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SHORT REVIEW

A review on iron chelators as potential therapeutic agents for the treatment of Alzheimer's and Parkinson's diseases

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Abstract

Iron plays a vital role in several cellular functions due to its unique physiochemical properties. Iron concentration increases in the brain with age due to multiple factors. Excessive amount of iron can lead to formation of reactive oxygen species. Neurodegenerative disorders are characterized by iron supplemented increase in oxidative stress and cellular damage. There is an urgent need of novel therapies which should not only provide symptomatic relief but also be able to modulate iron accumulation in the brain. Therefore, the development of novel iron chelators as neuroprotective agents for the treatment of neurodegeneration is an emerging trend. Several iron chelators including 8-hydroxyquinoline derivatives, dopaminergic agonists and natural products are under preclinical and clinical investigations for the treatment of neurodegenerative disorders.

Keywords Iron regulating proteins · Neurodegenerative disorders · Desferrioxamine · Dopamine D3 agonist · 8-Hydroxyquinoline

Introduction

Neurodegenerative disorders (NDDs) are characterized by loss of neurons from specific region of the brain. The pathological hallmarks of particular NDDs depend upon the vulnerability of the unique population of neurons. The multifactorial and complex nature of the pathophysiology responsible for a number of NDDs is under investigation [1]. The oxidative stress, metal dyshomeostasis and aging are presumably the common factors play a major role in onset of the disease. The existing therapies for NDDs provide only symptomatic relief without addressing the basic factors responsible for the disease. An enormous amount of efforts are being carried out for the effective management of this devastating group of disorders [2–8]. One of the key features of NDDs is their multifactorial nature, and therefore, drug design against these diseases is challenging.

Iron plays a vital role in several cellular functions including mitochondrial oxidation, cell growth, synthesis and metabolism of neurotransmitters such as dopamine (DA) [9]. It is a biodynamic agent due to its special physiochemical properties. Although iron is essential for the neuronal growth, its excess can cause the demise of neurons. Therefore, an optimal concentration of iron is essential in cellular compartments to avoid iron associated toxic effects, i.e., reactive oxygen species (ROS) generation. Iron storage proteins like ferritin and neuromelanin get saturated under iron overload condition, and the increase in labile iron pool leads to neurodegeneration.

It has been shown in the literature that altered brain metal homeostasis plays a critical role in the pathogenesis of NDDs [10]. The NDDs such as Alzheimer's diseases (AD) and Parkinson's disease (PD) are characterized by the increase in iron level in specific brain regions which leads to increased oxidative stress and cellular damage. The exact mechanism involved in triggering various neurodegenerative diseases, viz. AD and PD, still remains elusive. It is also unknown whether iron accumulation is primary causative agent responsible for the disease or a secondary consequence [11]. The distribution of iron is unequal within the normal brain and is majorly dependent on the type of the cells and region of the brain [12]. This review is mainly focused on role of iron and its chelators in pathogenesis and treatment of PD and AD, respectively.

PD is multifactorial NDDs arises due to degeneration of dopaminergic neurons in the substantia nigra pars compacta

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(SNPc) region of the brain. After AD, it is second most common NDDs affecting 1–2% of the population over the age of 65 [13]. The clinical manifestation of this disease appears upon the loss of 70–80% of dopamine in the SNPc regions of the brain, which makes it challenging to treat PD. The presence of α-synuclein (αSN) aggregates known as *Lewy body* (*LB*) is pathological hallmark of the disease. Mutation in αSN gene can cause earlier onset of PD. The occurrence of PD is also associated with mitochondrial dysfunction and oxidative stress. The role of iron in PD is fostered on the basis of number of observations such as elevated level of iron in PD brain compared to normal brain, co-localization of iron in the SNPc, iron-mediated ROS generation in dopaminergic neurons and modulation of αSN aggregation in the presence of iron in PD [2, 14].

AD is most common age-dependent chronic neurodegenerative disorder characterized by decline in memory and other psychological changes. The clinical manifestation of AD is the appearance of amyloid-β (Aβ) plaques and neurofibrillary tangles composite of hyperphosphorylated *Tau* protein. AD and PD share several common pathogenetic factors such as accumulation of iron, aggregation of protein, oxidative stress and mitochondrial dysfunction [15]. The iron-derived ROS are major culprit responsible for the inhibition of mitochondrial respiration and promotion of Aβ aggregation in the form of intracellular neurofibrillary plaques and tangles.

Given the fact that iron plays a critical role in NDDs, so, iron chelation therapy is under investigation to develop disease modifying agents [16–22]. Three different mechanisms have been proposed to substantiate iron chelation therapy in NDDs: first, the ability of iron chelators to tightly bind with free iron to prevent ROS generation which is mechanistically similar to desferrioxamine (DFO), the clinically available iron chelator. Second, the radical scavenging ability of iron chelators and third, the modulation of neurotrophic factors via inhibition of hypoxia induce factor (HIF) [23]. Also, several other metal chelators (including copper chelators) available in clinic can be repurposed for the treatment of treatment of NDDs [24]. In this regards, 8-hydroxyquinolines and their copper complexes have been evaluated as proteasome inhibitors and anti-cancer agents [24, 25].

