.; Kowdley, K.V. Hereditary hemochromatosis and diabetes mellitus: Implications for clinical practice. *Nat. Rev. Endocrinol.* **2010**, *6*, 26–33. [CrossRef]

50. McDermott, J.H.; Walsh, C.H. Hypogonadism in Hereditary Hemochromatosis. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 2451–2455. [CrossRef]

51. Gulati, V.; Harikrishna, P.; Palaniswamy, C.; Aronow, W.S.; Jain, D.; Frishman, W.H. Cardiac involvement in hemochromatosis. *Cardiol. Rev.* **2014**, *22*, 56–68. [CrossRef]

52. Levi, S.; Cozzi, A.; Arosio, P. Neuroferritinopathy: A neurodegenerative disorder associated with L-ferritin mutation. *Best Pract. Res. Clin. Haematol.* **2005**, *18*, 265–276. [CrossRef] [PubMed]

53. Levi, S.; Finazzi, D. Neurodegeneration with brain iron accumulation: Update on pathogenic mechanisms. *Front. Pharmacol.* **2014**, *5*, 99. [CrossRef] [PubMed]

54. Vashchenko, G.; MacGillivray, R.T.A. Multi-Copper Oxidases and Human Iron Metabolism. *Nutrients* **2013**, *5*, 2289–2313. [CrossRef]

55. Hare, D.J.; Cardoso, B.R.; Raven, E.P.; Double, K.L.; Finkelstein, D.I.; Szymlek-Gay, E.A.; Biggs, B.-A. Excessive early-life dietary exposure: A potential source of elevated brain iron and a risk factor for Parkinson's disease. *NPJ Parkinson Dis.* **2017**, *3*, 1. [CrossRef] [PubMed]

56. Liu, J.-L.; Fan, Y.-G.; Yang, Z.-S.; Wang, Z.-Y.; Guo, C. Iron and Alzheimer's Disease: From Pathogenesis to Therapeutic Implications. *Front. Neurosci.* **2018**, *12*, 632. [CrossRef] [PubMed]

57. Agrawal, S.; Fox, J.; Thyagarajan, B.; Fox, J.H. Brain mitochondrial iron accumulates in Huntington's disease, mediates mitochondrial dysfunction, and can be removed pharmacologically. *Free Radic. Biol. Med.* **2018**, *120*, 317–329. [CrossRef] [PubMed]

58. Petillon, C.; Hergesheimer, R.; Puy, H.; Corcia, P.; Vourc'H, P.; Andres, C.; Karim, Z.; Blasco, H. The Relevancy of Data Regarding the Metabolism of Iron to Our Understanding of Deregulated Mechanisms in ALS; Hypotheses and Pitfalls. *Front. Neurosci.* **2019**, *12*, 1031. [CrossRef] [PubMed]

59. Ostrerova-Golts, N.; Petrucelli, L.; Hardy, J.; Lee, J.M.; Farer, M.; Wolozin, B. The A53T alpha-synuclein mutation increases iron-dependent aggregation and toxicity. *J. Neurosci.* **2000**, *20*, 6048–6054. [CrossRef]

60. Rottkamp, C.A.; Raina, A.K.; Zhu, X.; Gaier, E.; Bush, A.I.; Atwood, C.S.; Chevion, M.; Perry, G.; Smith, M.A. Redox-active iron mediates amyloid-beta toxicity. *Free Radic. Biol. Med.* **2001**, *30*, 447–450. [CrossRef]

61. Sayre, L.M.; Perry, G.; Harris, P.L.R.; Liu, Y.; Schubert, K.A.; Smith, M.A. In situ oxidative catalysis by neurofibrillary tangles and senile plaques in Alzheimer's disease. *J. Neurochem.* **2000**, *74*, 270–279. [CrossRef]

62. Davalos, A.; Fernandez-Real, J.M.; Ricart, W.; Soler, S.; Molins, A.; Planas, E.; Genís, D. Iron-related damage in acute ischemic stroke. *Stroke* **1994**, *25*, 1543–1546. [CrossRef] [PubMed]

