Targeting dysregulation of brain iron homeostasis in ageing

Orly Weinreb∗, Tamar Amit and Moussa B.H. Youdim
Eve Topp Centers of Excellence for Neurodegenerative Diseases Research and Department of Pharmacology, Rappaport Family Research Institute, Technion-Faculty of Medicine, Haifa, Israel

Abstract

Brain iron is an essential nutrient for multiple functions, including gene expression, DNA synthesis, neurotransmission, myelination, oxygen transport, storage and activation, mitochondrial electron transport, numerous important metabolic processes and cofactor for several key enzymes of neurotransmitter biosynthesis. On the other hand, many investigators, among them the late Mark Smith, who was a pioneer neuroscientist and prominent investigator with regards to brain oxidative stress (OS) and iron in Alzheimer’s disease, have identified iron as a highly reactive element that can promote OS processes within the brain and might increase the toxicity of environmental or endogenous toxins. It is suggested that iron accumulation in the brain is capable of initiating free-radical reactions, which subsequently induce progressive loss of neurons, followed by a decrement in neuronal function characteristic of the ageing process. Indeed, it has become apparent that iron progressively accumulates in the brain as a function of age and that iron-induced OS can cause neurodegeneration. Chelation therapy was previously introduced as a novel therapy concept and rationale for the development of metal-binding drugs for neurodegeneration. The present review will discuss the involvement of dysregulation of brain iron homeostasis in the ageing process, addressing the potential importance of iron chelating therapeutic approaches.

Keywords: Brain, iron, ageing, iron chelation, neuroprotection

1. Introduction: Iron in the brain

In the central nervous system (CNS), iron is essential for multiple functions, including gene expression, DNA synthesis, neurotransmission, myelination, oxygen transport, storage and activation, mitochondrial electron transport, numerous important metabolic processes and as a cofactor for several key enzymes of neurotransmitter biosynthesis, such as dopamine (DA) and noradrenaline [1–3]. Iron deficiency can affect infant neurobehavioral and cerebral development, due to its role in neurogenesis and differentiation of cells and morphology in the hippocampus and striatum [3]. Brain iron homeostasis appears to rely on similar proteins and mechanisms that exist in peripheral organs. Iron (Fe) incorporation and transport in the brain is regulated by the interaction between the endothelial cells and astrocytes: in the brain, astrocytes are devoid of transferrin receptors (TfRs), suggesting that astrocytes incorporate iron by mechanism that is not related to TIR [4, 5]. The TIR1 in the luminal membrane of endothelial cells binds Fe3+–loaded transferrin and internalizes this complex in the endosomal compartment, where Fe3+ is reduced to Fe2+[4, 5]. The latter is transported across the endosomal membrane into the cytosol by the divalent metal transporter-1 (DMT1), and exported into the extracellular fluid by ferroportin [4]. Alternatively, it has
Fig. 1. Schematic illustration of the effect of iron homeostasis on the expression levels of iron-related proteins. In an environment of iron deficiency (e.g. iron chelation), iron regulatory proteins (IRPs) bind to iron-responsive elements (IREs) and facilitate the regulation of ferritin, ferroportin, transferrin receptor (TfR) and divalent metal transporter-1 (DMT1). In the case of ferritin and ferroportin, IRE’s in the 5′ untranslated region (UTR) of their mRNA bind to IRPs and prevent the initiation of their translation. For TfR1 and DMT1, the binding of IRPs to IREs, which are in the 3′ UTR of their mRNAs, results in upregulation of synthesis of these proteins through preventing their induced degradation by nucleases; collectively, iron uptake is increased and iron storage and export are inhibited. In conditions of iron accumulation, the IRPs are not active, thus allowing the translation of ferritin and ferroportin and reduction of TfR1 and DMT1 [3]. Ferritin comprises of two subunits: the high (H)-ferritin, a ferroxidase that is involved in rapid uptake and reutilization of iron and low (L)-ferritin, associated with long-term iron storage [6]. In all brain regions, both subunits are expressed, although H-ferritin is more widespread and the ratio of H-ferritin to L-ferritin depends on iron utilization by specific regional cells [6].