Iron imbalance in aging brain

Iron concentration increases in the brain with age due to multiple factors such as leaky blood brain barrier, neuroinflammation, inefficient chelation of iron in the brain and compromise in iron homeostasis. The selective increase in iron content with age in SNPc, putamen, globus pallidus and cortices makes these neurons vulnerable against oxidative stress-induced neurodegeneration [26]. Further, changes in the ratio of various iron bound molecular species like ferritin, neuromelanin, transferrin (Tf) and distribution of iron among aging neurons and glial cells are common phenomenon in NDDs. Total amount of ferritin increases with age in SNPc regions of the brain, while it remains constant in locus coeruleus; therefore, selective degeneration of dopaminergic neurons occurs in PD brain [27, 28]. The amount of neuromelanin–iron complex also goes up with age in the SNPc regions. The increase in the number of glial cells and MHC-II complex reactivity are cardinal features of aging brain [29, 30]. The interaction of active microglia with Aβ is well documented in literature [31], but the mechanism of neurodegeneration through microglia and neuronal interaction is still puzzling. The aberrant morphology of ferritin positive microglia cells could lead to source of neurodegeneration.

A strong correlation was predicated between aging brain and increase in blood brain permeability [32]. Iron level needs to be tightly regulated in the brain to prevent toxic side effects. The excess amount of freely available iron can generate ROS which react with various cellular components including genetic material and proteins. The release of iron from mitochondrial sulfur–iron cluster and from other iron storage sources can also be induced by ROS and accelerates neurodegeneration. Dopamine undergoes enzymatic or iron-mediated oxidation to form highly reactive toxic dopamine quinone. The conversion of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) to neurotoxin MPP^+ (1-methyl-4-phenylpyridinium) and aggregation of αSN into toxic oligomeric species is another iron-dependent phenomenon.

Role of iron in PD

The clinical manifestation of PD appears upon the loss of 70–80% of dopamine in the SNPc regions of the brain. PD is majorly sporadic in nature; however, less than 10% cases are linked to mutation in αSN gene. Accumulation of iron in PD is also associated with mitochondrial dysfunction and oxidative stress.

The change in iron concentration in basal ganglia among PD patients was first time observed in 1924 by Lhermitte et al. [33]. Subsequently, the observation was supported by various histopathological studies and in vivo imaging techniques [34, 35]. The shift in the ratio of Fe^{2+}/Fe^{3+} from 1:2 in healthy subjects to 2:1 in PD patients has been reported in SNPc regions of the brain [36]. The increase in the concentration of highly reactive iron species, Fe^{2+}, results in excess production of ROS via Fenton chemistry (Fig. 1).

A positive correlation was found between elevated level of magnetic resonance imaging (MRI) field-dependent relaxation rate in SNPc region and amount of specific iron pool in early PD patients [37, 38]. The transcranial sonogra-

$$H_2O_2 + Fe^{2+} \longrightarrow OH^- + OH^* + Fe^{3+}$$

$$Fe^{3+} + O^{2-*} \longrightarrow Fe^{2+} + O_2$$

$$O_2^{-*} + H_2O_2 \longrightarrow O_2 + OH^- + OH^*$$

Fig. 1 Fenton reaction by which H_2O_2 forms hydroxyl radical in iron rich environment

phy supports the notion of augmented iron level in basal ganglia and SNPc regions of the brain; however, low sensitivity techniques such as Mossbauer spectroscopy and atomic absorption spectroscopy could not detect the elevated iron level in PD patients [38, 39]. Several hypotheses such as ruptured blood brain barrier [40–42], inflammatory factors [43], increase in the number of lactoferrin receptors in neurons and expression of divalent metal transporter-1 (DMT1) receptors in dopaminergic neurons [44], altered iron transport by transferrin receptor (TfR) type 2 [45], decrease ferroxidase activity of ceruloplasmin (*Cp*) [4] and mutation in iron transport gene in PD patients have been suggested to explain the high iron concentration in SNPc regions. The postmortem analysis of PD brain revealed the decrease in ferritin synthesis due to sustained iron regulatory protein (IRP1) activity which eventually causes the increase of Fe^{2+} associated with neuromelanin in SNPc region. Neuromelanin-induced microglia activation is also responsible for dopaminergic neuronal cell death [46]. The low level of neuromelanin in SNPc is strongly associated with poor iron sequestering ability which is the characteristic features of PD. Interestingly, the increase in amount of total serum iron level is linked to decrease in the risk of developing PD. Dopamine can undergo auto-oxidation or enzyme-mediated oxidation to form DA o-quinone (DAQ) which is stable under pH 2.0, but at physiological pH it can further cyclize into various reactive species, viz. leukoaminochrome, aminochrome or 5,6-indolequinone [47]. These oxidized products of dopamine can participate in various neurotoxic reactions as depicted below (Fig. 2)