63. Millan, M.; Sobrino, T.; Castellanos, M.; Nombela, F.; Arenillas, J.F.; Riva, E.; Cristobo, I.; García, M.M.; Vivancos, J.; Serena, J.; et al. Increased body iron stores are associated with poor outcome after thrombolytic treatment in acute stroke. *Stroke* **2007**, *38*, 90–95. [CrossRef] [PubMed]

64. Hahn, P.; Milam, A.H.; Dunaief, J.L. Maculas affected by age-related macular degeneration contain increased chelatable iron in the retinal pigment epithelium and Bruch's membrane. *Arch. Ophthalmol.* **2003**, *121*, 1099–1105. [CrossRef] [PubMed]

65. Seravalle, G.; Dell'Oro, R.; Quarti-Trevano, F.; Spaziani, D.; Bertoli, S.; Airoldi, F.; Mancia, G.; Grassi, G. Sympathetic Overactivation in Patients With Essential Hypertension and Hepatic Iron Overload. *Hypertension* **2020**, *76*, 1444–1450. [CrossRef] [PubMed]

66. Kim, M.K.; Baek, K.H.; Song, K.-H.; Kang, M.I.; Choi, J.H.; Bae, J.C.; Park, C.-Y.; Lee, W.-Y.; Oh, K.W. Increased serum ferritin predicts the development of hypertension among middle-aged men. *Am. J. Hypertens.* **2012**, *25*, 492–497. [CrossRef] [PubMed]

67. Chaudhary, K.; Chilakala, A.; Ananth, S.; Mandala, A.; Veeranan-Karmegam, R.; Powell, F.L.; Ganapathy, V.; Gnana-Prakasam, J.P. Renal iron accelerates the progression of diabetic nephropathy in the HFE gene knockout mouse model of iron overload. *Am. J. Physiol. Ren. Physiol.* **2019**, *317*, F512–F517. [CrossRef]

68. Gujja, P.; Rosing, D.R.; Tripodi, D.J.; Shizukuda, Y. Iron overload cardiomyopathy: Better understanding of an increasing disorder. *J. Am. Coll. Cardiol.* **2010**, *56*, 1001–1112. [CrossRef]

69. Cornelissen, A.; Guo, L.; Sakamoto, A.; Virmani, R.; Finn, A.V. New insights into the role of iron in inflammation and atherosclerosis. *EBioMedicine* **2019**, *47*, 598–606. [CrossRef]

70. Salonen, J.T.; Nyyssönen, K.; Korpela, H.; Tuomilehto, J.; Seppänen, R.; Salonen, R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* **1992**, *86*, 803–811. [CrossRef]

71. Jiang, R.; Manson, J.E.; Meigs, J.B.; Ma, J.; Rifai, N.; Hu, F.B. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* **2004**, *291*, 711–717. [CrossRef]

72. Simcox, J.A.; McClain, D.A. Iron and diabetes risk. *Cell Metab.* **2013**, *17*, 329–341. [CrossRef] [PubMed]

73. Aregbesola, A.; Voutilainen, S.; Virtanen, J.K.; Mursu, J.; Tuomainen, J.-P. Gender difference in type 2 diabetes and the role of body iron stores. *Ann. Clin. Biochem.* **2017**, *54*, 113–120. [CrossRef] [PubMed]

74. Chaudhary, K.; Promsote, W.; Ananth, S.; Veeranan-Karmegam, R.; Tawfik, A.; Arjunan, P.; Martin, P.; Smith, S.B.; Thangaraju, M.; Kisselev, O.; et al. Iron Overload Accelerates the Progression of Diabetic Retinopathy in Association with Increased Retinal Renin Expression. *Sci. Rep.* **2018**, *8*, 3025. [CrossRef] [PubMed]

75.	Richmond, H.G. Induction of Sarcoma in the Rat by Iron–Dextran Complex. *BMJ* **1959**, *1*, 947–949. [CrossRef] [PubMed]