On the other hand, iron is a highly reactive element and dysfunction of iron homeostasis is accompanied by concomitant oxidation processes within the living organism. Smith and collaborators [7, 8] were among the first investigators who suggested that high concentration of reactive iron can induce oxidative stress (OS), because of its interaction with hydrogen peroxide (H₂O₂) in the Fenton reaction, resulting in an increased formation of hydroxyl free radicals in the neurodegenerative brain. Indeed, in many of the neurodegenerative diseases (e.g. AD, Parkinson’s disease (PD), Huntington’s disease, Friedreich ataxia and amyotrophic lateral sclerosis), as well as in the normal ageing process, excessive generation of OS and accumulation of iron levels and deposition have been observed in specific brain regions and targeted as contributing factors to the pathogenesis and pathology [8, 14–19]. Free radical-related OS causes a molecular damage that can then lead to a critical failure of biological functions, protein modification, misfolding and aggregation and ultimately neuronal death [9–12] (Fig. 2). Additionally, iron accumulation might increase the neurotoxicity of endogenous or environmental toxins; for example, iron homeostasis was reported to be linked to activation of the N-methyl-D-aspartic acid (NMDA) receptor; a signaling neurotoxicity cascade that involves nitric oxide synthase (NOS) and adaptor proteins that interact with ferroprotein [13].

The present review discusses dysregulation of brain iron homeostasis that may be an essential factor in the ageing process, and addresses the potential importance of iron binding therapeutic approaches.
Fig. 2. Schematic illustration of the potential iron dyshomoeostasis-induced neurodegenerative pathways in ageing and their prevention by iron chelators/radical scavengers. During the ageing process, high concentration of reactive iron can induce oxidative stress (OS), due to its interaction with hydrogen peroxide (H$_2$O$_2$) in the Fenton reaction, resulting in an increased formation of hydroxyl (HO$^-$) free radicals. OS may also be mediated by β-amyloid (Aβ)-generated reactive oxygen species (ROS). The age-related increase in cerebral oxidative damage has been mainly demonstrated by lipid peroxidation, protein oxidation and oxidative modifications in DNA. An additional possible pathway that may accompany ageing is an increase in the levels of monounsaturated oxidase (MAO), an enzyme that catalyzes the oxidative deamination of neurotransmitters, in which the byproducts H$_2$O$_2$ and aldehydes are subsequently generated and can form free radicals. Within the brain, a class of iron-dependent and oxygen-sensor enzymes, hypoxia inducible factor (HIF) prolyl-4-hydroxylases (PHDs) target the regulatory HIF-1α for hydroxylation and degradation and can prevent HIF-1-adaptive target genes transcription. Iron chelators/radical scavenger can prevent generation of ROS, either through direct prevention of H$_2$O$_2$ production, or alternatively by inhibition of Fenton reaction. Iron chelators target the APP 5′ UTR thus, possessing the capacity to reduce APP translation and subsequently Aβ generation levels. Additionally, these compounds can restrain induction of PHDs by chelating iron, which resulted in increased transcription of HIF-1α and HIF-1-target genes involved in the adaptation and protection of neuronal cells.

2. Iron accumulation, oxidative stress and ageing of the brain

Ageing in humans is often characterized by changes in brain volume, accompanied by a decline in motor and cognitive performance [20]. Brain ageing is associated with the progressive imbalance between antioxidant defenses and intracellular generation of reactive oxygen species (ROS) [21, 22]. Age-related increases in oxidative brain damage has been mainly exemplified by lipid peroxidation, protein oxidation and oxidative modifications in DNA [23]. Previously, age-related memory impairment has been shown to be associated with a decrease in brain and plasma antioxidants [24–26] and iron accumulates in the human brain as a function of age [17, 27]. The process of iron accumulation involves the accumulation of iron-containing molecules (primarily ferritin) in the microglia, astrocytes and oligodendrocytes, particularly in selective brain regions (e.g. cerebellum, basal ganglia and substantia nigra (SN)) [28–30] that are targeted in ageing and age-related neurodegenerative diseases [6, 14, 17, 31–38]. Zecca et al. [18, 39] have described the brain regional selectivity of iron accumulation during human ageing, showing that the SN in old individuals (60–90 years of age) contained higher concentrations of both ferritin subunits, the H-ferritin and L-ferritin and loads of extraneuronal iron deposits, compared to locus coeruleus. In old individuals, iron deposits were observed in non-melanized neurons of the SN, but not in neuromelanin-containing neurons of SN and locus coeruleus [18, 35, 40]. Moreover, it was proposed that increased iron levels in certain brain areas can result from alterations in brain vascularization that occur during ageing and neurodegeneration [41–43].
During ageing, brain iron storage is partially converted from its stable/soluble form, ferritin, to its degradative, high reactive form, haemosiderin and other oxyhydroxides [44]. Dysregulation of brain iron homeostasis through disruption of iron regulatory proteins may also induce neuronal vulnerability to OS [32, 45]. Consequently, the toxicity of iron as an inducer of OS in the brain has been proposed to depend on controlling iron-containing molecules in the brain [44, 46]. It is also suggested that brain iron accumulation capable of initiating free-radicals reactions, can subsequently induce a progressive loss of neurons, followed by a decrement in neuronal function characteristic of the ageing process [18, 47, 48]. Indeed, a previous study in human elderly subjects suggested a correlation between dysregulation of iron contents, observed by quantitative magnetic resonance (MR), and cognitive function [49]. In preclinical studies, it was also shown that iron load in an early stage of life induced iron accumulation in basal ganglia, accompanied by memory impairments in adulthood [50] and behavioral deficits associated with OS induction in the brain [51]. Furthermore, it was found that in aged animals, iron accumulation altered antioxidant capacity and thiol redox state [52]. Collectively, it has become apparent that age-related iron accumulation, may induce OS, and thus can cause neurodegenerative disorders associated with ageing [17, 46, 53, 54].