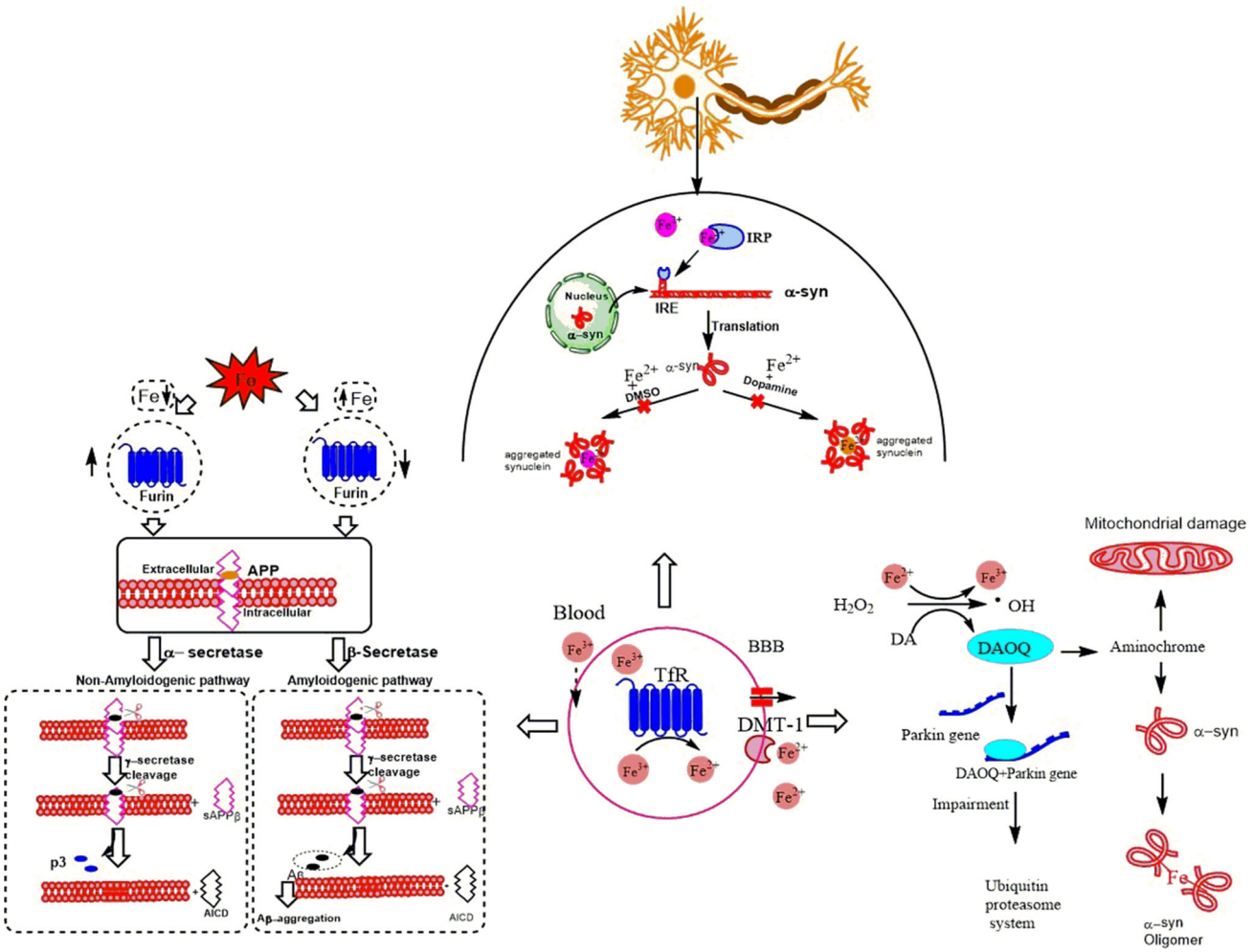


Fig. 2 Role of iron in NDDs: iron is import into the cells by TfR. αSyn translation is regulated by an iron-responsive element (IRE). Furin activity is responsible for cleavage of APP. Dopamine undergo oxidation in the presence of H_2O_2 to form DA o-quinone (DAQ)

[10]. DAQ can form stable adduct with parkin gene, a part of ubiquitin-protein ligase, and eventually responsible for impairment of ubiquitin proteasome system (UPS). DAQ is considered most reactive species among all the other oxidized products, which is responsible for depletion of glutathione. Aminochrome induces the conversion of αSN monomer into toxic oligomeric species, while leukoaminochrome does not interact with αSN [44]. Aminochrome also inhibits mitochondria complex I and promotes protein degradation through several mechanisms. Metals such as iron, copper and manganese can either induce metal-mediated oxidation of DA or can make a complex with DA. The toxicity of DA-metal complexes toward the dopaminergic neurons depends on the uptake ability of the cells. The metal-mediated oxidation of DA increases the amount of Fe^{2+} which further exacerbates the oxidative stress.