76.	Greenberg, G. Sarcoma after intramuscular iron injection. *BMJ* **1976**, *1*, 1508–1509. [CrossRef]

77.	Fonseca-Nunes, A.; Jakszyn, P.; Agudo, A. Iron and cancer risk–a systematic review and meta-analysis of the epidemiological evidence. *Cancer Epidemiol. Biomark. Prev.* **2014**, *23*, 12–31. [CrossRef]

78.	Yu, Y.C.; Luu, H.N.; Wang, R.; Thomas, C.E.; Glynn, N.W.; Youk, A.O.; Behari, J.; Yuan, J.M. Serum Biomarkers of Iron Status and Risk of Hepatocellular Carcinoma Development in Patients with Nonalcoholic Fatty Liver Disease. *Cancer Epidemiol. Biomark. Prev.* **2022**, *31*, 230–235. [CrossRef]

79.	Chua, A.C.; Klopcic, B.; Lawrance, I.C.; Olynyk, J.K.; Trinder, D. Iron: An emerging factor in colorectal carcinogenesis. *World J. Gastroenterol.* **2010**, *16*, 663–672. [CrossRef]

80.	Huang, X. Does iron have a role in breast cancer? *Lancet Oncol.* **2008**, *9*, 803–807. [CrossRef]

81.	Tasevska, N.; Sinha, R.; Kipnis, V.; Subar, A.F.; Leitzmann, M.F.; Hollenbeck, A.R.; E Caporaso, N.; Schatzkin, A.; Cross, A.J. A prospective study of meat, cooking methods, meat mutagens, heme iron, and lung cancer risks. *Am. J. Clin. Nutr.* **2009**, *89*, 1884–1894. [CrossRef]

82.	Cross, A.J.; Pollock, J.R.; Bingham, S. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res.* **2003**, *63*, 2358–2360. [PubMed]

83.	Weber, S.; Parmon, A.; Kurrle, N.; Schnütgen, F.; Serve, H. The Clinical Significance of Iron Overload and Iron Metabolism in Myelodysplastic Syndrome and Acute Myeloid Leukemia. *Front. Immunol.* **2021**, *11*, 627662. [CrossRef] [PubMed]

84.	Cloonan, S.M.; Glass, K.; Laucho-Contreras, M.E.; Bhashyam, A.R.; Cervo, M.; Pabón, M.A.; Konrad, C.; Polverino, F.; Siempos, I.I.; Perez, E.; et al. Mitochondrial iron chelation ameliorates cigarette smoke-induced bronchitis and emphysema in mice. *Nat Med.* **2016**, *22*, 163–174. [CrossRef] [PubMed]

85.	DeMeo, D.L.; Mariani, T.; Bhattacharya, S.; Srisuma, S.; Lange, C.; Litonjua, A.; Bueno, R.; Pillai, S.G.; Lomas, D.A.; Sparrow, D.; et al. Integration of Genomic and Genetic Approaches Implicates IREB2 as a COPD Susceptibility Gene. *Am. J. Hum. Genet.* **2009**, *85*, 493–502. [CrossRef]

86.	Axford, J.S. Rheumatic manifestations of haemochromatosis. *Baillieres Clin. Rheumatol.* **1991**, *5*, 351–365. [CrossRef]

87.	Van Vulpen, L.; Roosendaal, G.; Van Asbeck, B.S.; Mastbergen, S.C.; Lafeber, F.P.J.G.; Schutgens, R.E.G. The detrimental effects of iron on the joint: A comparison between haemochromatosis and haemophilia. *J. Clin. Pathol.* **2015**, *68*, 592–600. [CrossRef]

88.	Schaible, U.E.; Kaufmann, S.H. Iron and microbial infection. *Nat. Rev. Microbiol.* **2004**, *2*, 946–953. [CrossRef]

89.	Wessling-Resnick, M. Iron Homeostasis and the Inflammatory Response. *Annu. Rev. Nutr.* **2010**, *30*, 105–122. [CrossRef]

90.	Gordeuk, V.R.; Ballou, S.; Lozanski, G.; Brittenham, G.M. Decreased concentrations of TNFα in supernatants of monocytes from homozygotes for hereditary hemochromatosis. *Blood* **1992**, *79*, 1855–1860. [CrossRef]