An additional prominent feature that accompanies ageing is an increase in the levels of monoamine oxidase (MAO), an enzyme that catalyzes the oxidative deamination of neurotransmitters, in which the byproducts H2O2 and aldehydes are subsequently generated [55] (Fig. 2). Given that these byproducts are compelling inductors of lipid peroxidation, it is assumed that activation of MAO is associated with age-related disturbances of the homeostasis and generation of free radicals in involution of the nervous tissue [56]. Indeed, it was shown that in the mouse brain, MAO-A activity remained stable between 2–24 months, while MAO-B activity increased significantly between 2–16 months [57]. Quantitative radiography studies also showed an age-related increase in MAO-B in various mouse brain structures [58]. Activity studies have reported high levels of brain MAO-B in aged-related neurodegenerative diseases, such as PD and AD [59–62]. The increase in MAO-B activity during ageing and associated neurodegenerative diseases is exceptional, compared to most of enzyme activities that are usually decreased, and together with the generation of highly toxic byproducts, it was indicated as being detrimental to neurons [63–65].

3. Iron chelation therapeutic approaches

From the above overview, it may be speculated that the regulated suppression of labile iron levels in the brain would decrease the rate of accumulation of over-oxidized materials inside neurons and in this way, favorably influence deteriorated ageing processes. Chelation therapy was previously introduced as a novel therapy concept and rational for the development of metal-binding drugs for neurodegeneration (see reviews: [66–69]). The next two sections will discuss the potential benefits of selective natural and hybrid iron-chelating compounds to retard/prevent the primary or secondary iron neurotoxicity in ageing (Fig. 2).

3.1. Natural iron-binding compounds

Particular attention has been focused on studying the potential beneficial effects of naturally occurring (iron chelating/antioxidant) flavonoid-type compounds on ageing and aged related neurodegenerative diseases (see review: [70]). Flavonoids are the largest polyphenol group present in green tea, in particular a subclass known as flavanols, namely catechins [71]. The principal flavanols found in green tea are: (+)-catechin (C), (–)-epicatechin (EC), (+)-gallocatechin (GC), (–)-epigallocatechin (EGC), (+)-catechin-3-O-gallate (CG), (–)-epicatechin-3-O-gallate (ECG), (+)-gallocatechin-3-O-gallate (GCG) and (–)-epigallocatechin-3-O-gallate (EGCG). Among these sub-subclasses, EGCG (Fig. 3a) is the major constituent of green tea, accounting for more than 10% of the extract dry weight, whereas the others are found in lower abundance [72, 73]. Extensive research has indicated that green tea catechins are potent antioxidants, due to their ability to directly scavenge ROS, to induce endogenous antioxidant enzymes and to bind and chelate excess divalent metal ions (e.g. Fe3+) to form inactive complexes (see reviews: [74–76]). The phenolic hydroxyl groups on the aromatic rings of EGCG confer its antioxidant and iron chelating activities [77–80] (Fig. 3a). Recent studies examined the potency of EGCG and EC to prevent DNA damage caused by Fe3+ and H2O2, suggesting that the bind-
Fig. 3. Chemical structures of iron chelating/radical scavenger compounds; a. (−)-epigallocatechin-3-gallate (EGCG); b. desferrioxamine (DFO); c. M30 (5-[N-methyl-N-propargylaminomethyl]-8-hydroxyquinoline).

ing of EGCG and EC to iron is essential for their antioxidative activity [75, 79]. In this respect, green tea extract has been shown to strongly inhibit lipid peroxidation chain reactions promoted by iron-ascorbate in homogenates of mouse brain mitochondrial membranes [81] and gerbil brains [82]. EGCG has been also shown to inhibit MAO-B activity in C6 astrocyte cells [83] and adult rat brains [84].