Role of iron in αSN aggregation

The cardinal hallmark of PD pathology is the appearance of intracytoplasmic inclusions known as of LBs in the PD brain [48]. LBs are aggregated forms of a small 140 amino acid containing protein known as αSyn. The role of αSyn in PD pathogenesis has been described in detail in our earlier publication [49]. Primary structure of αSyn can be divided into three parts: first, N-terminal containing residues 1–60 which are responsible for membrane binding property. Second, central non-amyloid beta component (NAC) from 61 to 95 amino acid residues responsible for β sheet formation and third, C-terminal from 96 to 140 amino acid residues imparts chaperone property to αSyn [50]. Mutations in the gene (*SNCA*) encoding αSyn can increase the aggregation property of this protein which can cause familial early onset of the disease. In 1920s, *Lehermitte* et al. observed co-localization of iron with LBs using Pearl's staining. Metal imbalance is responsible for the loss of dopaminergic neurons in the SNPc region of brain [51]. Total nigral iron level was found to be increased in PD brain compared to the control. Metals, especially iron, can modulate αSyn aggregation either via long-range interaction or metal-induced oxidation of protein. Nuclear magnetic resonance (NMR) titration indicated the presence of metal binding residues ASP-121, ASN-122 and GLU-123 at C-terminus of the protein [52, 53]. Further, the presence of iron-responsive element (IRE) in 5′-untranslated region (UTR) suggested that iron plays a critical role in the synthesis of this protein (Fig. 2) [54]. Post-translational modifications such as phosphorylation of SER-129 and TRY-125 at C-terminus alter binding affinity of αSyn toward metals [55]. In in vitro experiments, the αSyn aggregates formed in the presence of iron are sodium dodecyl sulfate resistant and could rupture the lipid bilayer by forming pore like structures [56]. It can also reconvert Fe^{3+} into Fe^{2+} in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). The presence of dopamine or H_2O_2 exacerbates this iron-mediated cytotoxicity toward cell lines.

Cu^{2+} modulates αSyn aggregation due to the presence of several binding sites in the protein. The Cu^{2+}-αSyn complex is cytotoxic in nature toward the SHSY-5Y neuroblastoma cells. The complex has the ability to oxidize certain cellular reductants, i.e., ascorbic acid, and GSH, which leads to generation of H_2O_2 [53].

Iron and AD

The key features of AD are presence of high amount of metals in the extracellular deposition of amyloid precursor protein (APP)-derived amyloid β (Aβ) plaques, and intracellular neurofibrillary tangles (NFTs). The elevated level of iron and its role in senile plaque formation and NFTs is well established in literature [57–59]. Aβ-mediated toxicity is dependent on the length of the peptide, its oligomerization state and concentration. Metal dyshomeostasis is responsible for misfolding of Aβ, tau hyperphosphorylation and oxidative stress [60]. Iron-mediated oligomerization of Aβ into toxic species has been explored in the cell culture and *Drosophila* animal models [61–63]. High binding affinity of Aβ toward metals and its ability to reduce the Fe^{3+} is the leading cause for generation of ROS. Iron is also responsible for tau phosphorylation and aggregation. Hyperphosphorylated tau accumulates in NFTs, thereby induces antioxidant heme oxygenase-1 (HO-1) protein [4, 9]. Although HO-1 is antioxidant in nature, it induces Fenton reaction via release of Fe^{2+}.

The identification of novel iron-responsive element (IRE) within 5′ UTR of APP gives an important linkage indicting the role of iron in AD pathogenesis. Interestingly, DFO, a potent iron chelators, could reduce IRP binding to APP 5′UTR region, whereas interleukin 1 stimulation has an opposite effect. APP undergoes proteolytic cleavage by non-amyloid and amyloid pathways in the normal and disease conditions, respectively [9]. The action of α-secretase followed by γ secretase generates APP intracellular domain. Alternatively, the attack of β secretase followed by γ secretase produces Aβ. The development of novel secretase inhibitors for the treatment of AD is still under investigation [64]. Iron has dual mode of action as it controls APP expression and also modulates furin protein which is responsible for Aβ generation. Abundance of iron stimulates Aβ production by decreasing the furin activity (Fig. 2). Intriguingly, APP's ferroxidase activity helps in iron export and reduces ROS generation. The presence of iron in Aβ plaque was also supported by decrease in hippocampal T_2*MRI in postmortem analysis of AD patients brain. Tf is one of the major proteins which play a vital role in cellular metal distribution. The significant increase in levels of Tf with concomitant decease in iron mobilization capacity (transferrin/iron) was observed in