91.	Wiener, E. Impaired phagocyte antibacterial effector functions in beta-thalassemia: A likely factor in the increased susceptibility to bacterial infections. *Hematology* **2003**, *8*, 35–40. [CrossRef]

92.	Doherty, C.P. Host-Pathogen Interactions: The Role of Iron. *J. Nutr.* **2007**, *137*, 1341–1344. [CrossRef] [PubMed]

93.	Strohmeyer, G.; Niederau, C.; Stremmel, W. Survival and causes of death in hemochromatosis. Observations in 163 patients. *Ann. N. Y. Acad. Sci.* **1988**, *526*, 245–257. [CrossRef] [PubMed]

94.	Schafer, A.I.; Rabinowe, S.; Le Boff, M.S.; Bridges, K.; Cheron, R.G.; Dluhy, R. Long-term efficacy of deferoxamine iron chelation therapy in adults with acquired transfusional iron overload. *Arch. Intern. Med.* **1985**, *145*, 1217–1221. [CrossRef] [PubMed]

95.	Elalfy, M.S.; Adly, A.; Awad, H.; Tarif Salam, M.; Berdoukas, V.; Tricta, F. Safety and efficacy of early start of iron chelation therapy with deferiprone in young children newly diagnosed with transfusion-dependent thalassemia: A randomized controlled trial. *Am. J. Hematol.* **2018**, *93*, 262–268. [CrossRef] [PubMed]

96.	Yang, L.P.; Keam, S.J.; Keating, G.M. Deferasirox: A review of its use in the management of transfusional chronic iron overload. *Drugs* **2007**, *67*, 2211–2230. [CrossRef]

97.	Simůnek, T.; Boer, C.; Bouwman, R.A.; Vlasblom, R.; Versteilen, A.M.; Štěrba, M.; Gersl, V.; Hrdina, R.; Poňka, P.; De Lange, J.J.; et al. SIH—a novel lipophilic iron chelator—protects H9c2 cardiomyoblasts from oxidative stress-induced mitochondrial injury and cell death. *J. Mol. Cell. Cardiol.* **2005**, *39*, 345–354. [CrossRef]

98.	Thelander, L.; Gräslund, A. Mechanism of inhibition of mammalian ribonucleotide reductase by the iron chelate of 1-formylisoquinoline thiosemicarbazone. Destruction of the tyrosine free radical of the enzyme in an oxygen-requiring reaction. *J. Biol. Chem.* **1983**, *258*, 4063–4066. [CrossRef]

99.	Chaston, T.B.; Lovejoy, D.B.; Watts, R.N.; Richardson, D.R. Examination of the antiproliferative activity of iron chelators: Multiple cellular targets and the different mechanism of action of triapine compared with Desferrioxamine and the potent pyridoxal isonicotinoyl hydrazone analogue 311. *Clin. Cancer Res.* **2003**, *9*, 402–414.

100.	Rao, V.A.; Klein, S.R.; Agama, K.K.; Toyoda, E.; Adachi, N.; Pommier, Y.; Shacter, E.B. The iron chelator Dp44mT causes DNA damage and selective inhibition of topoisomerase IIalpha in breast cancer cells. *Cancer Res.* **2009**, *69*, 948–957. [CrossRef]

101.	Guo, Z.-L.; Richardson, D.R.; Kalinowski, D.S.; Kovacevic, Z.; Tan-Un, K.C.; Chan, G.C.-F. The novel thiosemicarbazone, di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC), inhibits neuroblastoma growth in vitro and in vivo via multiple mechanisms. *J. Hematol. Oncol.* **2016**, *9*, 98. [CrossRef]

102.	Ichikawa, Y.; Ghanefar, M.; Bayeva, M.; Wu, R.; Khechaduri, A.; Prasad, S.V.N.; Mutharasan, R.K.; Naik, T.J.; Ardehali, H. Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. *J. Clin. Investig.* **2014**, *124*, 617–630. [CrossRef] [PubMed]