Although the question of the precise brain permeability of green tea catechins is still to be determined, green tea ingestion does appear to inversely correlate with the incidence of brain ageing, cognition and neurodegeneration. A previous epidemiological study, aimed at investigating the association between consumption of green tea and cognitive function in elderly Japanese subjects, found that higher consumption of green tea was associated with lower prevalence of cognitive impairment [85]. A recent cross-sectional study that assessed green tea intake in 2501 participants and 1438 cognitively intact participants over 2 years, indicated that green tea was inversely associated with cognitive impairment, but not with cognitive decline, possibly due to the small number of green tea drinkers in this cohort [86]. To add to this, more recently, green tea consumption was associated with better cognitive performance in community-living Chinese older adults group [87], as well as a lower prevalence of depressive symptoms in elderly population over 70 years old in Japan [88]. Recent findings have shown a significant improvement in Unified Parkinson’s Disease Rating Scale (UPDRS) scores at 6 months for PD patients taken daily green tea polyphenols, compared with placebo patient’s group [89].

Preclinical animal studies with green tea extract, or its individual catechin components have shown positive effects on cognitive and behavioral abilities during
and long-term memory formation regulated by green factor that binds to the promoter regions of many genes, and SAM-P8 mice [92, 93, 95]. CREB is a transcription the hippocampus of senescence-accelerated C57BL/6J green tea catechins-chronic treatment is associated ment observed in cognitive performances following reviews: [76, 100]). It was suggested that the improve- subsequence CREB-regulated gene expression (see (ERK) 1/2/), their downstream substrate, CREB and extracellular signal-regulated protein kinase pathways: phosphatidylinositol-3-kinase (PI3K)/AKT phosphorylation of neuronal pro-survival signaling pathways: phosphatidylinositol-3-kinase (PI3K)/AKT and extracellular signal-regulated protein kinase (ERK) 1/2/), their downstream substrate, CREB and subsequent CREB-regulated gene expression (see reviews: [76, 100]). It was suggested that the improve-ment observed in cognitive performances following green tea catechins-chronic treatment is associated with increased levels of CREB phosphorylation in the hippocampus of senescence-accelerated C57BL/6j and SAM-P8 mice [92, 93, 95]. CREB is a transcription factor that binds to the promoter regions of many genes, associated with memory and synaptic plasticity that may play a crucial role in long-term potentiation (LTP) and long-term memory formation regulated by green tea catechins, as recently addressed by Spencer and collaborators [100]. In this regards, two target genes of CREB, having regulatory roles in synaptic plasticity and survival, brain-derived neurotrophic factor (BDNF) and Bcl-2 were also increased in the hippocampus of old rats after prolonged administrations of green tea infusion [95, 100]. Further investigations to clarify the association between iron chelation and CREB activation signaling cascade are in progress.

An additional level of neuroprotection by iron-complexing compounds involves the stabilization of the transcriptional activator, hypoxia-inducible factor (HIF)-1 and expression of its target protective genes, such as erythropoietin, vascular endothelial growth factor (VEGF), TIR receptor and beme oxygenase [101, 102]. Within the cells, HIF-1 is under the control of a class of iron-dependent and oxygen-sensor enzymes, HIF prolyl-4-hydroxylases (PHDs) that target HIF-1α for degradation by the proteasome [101] (Fig. 2). Inhibition of PHDs enzymes under iron chelating conditions results in stabilization of the HIF-1α protein, heterodimerization and activa- tion of nuclear translocation and subsequently binding to hypoxia responsive elements of promoters of spe- cific HIF-1α-adaptive target genes [103]. In brains of aged mice, it was demonstrated that hypoxia-induced HIF-1α accumulation was attenuated, presumably in response to increased post-transcriptional degrada-tion of HIF-1α that resulted from up-regulation of PHD [104]. The possibility of modulating HIF-1 activity by targeting the free-labile intracellular iron pool by iron binding molecules and inhibitors of PHDs is currently gaining recognition, posing HIF-1 as a potential therapeutic target for ageing and aged-related neurodegenerative diseases [103–107]. Indeed, green tea catechins were previously shown to induce HIF-1α protein and mRNA expression levels of HIF-1α-target genes, while this effect was blocked by iron and ascorbate, indicating that these natural occur-ring compounds may activate HIF-1α through iron chelation [108]. It is suggested that in the ageing brain, a reduction in the chelatable iron pool by green tea catechins may result in the inhibition of PHDs and consequently in concerted activation of HIF-1 and their respective related-adaptive genes. Future studies are required to further clarify the involvement of the HIF signaling system in the pro- tective mechanism of action of green tea catechins on ageing-related molecular alterations and-cognitive decline.
Finally, another aspect regarding the EGCG mechanism of action involves its neuroprotective effects in ageing pathology in AD. Indeed, ageing of the brain has been demonstrated to be the main risk factor for AD, with recent studies suggesting that the primary link between AD and brain ageing may be an aged related bioenergetic stress alterations in the mitochondrial electron transport chain function, resulting in increased OS, apoptosis and enhancement of the amyloid precursor protein (APP) processing to amyloid beta peptide (Aβ) [see review, 109]. EGCG was previously demonstrated to reduce both the immature and full-length APP in neuronal cells and mice hippocampus, as well as promote the generation of soluble APPs (sAPPs) through activation of α-secretase cleavage, accompanied by a significant reduction in cerebral Aβ levels and plaques in AD transgenic mice [67, 110–112]. Taken together, these findings suggest that natural iron chelating compounds, such as EGCG, possess beneficial properties in aged-related pathologies.