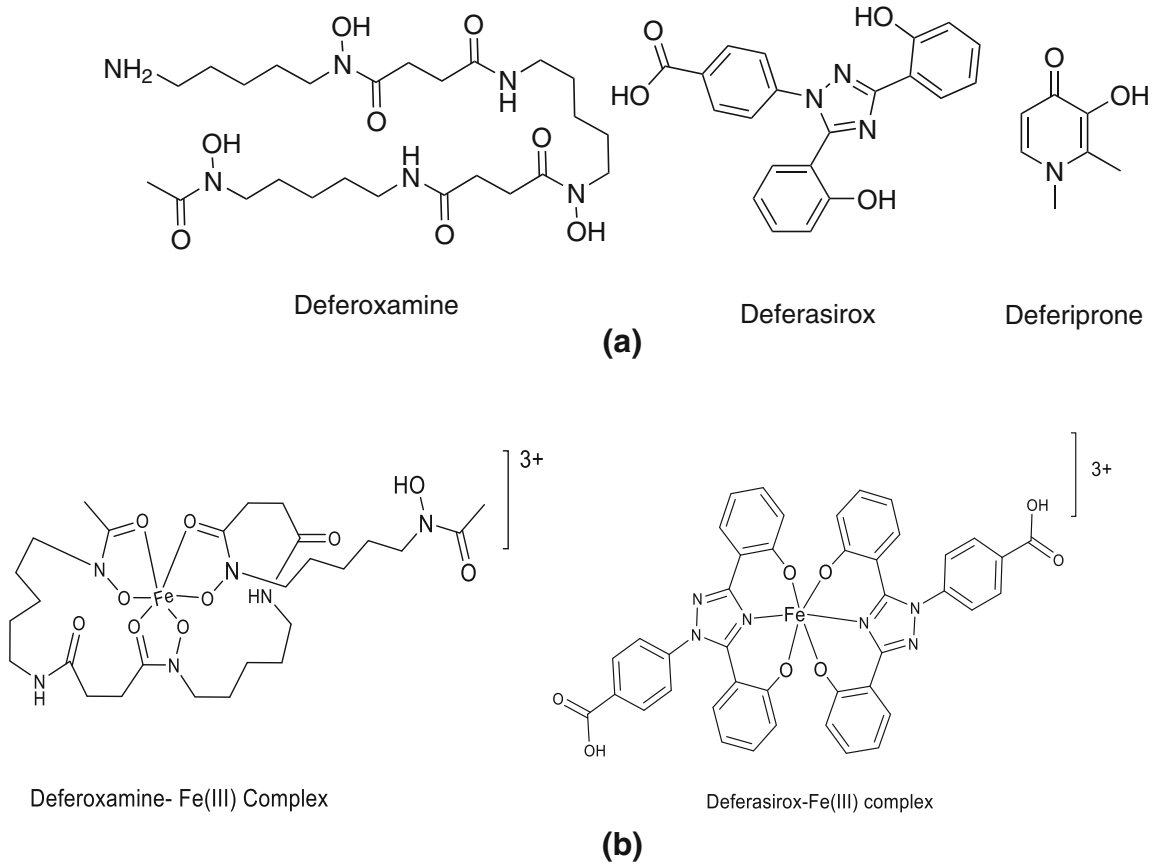


Fig. 3 **a** Commercially available iron chelators for the treatment of systemic iron overload. **b** The hypotized structure of the complex with iron, specifying the oxidation state of iron

AD patient [65]. Further, a decreased plasma iron level in AD patients is correlated with saturation of iron storage proteins such as ferritin or Tf. In another study, a strong correlation between ferritin and APEO E4 protein levels is implicated to play a role in AD pathogenesis [9, 66].

Metal dis-homeostasis and UPS

Proteinopathies including AD and PD share similar pathogenic mechanism [67]. An imbalance between generation and clearance of disease specific protein led to onset the path for several diseases including NDDs. Protein homeostasis is an integrated and tightly regulated in the cells through proteolytic machinery. UPS plays a critical role in clearance of misfolded proteins [68]. It is well known that metal dyshomeostasis significantly contributes to onset of NDDs though several mechanisms including cross talk with UPS. However, the complete mechanism is still under investigation. It has been shown in the literature that deregulation of UPS is responsible for accumulation of metal derived oxidative stress and protein aggregation [69]. The administration of lactacystin, a UPS inhibitor, in SNPc region of the brain causes dramatic loss of dopaminergic neurons, change in the ration of IRP/IRE and excessive iron accumulation [70]. Further, synthetic iron chelators are able to reverse lactacystin-induced neurodegeneration in in vitro and in vivo PD animal models [71]. Similarly, copper-induced alteration in the structure of UPS strongly indicated the impact on gate opening of 20S proteasome [72].