103. Zhu, Y.; Chang, J.; Tan, K.; Huang, S.K.; Liu, X.; Wang, X.; Cao, M.; Zhang, H.; Li, S.; Duan, X.; et al. Clioquinol Attenuates Pulmonary Fibrosis through Inactivation of Fibroblasts via Iron Chelation. *Am. J. Respir. Cell Mol. Biol.* **2021**, *65*, 189–200. [CrossRef] [PubMed]

104. Wang, Y.; Branicky, R.; Stepanyan, Z.; Carroll, M.; Guimond, M.P.; Hihi, A.; Hayes, S.; McBride, K.; Hekimi, S. The anti-neurodegeneration drug clioquinol inhibits the aging-associated protein CLK-1. *J. Biol. Chem.* **2009**, *284*, 314–323. [CrossRef] [PubMed]

105. Fleming, D.J.; Jacques, P.F.; Massaro, J.; D'Agostino, R.B., Sr.; Wilson, P.W.; Wood, R.J. Aspirin intake and the use of serum ferritin as a measure of iron status. *Am. J. Clin. Nutr.* **2001**, *74*, 219–226. [CrossRef]

106. Ayyadevara, S.; Bharill, P.; Dandapat, A.; Hu, C.; Khaidakov, M.; Mitra, S.; Reis, R.J.S.; Mehta, J.L. Aspirin Inhibits Oxidant Stress, Reduces Age-Associated Functional Declines, and Extends Lifespan of Caenorhabditis elegans. *Antioxid. Redox Signal.* **2013**, *18*, 481–490. [CrossRef]

107. Kennedy, T.P.; Rao, N.V.; Noah, W.; Michael, J.R.; Jafri, M.H., Jr.; Gurtner, G.H.; Hoidal, J.R. Ibuprofen prevents oxidant lung injury and in vitro lipid peroxidation by chelating iron. *J. Clin. Investig.* **1990**, *86*, 1565–1573. [CrossRef]

108. Faure, M.; Cilibrizzi, A.; Abbate, V.; Bruce, K.; Hider, R. Effect of iron chelation on anti-pseudomonal activity of doxycycline. *Int. J. Antimicrob. Agents* **2021**, *58*, 106438. [CrossRef]

109. Li, X.; Wang, X.; Snyder, M.P. Metformin Affects Heme Function as a Possible Mechanism of Action. *G3 Genes Genomes Genet.* **2019**, *9*, 513–522. [CrossRef]

110. Martin-Montalvo, A.; Mercken, E.M.; Mitchell, S.J.; Palacios, H.H.; Mote, P.L.; Scheibye-Knudsen, M.; Gomes, A.P.; Ward, T.M.; Minor, R.K.; Blouin, M.J.; et al. Metformin improves healthspan and lifespan in mice. *Nat. Commun.* **2013**, *4*, 2192. [CrossRef]

111. Huang, H.L.; Shaw, N.S. Role of Hypolipidemic Drug Clofibrate in Altering Iron Regulatory Proteins IRP1 and IRP2 Activities and Hepatic Iron Metabolism in Rats Fed a Low-Iron Diet. *Toxicol. Appl. Pharmacol.* **2002**, *180*, 118–128. [CrossRef]

112. Brandstädt, S.; Schmeisser, K.; Zarse, K.; Ristow, M. Lipid-lowering fibrates extend *C. elegans* lifespan in a NHR-49/PPARalpha-dependent manner. *Aging* **2013**, *5*, 270–275. [CrossRef] [PubMed]

113. Nogueira-Recalde, U.; Lorenzo-Gómez, I.; Blanco, F.J.; Loza, M.I.; Grassi, D.; Shirinsky, V.; Shirinsky, I.; Lotz, M.; Robbins, P.D. Domínguez, E.; et al. Fibrates as drugs with senolytic and autophagic activity for osteoarthritis therapy. *EBioMedicine* **2019**, *45*, 588–605. [CrossRef] [PubMed]