3.2. Hybrid iron-chelating drugs

Novel therapeutic approaches for the treatment of neurodegenerative disorders comprise candidates designed specifically to act on multiple central nervous targets [112, 113]. Based on a multimodal drug design paradigm, Youdim and collaborators have recently synthesized a multifunctional, non-toxic, brain permeable iron chelator, M30 (Fig. 3c), possessing the neuroprotective N-propargyl moiety of the anti-Parkinsonian and MAO-B inhibitor drug, rasagiline (Azilect®, Teva, Pharmaceutical Inc.) and the antioxidant-iron chelator moiety of an 8-hydroxyquinoline derivative of the iron chelator, VK28 [113–115]. Studies have revealed that M30 has a lower affinity for iron than that of the prototype iron chelator, DFO, although M30 is a better inhibitor against iron-induced lipid peroxidation, with higher IC50 value (12 μM) comparable to that of DFO [114, 115]. It is likely that the very high iron chelating property of DFO contributes to its cytotoxicity, which precludes its application for prolonged period of time in pathological conditions unrelated to systemic iron overload. By contrast, a brain permeable compound with moderate iron chelating affinity may be a more appropriate and promising agent for age-related neurodegenerative disease therapies in which iron is selectively accumulated in various brain regions. In addition, M30 was found to be a highly potent brain selective inhibitor of both MAO-A and -B activities [114]. Indeed, M30 was shown to possess a wide range of pharmacological activities, including neurorescue effects, induction of neuronal differentiation accompanied by induction of growth-associated protein 43 (GAP 43), BDNF and the neuronal survival pathway the serine/threonine kinase Akt [116–118]. In preclinical studies, M30 was shown to prevent the loss of mouse tyrosine hydroxylase (TH)-positive neurons, iron increase and microglial activation in the ipsilateral SN- induced by post-intranigral injection of the ubiquitin-proteasome inhibitor, lactacystin [119]. Recently, it was shown that in C57BL mice, M30 treatment significantly up-regulated a number of neuroprotective-adaptive mechanisms and pro-survival signaling pathways in the brain, associated with the iron-oxygen regulated HIF-1-system [120].

In respect to ageing, we have recently demonstrated that systemic chronic treatment of aged mice with M30 had a significant positive impact on neuropsychiatric functions and cognitive age-related impairment [121]. In particular, a significant induction of locomotor activity and higher preference of exploring the novel object recognition were observed in the groups treated with M30, compared with the vehicle-treated aged group. These beneficial responses of M30 might be attributable, at least partly, to the following mechanisms; first, given the evidence supporting a role of free radicals production and OS in brain dysfunction during the ageing process [21, 22], the neuroprotective action of M30 may be mediated by a reduction of OS, either through its iron chelating potential or its hydroxyl radical scavenging properties [114]. Additionally, the cerebral iron staining decreased after M30 treatment in aged mice, compared with the vehicle-treated aged group, indicating that the drug can prevent or attenuate the progression of neuronal degeneration by the reduction of excessive iron and its redox activity [121]. Second, M30 may beneficially influence cognitive deterioration through inhibition of brain MAO-A and -B enzymes [121].