Iron chelators as possible therapeutic agents for the treatment of neurodegenerative disorders

There are several metal chelators such as desferrioxamine (DFO), deferiprone (DFP), deferasirox and penicillamine (Fig. 3) in clinic to treat systemic metal dyshomeostasis [16]. DFP is the first orally active iron chelator used clinically [16, 73].

DFO and its analogs

The siderosis in the specific region of the brain was explored as a marker of PD and also as a target of metal chelators

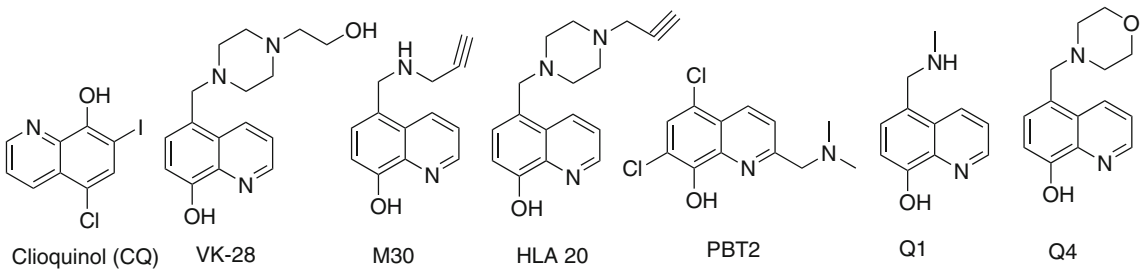


Fig. 4 8-Hydroxyquinoline (8-HQ) analogs with ability to chelate iron

for the neuroprotective and neurorestorative therapies [74]. DFO, a hexadentate siderophore obtained from *Streptomyces pilosus*, is currently one of the drugs of choice for the treatment of iron overload. Intranasal administration of DFO significantly improved PD symptoms in MPTP-treated mice [75, 76]. At high concentration, 100 μM, DFO dose dependently reduced iron-induced oxidative stress in SK-N-SH cell line and dopaminergic cells aggregation [77]. It was found promising in aceruloplasminemia patients in the clinical trial [78]. It suffers from poor oral bioavailability and short half ($t_{1/2}$ = 12 min). Further, its entry into the brain is poor due to its bigger size and hydrophilic nature [77].

The limitations associated with application of DFO in the treatment of iron overload led to the discovery of novel synthetic metal chelators, DFP. DFP, a regional orally bioavailable siderophore, belongs to bidentate hydroxypyridinone series of compounds. It is efficacious in MPTP and 6-OHDA-induced animal models of PD [3, 79, 80]. DFP, an in vivo active membrane permeable neuroprotective bidentate ligand, can selectively rescue mitochondria from iron accumulation [80]. It is able to increase number of tyrosine hydroxylase (TH) positive cells a marker of dopamine level in SNPc region of the brain in MPTP-treated animals [79]. Based on the initial in vivo activity, DFP was tested in early stage of PD patients in 12-month clinical trial. Gratifyingly, the patients showed promising improvement in the disease symptoms compared to the control group [81]. Iron plays a central role in the generation of ROS in PD brain, and its plasma level is mainly modulated by a copper ferroxidase-dependent enzyme known as *CP*. The enzyme transfers the free plasma Fe^{2+} into apotransferrin. Low *CP* activity has been reported in SNPc regions of the brain in sporadic and individuals bearing D544E protein gene variant. In a small clinical trial study, DFP, at the dose of 30 mg/kg/day for 6–12 months, in early stage PD patient selectively reduced high level of iron in the SNPc regions [79, 82]. Interestingly, the reduction in UPDSR motor scores and iron level were found in patients with high CP activity.

The substantial structural differences among DFO and DFP are suggestive that the two agents might be chelating different iron pools. Presumably, DFP could chelate the intracellular iron, whereas DFO acts effectively on extracellular iron [83]. Clinical trials of combination therapy of these agents were carried out in thalassemia patients to gain an advantage of this dual mode of action [41, 84].

8-Hydroxyquinoline (8-HQ) analogs

Several 8-HQ derivatives demonstrated considerable potential for the treatment of neurodegeneration. One such compound, clioquinol (CQ, Fig. 4), a metal protein attenuating (MPA) iron chelators was tested in phase II clinical trial in advanced stage AD patients. A significant decrease in the Aβ42 level was observed in CQ-treated patients [85]. CQ, lipophilic metal chelators, is able to reverse iron-induced toxicity in AD and PD animal models [81, 86, 87]. Anderson et al. tested CQ in MPTP-induced PD animal model [88]. The transgenic mice expressing heavy subunit of ferritin in the SNPc regions of the brain were treated with MPTP which was followed by measurement of TH positive cells, level of striatal DA, DOPAC (3,4-dihydroxyphenylacetic acid) and homovanillic acid. The loss of neurotransmitters was significantly attenuated in the ferritin expressing animals. Similar to ferritin treatment, CQ pretreatment could rescue MPTP-treated animals against oxidative stress-induced neuronal loss. Further, the striatal dopamine (DA) level was reduced up to 80% in the untreated animals, while the loss was approximate 41% in CQ pretreated animals. CQ being non-specific metal chelators, it can lead to subacute myelo-optic neuropathy. It strongly binds with Co^{2+}, which is responsible for the low level of vitamin B_{12} in PD brain [89]. Chronic administration of CQ in transgenic animals over expressing hA53T αSyn for 5 months starting from the age of 3–8 months significantly reduced nigral dopaminergic cell loss and exhibited behavioral improvement in in vivo animal models [87].