114. Mandala, A.; Chen, W.J.; Armstrong, A.; Malhotra, M.R.; Chavalmane, S.; McCommis, K.S.; Chen, A.; Carpenter, D.; Biswas, P.; Gnana-Prakasam, J.P. PPARα agonist fenofibrate attenuates iron-induced liver injury in mice by modulating the Sirt3 and β-catenin signaling. *Am. J. Physiol. Liver Physiol.* **2021**, *321*, G262–G269. [CrossRef]

115. Mandala, A.; Armstrong, A.; Girresch, B.; Zhu, J.; Chilakala, A.; Chavalmane, S.; Chaudhary, K.; Biswas, P.; Ogilvie, J.; Gnana-Prakasam, J.P. Fenofibrate prevents iron induced activation of canonical Wnt/β-catenin and oxidative stress signaling in the retina. *NPJ Aging Mech. Dis.* **2020**, *6*, 12. [CrossRef] [PubMed]

116. Lee, S.C.; Park, S.W.; Kim, D.K.; Lee, S.H.; Hong, K.P. Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* **2001**, *38*, 166–170. [CrossRef]

117. Santos, E.L.; de Picoli Souza, K.; da Silva, E.D.; Batista, E.C.; Martins, P.J.F.; D'Almeida, V.; Pesquero, J.B. Long term treatment with ACE inhibitor enalapril decreases body weight gain and increases life span in rats. *Biochem. Pharmacol.* **2009**, *78*, 951–958. [CrossRef] [PubMed]

118. Jiao, Y.; Wilkinson, J., 4th; Christine Pietsch, E.; Buss, J.L.; Wang, W.; Planalp, R.; Torti, F.M.; Torti, S.V. Iron chelation in the biological activity of curcumin. *Free Radic. Biol. Med.* **2006**, *40*, 1152–1160. [CrossRef]

119. Botelho, F.V.; Alvarez-Leite, J.I.; Lemos, V.S.; Pimenta, A.M.; Calado, H.D.; Matencio, T.; Miranda, C.T.; Pereira-Maia, E.C. Physicochemical study of floranol, its copper(II) and iron(III) complexes, and their inhibitory effect on LDL oxidation. *J. Inorg. Biochem.* **2007**, *101*, 935–943. [CrossRef]

120. Hurrell, R.F.; Juillerat, M.A.; Reddy, M.B.; Lynch, S.R.; Dassenko, S.A.; Cook, J.D. Soy protein, phytate, and iron absorption in humans. *Am. J. Clin. Nutr.* **1992**, *56*, 573–578. [CrossRef]

121. Zhen, A.W.; Nguyen, N.H.; Gibert, Y.; Motola, S.; Buckett, P.; Wessling-Resnick, M.; Fraenkel, E.; Fraenkel, P.G. The small molecule, genistein, increases hepcidin expression in human hepatocytes. *Hepatology* **2013**, *58*, 1315–1325. [CrossRef]

122. Guo, M.; Perez, C.; Wei, Y.; Rapoza, E.; Su, G.; Bou-Abdallah, F.; Chasteen, N.D. Iron-binding properties of plant phenolics and cranberry's bio-effects. *Dalton Trans.* **2007**, *43*, 4951–4961. [CrossRef] [PubMed]

123. Weinreb, O.; Amit, T.; Mandel, S.; Youdim, M.B. Neuroprotective molecular mechanisms of (-)-epigallocatechin-3-gallate: A reflective outcome of its antioxidant, iron chelating and neuritogenic properties. *Genes Nutr.* **2009**, *4*, 283–296. [CrossRef]

124. Perez, C.A.; Wei, Y.; Guo, M. Iron-binding and anti-Fenton properties of baicalein and baicalin. *J. Inorg. Biochem.* **2009**, *103*, 326–332. [CrossRef] [PubMed]

125. Tang, L.; Ye, K.; Yang, X.; Zheng, J. Apocynin Attenuates Cerebral Infarction after Transient Focal Ischaemia in Rats. *J. Int. Med. Res.* **2007**, *35*, 517–522. [CrossRef] [PubMed]

126. Dhanasekaran, M.; Tharakan, B.; Manyam, B.V. Antiparkinson drug—Mucuna pruriens shows antioxidant and metal chelating activity. *Phytother. Res.* **2007**, *22*, 6–11. [CrossRef] [PubMed]