Another interesting finding was the observation that M30 treatment reduced the levels of β-amyloid (Aβ) plaques in the cortex and hippocampus of aged mice, compared with vehicle-treated aged animals. It appears that this effect may be associated with the reduction in the levels of APP, previously observed with M30 [118, 122]. In this context,
previous in vitro studies have described the regulatory effect of M30 on APP expression/processing resulting in reduced APP expression and Aβ generation in SH-SYSY neuronal cells and CHO cells stably transfected with the “Swedish” mutation [116]. It was suggested that metal chelators can reduce APP levels by modulating APP translation via IRE existed in the 5' untranslated region of the APP transcript [110, 123–125]. Recently, Duce et al. [126] have found that APP possesses a ferroxidase activity, mediated via a similar motif found in the ferroxidase active site of H-ferritin and inhibited specifically by Zn²⁺. This finding, and the reported iron-export properties of APP from the cytoplasm to the surface [126], indicate an important biological activity for this protein, whose role is still under-investigation. Indeed, M30 was found in vitro to suppress the translation of a luciferase reporter gene fused to the APP mRNA 5' untranslated region [118]. In addition, it was shown that M30 can activate the non-amyloidogenic pathway of APP processing and increase the amount of secreted sAPPα derivative, as also described for other propargyl-containing compounds [127, 128]. These effects may be beneficial in aged animals, in the face of previous findings demonstrating increased amyloid deposition early in the ageing process in various species [129–132]. The accumulation of Aβ with ageing seems to be a combination of decreased efflux transport of endogenously generated Aβ and increased influx transport from the vascular compartment, and it is likely that the proportions from each Aβ source change with time [133]. It has been demonstrated that the interaction of APP and β-site amyloid cleavage enzyme 1 (BACE1) is enhanced with ageing [134, 135]. Furthermore, increases in APP, γ-secretase and BACE1 have been observed in correlation with age in cells and in vivo [136, 137]. Indeed, ageing is viewed, as the most significant risk factor for AD, closely correlated with AD neuropathology and there is presumably a continuum in Aβ accumulation from normal ageing to AD, although the mechanism underlying this transition is not yet clarified.

4. Concluding remarks

In the past decade, the involvement of brain iron homeostasis in pathologies and cognitive deficits in ageing and aged-related neurodegenerative diseases has been a controversial and debatable issue, mainly as iron may be defined as a “two-edged sword”, being a central nutrient but with highly reactive toxic properties in the brain [138]. It is apparent that various chronic neurodegenerative disorders (e.g. PD, AD, multiple sclerosis, amyotrophic lateral sclerosis, Friedreich’s ataxia, Aceruloplasminemia, Prion’s disease) exhibit changes in brain iron levels, which are linked to age-related degenerative processes [139]. Elucidation of the molecular mechanisms involved in iron toxicity is an imperative step in studying disorders that involve iron accumulation, as well as for the development of new pharmacological interventions based on iron chelation to delay neurodegeneration. Several iron-chelating compounds, approved clinically for transfusional iron overload in thalassemia, such as DFO, deferasirox and deferiprone, have been demonstrated to possess beneficial effects in preclinical models of aged-related neurodegenerative diseases, in particular AD [140–142]. Currently the second-generation metal chelator clioquinol, PBT2, has completed early phase clinical trials in AD patients [143]. The use of natural iron-binding compounds, or those designed to possess of multimodal properties, aimed at attenuating the deleterious effects of brain iron (Fig. 2) and addressing several aged-related central nervous system etiologies allied to iron dyshomeostasis, represent a novel preventive approach to treating the progression of neurodegeneration in ageing and aged related disorders. Adjacent to EGCG, other potential flavonoids and other natural antioxidant/iron chelating compounds, such as curcumin [144, 145], quercetin [146] and derivative of silybin, the major active component of flavonolignans [147] have been described to possess beneficial effects in vitro and in vivo models of ageing and aged related neurodegenerative diseases (e.g. AD). However, further investigation is needed to assess these for their clinical relevance. Thus far, there are only a small number of iron chelating compounds that are under investigation clinically, whilst others are in an earlier stage of development. As such, future preclinical research is vital to endorse this novel therapeutic strategy.