There are several literature evidences indicating a linkage between Tau protein, components of Lewy bodies and PD pathogenesis [90, 91]. Tau knockout mice displayed typical PD like syndrome including neuronal loss in SNPc regions, and accumulation of iron in the brain. The earlier detection of PD is still a challenging task, so neurorestorative treatment is a better option. CQ was evaluated in the Tau knockout mice

model for PD [92]. The significant improvement in the behavior of CQ-treated animals was correlated with the decreased level of iron in SNPc regions of the brain, increased level of neurotrophic factors and TH activity.

DFO a potent iron chelators showed bell-shape concentration-dependent effect in 6-OHDA PD animal model at very low dose compared to 6-OHDA alone [3]. The mechanism of action of DFO is probably mediated via iron chelation rather than detoxifying the neurotoxin. This led the foundation for the development of novel series of compounds, VK-28, (Fig. 4) having potent iron chelation ability, brain permeability, monoamine oxidase inhibitory (MAO) property and neuroprotective ability [93]. In this series of analogs, it was also observed that phenolic and quinolinic moieties containing iron chelators were found to be poor inhibitors of MAO in comparison with selegiline. On the other hand, pyridinium compounds, i.e., 2,2′-dipyridyl and MPTP, selectively inhibited MAO-B, while isoquinoline drugs specifically reduced MAO-A activity [93]. The MAO inhibitory property of quinolinic derivatives was reversed in the presence of high iron concentration, but the activity of pyridyl analogs remained unchanged under the same experimental conditions. Gratifyingly, in in vivo animal models, VK-28 (Fig. 4) was able to protect neuronal cells against 6-ODA-induced toxicity and inhibited iron-induced lipid peroxidation to same extent as DFO [94, 95].

The increase in nigral iron, MAO-B activity and decrease glutathione are the characteristic features of PD [94]. It was hypothesized that dual iron chelators and MAO inhibitors should be able to provide disease modifying property along with symptomatic treatment for the neurodegenerative diseases such as PD and AD. It is well established in the literature that the presence of the propargyl moiety in rasagiline is responsible for the potent MAO-B inhibitory activity and neuroprotection ability of this molecule [96].

VK-28 did not affect MAO probably due to the absence of propargyl group; therefore, novel propargyl containing compounds were synthesized and evaluated for iron chelation and MAO inhibitory properties [94, 97]. Intriguingly, HLA-20 (Fig. 4) selectively inhibited MAO-B, whereas M-30 (Fig. 4) was considered as suicidal inhibitor of MAO. The propargyl amine also imparted neuroprotective activity mediated by upregulation of B cell lymphoma 2 (Bcl-2), B cell lymphoma-extra large (Bcl-xl) and activation of protein kinase Cα (PKCα).

M30 is also a propargyl amine containing potent multifunctional brain permeable therapeutic agent exhibiting significant MAO inhibitory property, and in vivo efficacy in 6-OHDA, MPTP and lactacystin PD animal models [97]. It is a cell permeable antioxidant compound with strong ability to chelate Fe^{3+} in a dose-dependent manner in SNPc regions of PD brain [98, 99]. The TfR staining of the SNPc region of the mice treated with M30 indicated significant increase in TfR compared to MPTP-treated animals. Further, it is able to rescue the cells and mitochondria against oxidative stress-induced cell death. The induction of neuronal differentiation, impact on APP processing, reduction in pro-apoptotic protein Bcl-2-associated death promoter (*Bad*) and *Bcl-2*-associated X protein (*BAX*), and the outgrowth of neurites were observed in M30-treated animals. Neurotrophic factors such as brain derived neurotrophic factors (BDNF) and glial cell derived neurotrophic factor (GDNF) could rescue the dying neurons in PD brain. M30 is a potent up-regulator of HIF, which is responsible for increase in neurotrophic factors [100]. M30 has an impact on various downstream pathways such as mitogen-activated protein kinase (MAPK)/ERK kinase, protein kinase B (PKB/Akt) and glycogen synthase kinase-3β (GSK-3β). It is also able to increase the level of neurotransmitters such as dopamine and noradrenalin.