127. Farombi, E.O.; Nwaokeafor, I.A. Anti-oxidant mechanisms of kolaviron: Studies on serum lipoprotein oxidation, metal chelation and oxidative membrane damage in rats. *Clin. Exp. Pharmacol. Physiol.* **2005**, *32*, 667–674. [CrossRef]

128. Phiwchai, I.; Yuensook, W.; Sawaengsiriphon, N.; Krungchanuchat, S.; Pilapong, C. Tannic acid (TA): A molecular tool for chelating and imaging labile iron. *Eur. J. Pharm. Sci.* **2018**, *114*, 64–73. [CrossRef]

129. Geissler, C.; Singh, M. Iron, meat and health. *Nutrients* **2011**, *3*, 283–316. [CrossRef]

130. Kastman, E.; Willette, A.A.; Coe, C.L.; Bendlin, B.; Kosmatka, K.J.; McLaren, D.G.; Xu, G.; Canu, E.; Field, A.S.; Alexander, A.L.; et al. A Calorie-Restricted Diet Decreases Brain Iron Accumulation and Preserves Motor Performance in Old Rhesus Monkeys. *J. Neurosci.* **2010**, *30*, 7940–7947. [CrossRef]

131. Minor, R.K.; Allard, J.S.; Younts, C.M.; Ward, T.M.; de Cabo, R. Dietary Interventions to Extend Life Span and Health Span Based on Calorie Restriction. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2010**, *65*, 695–703. [CrossRef]

132. Dexter, D.T.; Statton, S.A.; Whitmore, C.; Freinbichler, W.; Weinberger, P.; Tipton, K.F.; Della Corte, L.; Ward, R.J.; Crichton, R.R. Clinically available iron chelators induce neuroprotection in the 6-OHDA model of Parkinson's disease after peripheral administration. *J. Neural. Transm.* **2011**, *118*, 223–231. [CrossRef] [PubMed]

133. Martin-Bastida, A.; Ward, R.J.; Newbould, R.; Piccini, P.; Sharp, D.; Kabba, C.; Patel, M.C.; Spino, M.; Connelly, J.; Tricta, F.; et al. Brain iron chelation by deferiprone in a phase 2 randomised double-blinded placebo controlled clinical trial in Parkinson's disease. *Sci. Rep.* **2017**, *7*, 1398. [CrossRef] [PubMed]

134. Boddaert, N.; Sang, K.H.L.Q.; Rötig, A.; Leroy-Willig, A.; Gallet, S.; Brunelle, F.; Sidi, D.; Thalabard, J.-C.; Munnich, A.; Cabantchik, Z.I. Selective iron chelation in Friedreich ataxia: Biologic and clinical implications. *Blood* **2007**, *110*, 401–408. [CrossRef] [PubMed]

135. Preza, G.C.; Ruchala, P.; Pinon, R.; Ramos, E.; Qiao, B.; Peralta, M.A.; Sharma, S.; Waring, A.; Ganz, T.; Nemeth, E. Minihepcidins are rationally designed small peptides that mimic hepcidin activity in mice and may be useful for the treatment of iron overload. *J. Clin. Investig.* **2011**, *121*, 4880–4888. [CrossRef] [PubMed]

136. Gardenghi, S.; Ramos, P.; Marongiu, M.F.; Melchiori, L.; Breda, L.; Guy, E.; Muirhead, K.; Rao, N.; Roy, C.N.; Andrews, N.; et al. Hepcidin as a therapeutic tool to limit iron overload and improve anemia in β-thalassemic mice. *J. Clin. Investig.* **2010**, *120*, 4466–4477. [CrossRef] [PubMed]

137. Guo, S.; Casu, C.; Gardenghi, S.; Booten, S.; Aghajan, M.; Peralta, R.; Watt, A.; Freier, S.; Monia, B.P.; Rivella, S. Reducing TMPRSS6 ameliorates hemochromatosis and β-thalassemia in mice. *J. Clin. Investig.* **2013**, *123*, 1531–1541. [CrossRef] [PubMed]