Acknowledgments

The authors gratefully acknowledged the support of the Alzheimer’s Association (Chicago, USA) and the
References


Ji X, Huang L, Lin Q, Huang H. Characteristics and Kinet- 
Perron NR, Hodges JN, Jenkins M, Brumaghim JL. Predict-
Kumamoto M, Sonda T, Nagayama K, Tabata M. Effects of 
Weinreb O, Amit T, Mandel S, Youdim MB. Neuroprotective 
Higdon JV, Frei B. Tea catechins and polyphenols: Health 
Wu CD, Wei GX. Tea as a functional food for oral health. 
Lin YS, Tsai YJ, Tsay JS, Lin JK. Factors affecting the levels 
Joseph J, Cole G, Head E, Ingram D. Nutrition, brain aging, 
Bolognin S, Drago D, Messori L, Zatta P. Chelation ther-
Van der Schyf CJ, Gal S, Geldenhuys WJ, Youdim MB. 
[63] Bortolato M, Chen K, Shih JC. Monosomme oxidase inactiva-
tion: From pathophysiology to therapeutics. Advanced Drug 
[64] Nicostra A, Piermici F, Parvez H, Senatori O. Monosomme oxidase expression during development and aging. Neuro-
70. 
[66] Van der Schyf CJ, Gal S, Geldenhuys WJ, Youdim MB. Multifunctional neuroprotective drugs targeting monosomme oxidase inhibition, iron chelation, adenine receptors, and cholinergic and glutamatergic action for neurodegenera-
[67] Mandel SA, Amit T, Kallon L, Reznichenko L, Weinreb O, Youdim MB. Cell signaling pathways and iron chelation in the neurorestorative activity of green tea polyphenols: Spe-
[68] Bolognini S, Dong D, Messori L, Zatta P. Chelation ther-
ety as novel pharmacological therapeutic agents for Alzheimer’s disease: A tribute to Moussa Youdim. Journal Neural Trans-
[70] Joseph J, Cole G, Head E, Ingram D. Nutrition, brain aging, 
[72] Lin YS, Tsai YJ, Tsay JS, Lin JK. Factors affecting the levels 
31. 
[74] Levites Y, Youdim MBH, Maor G, Mandel S. Attenu-
ation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-kappaB) activation and cell death by tea 
[75] Lee SR, Im KI, Suh SI, Jung JG. Protective effect of green tea polyphenol (−)-epigallocatechin gallate and other anti-
oxidants on lipid peroxidation in gerbil brain homogenates. 
[76] Mazzia EA, Harris N, Solomon KF. Food constituents attenu-
ate monomosome oxidase activity and provitaminal levels in CS 
tion. A cross-sectional study from the Tsuγaya Project 1. The American Journal of Clinical Nutrition. 2006;83(2):355-
61. 
[79] Ng TP, Feng L, Niti M, Kua EH, Yap KB. Tea consumption and cognitive impairment and decline in older Chinese adults. The American Journal of Clinical Nutrition. 2008;88(1):224-
blind, Placebo Controlled, Delayed Start Study to Assess Safety, Tolerability and Efficacy of Green Tea Polyphenols in Parkinson’s Disease: XVIII WFN World Congress on Parkin-
som’s Disease and Related Disorders, Miami Beach, FL, USA, December 13-16. 2009. 
blind, Placebo Controlled, Delayed Start Study to Assess Safety, Tolerability and Efficacy of Green Tea Polyphenols in Parkinson’s Disease: XVIII WFN World Congress on Parkin-
som’s Disease and Related Disorders, Miami Beach, FL, USA, December 13-16. 2009. 
[83] Mazzio EA, Harris N, Solomon KF. Food constituents atten-
uate monomosome oxidase activity and provitaminal levels in CS 
[85] Chen YC, Hosoda K, Tsai CJ, Yamamoto S, Wang MF. Favorable effects of tea on reducing the cognitive deficits and brain morphological changes in senescence-accelerated 
[90] Feng L, Gwee X, Kua EH, Ng TP. Cognitive function 
and tea consumption in community dwelling older Chinese in 
[92] Chen YC, Hosoda K, Tsai CJ, Yamamoto S, Wang MF. Favorable effects of tea on reducing the cognitive deficits and brain morphological changes in senescence-accelerated 
J mice by regulating hippocampal cyclic amm-sequence ele-
ment binding protein signaling cascade. Neuroscience. 2009;

[94] Haseg AM, Hashimoto M, Kataoka M, Tanabe Y, Hara Y,
Shudo O. Long-term administration of green tea catechins
improves spatial cognition learning ability in rats. The Journal

[95] Assuncao M, Santos-Marques MJ, Carvalho F, Andrade JP.
Green tea averts age-dependent decline of hippocampal sig-
aling systems related to antioxidant defenses and survival.

NV, Andrade JP. Chronic green tea consumption prevents
age-related changes in rat hippocampal formation. Neurobi-

[97] He M, Zhao L, Wei MJ, Yan WE, Zhao HS, Chen FJ. Neuro-
protective effects of (−)-epigallocatechin-3-gallate on aging
mice induced by D-galactose. Biological & Pharmaceutical

[98] de Lima MN, Dias CP, Terres JP, Demolles A, Giacca VA,
Scailo-F3, et al. Reversion of age-related recognition memory
impairment by iron chelation in rats. Neurobiology of Aging.

[99] Ryu H, Lee J, Impey S, Ratam RR, Ferranti RJ. Antiox-
dants modulate mitochondrial PKA and increase CREB
binding to D-loop DNA of the mitochondrial genome in
neurons. Proc Natl Acad Sci USA. 2005;102(39):13915-
343.

[100] Spencer JP, Vannoz D, Renaudis C. Flavonoids and
cognition: The molecular mechanisms underlying their
behavioural effects. Archives of Biochemistry and Bio-

[101] Schofield CJ, Ratcliffe PF. Oxygen sensing by HIF hydrox-
343-54.

[102] Weinreb O, Amit T, Mandel S, Youdim MB. Neuroprotec-
tive multifunctional iron chelators: From redox-sensitive
process to novel therapeutic opportunities. The FASEB Journal.
2008;22(5):1296-305.

Fridkin M, et al. Novel multifunctional neuroprotective iron
chelator-monoamine oxidase inhibitor drugs for neurode-
generative diseases: In vitro studies on antioxidant activity,
prevention of lipid peroxide formation and monoamine
95(1):68-78.

Fridkin M, et al. Novel bifunctional iron-chelators as potential
agents for neuroprotection in Alzheimer’s, Parkinson’s, and other neu-
rodegenerative diseases. Bioorganic & Medicinal Chemistry.

M, Youdim MB. Therapeutic targets and potential of the novel
brain-permeable multifunctional iron chelator-monamine oxidase
inhibitor drug, M-30, for the treatment of Alzheimer’s
disease. Journal of Neurochemistry. 2007;100(2):495-
502.

[106] Avramovich-Tirosh Y, Bar-Am O, Amit T, Youdim MB,
Weinreb O. Up-regulation of Hypoxia-inducible Factor (HIF)-1α


[108] Zhou YD, Kim YP, Li XC, Barson SR, Agarwal AK,
Hodges TW, et al. Hypoxia-inducible factor-1 activation by
(−)-epigallocatechin gallate: Potential adverse effects of cancer
treatment and restoration of lactacystin-induced neuroprotective
effects of (−)-epigallocatechin-3-gallate in cell cultures: Implications
for iron chelation in Alzheimer’s disease. Journal of Neuro-
chemistry. 2006;97(2):527-36.

D, et al. Green tea epigallocatechin-3-gallate (EGCG) modu-
lates amyloid precursor protein clearance and reduces cerebral
amyloidosis in Alzheimer transgenic mice. The Journal of Neuro-

[110] Ami T, Avramovich-Tirosh Y, Youdim MB, Mandel S.
Targeting multiple Alzheimer’s disease etiologies with mul-
timodal neuroprotective and neurorestorative iron chelators.

[111] Youdim MB, Raccuia JJ. Multi-functional drugs for various CNS targets in the treatment of neurodegenerative

[112] Zhou Y, Kim Y, Li X, Barson SR, Agarwal AK,
Hodges TW, et al. Hypoxia-inducible factor-1 activation by
(−)-epigallocatechin gallate: Potential adverse effects of cancer

[113] Swerdlow RH. Brain aging, Alzheimer’s disease, and mito-
chondria. Biochemica et biophysica acta. 2011;1812(12):1630-
1651.

[114] Reznichenko L, Amit T, Zheng H, Avramovich-Tirosh Y,
(−)-epigallocatechin-3-gallate in cell cultures: Implications
for iron chelation in Alzheimer’s disease. Journal of Neuro-
chemistry. 2006;97(2):527-36.

Fridkin M, et al. Novel multifunctional neuroprotective iron
chelator-monoamine oxidase inhibitor drugs for neurode-
generative diseases: In vivo studies on antioxidant activity,
prevention of lipid peroxide formation and monoamine
95(1):68-78.

Fridkin M, et al. Novel bifunctional iron-chelators as potential
agents for neuroprotection in Alzheimer’s, Parkinson’s, and other neu-
rodegenerative diseases. Bioorganic & Medicinal Chemistry.

M, Youdim MB. Therapeutic targets and potential of the novel
brain-permeable multifunctional iron chelator-monamine oxidase
inhibitor drug, M-30, for the treatment of Alzheimer’s
disease. Journal of Neurochemistry. 2007;100(2):495-
502.

[118] Avramovich-Tirosh Y, Bar-Am O, Amit T, Youdim MB,


vention and restoration of lactacystin-induced neuroprotective