HLA20 (Fig. 4), a chlorinated cell permeable 8-hydroxyquinoline analog, was firstly synthesized by Fridkin et al. It effectively protected the differentiated P19 (mouse embryonal carcinoma cell line) cells against 6-OHDA-induced toxicity [101]. HLA20 showed strong iron chelation in electron paramagnetic resonance (EPR) studies, potent free radical scavenging capability, MAO-B inhibitory activity and good permeability through K562 cell membranes [101]. Among the novel multifunctional iron chelators, HLA-20 and M-30 were the most effective drugs in terms of iron chelation potency, radical scavenging ability and iron-induced membrane lipid peroxidation inhibitory activity [94]. Indeed, iron chelators have the potential to prevent iron-induced ROS generation, oxidative stress and aggregation of αSyn and Aβ.

PBT2 (Fig. 4) is a 8-hydroxyquinoline derivative and devoid of iodine-induced toxic effect due to the absence of iodine at C-7 position. PBT2, a second generation MPAC, is having an extra tertiary amine in the structure which is probably responsible for better solubility, and efficacy in preclinical studies [102]. Oral administration of PBT2 to Tg2576 mice reduced Aβ aggregates and plaques [103]. PBT2 treatment was able to significantly reduce oligomeric Aβ in double-transgenic APP/PS1 mice. Further, it has shown promising activity in Phase II clinical trials [104].

Two novel 8HQ-based iron chelators, Q1 and Q4 (Fig. 4), were found to decrease mitochondrial iron accumulation and oxidative stress in cellular and animal models of PD. At submicromolar concentration, Q1 selectively decreased the mitochondrial iron pool in SHSY-5Y cell line, whereas Q4 effectively chelated the cytoplasmic iron pool. Q1 turns out to be more potent compared to Q4 in suppressing superoxide production in the mitochondria. Intriguingly, Q1 and Q4 were equally effective in inhibiting rotenone-induced 4-hydroxynonenal (4-HNE) adduct. Structurally, Q1 and Q4 are derivative of 8-OHQ possessing a methylaminomethyl

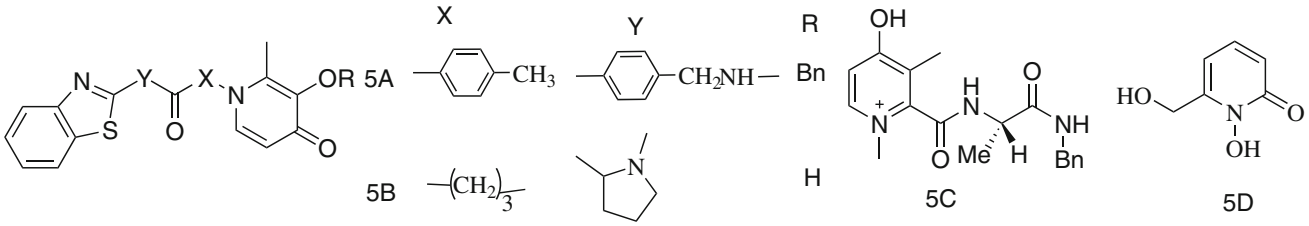


Fig. 5 Hydroxypyridone (HP) derivatives; A and B. BTA–HP hybrid compounds, C. 3-hydroxypyridin-4-one, D. 1-hydroxypyridin-2-one (HOPO)

and morpholino-methyl moieties, respectively, at C5 position [105]. The potent mitochondrial iron chelating capacity of Q1 compared to Q4 can be attributed to these structural differences. Interestingly, both compounds rescued dopaminergic cells line, SHSY-5Y, against rotenone-induced oxidative damage which is an indicator of their mechanism of action.

Hydroxypyridone derivatives

3-Hydroxy-4-pyridinone (3,4-HP) is a well-established moiety for high affinity toward iron, ROS and low toxicity properties [106]. Thioflavin-T (ThT) is a widely used benzothiazole (BTA) derivative with strong binding ability to Aβ aggregates. Given the fact that AD is multifactorial in nature; therefore, 3,4-HP and BTA were connected through a suitable linker to develop BTA-HP series as a multifunctional drug molecules [107]. Molecular docking studies revealed the critical interaction of designed analogs with catalytic and peripheral sites of the acetylcholinesterase (AChE). Spectrophotometric method was adopted for iron chelation studies at different pH, for determination of bischelated (FeL_2) and trischelated (FeL_3) species. The pFe value for the lead molecule 5A (Fig. 5) at pH 7.4 was found to be comparable to strong iron chelators DFP (pFe = 19.2 vs. 20.8 for 5A and DFP, respectively). In DPPH assay, compounds with free hydroxyl group can quench free radical effectively in comparison with O-protected compounds. Antioxidant potency is also related to presence or absence of aromatic fragment between HP and BTA groups. In molecular docking studies, the designed compounds showed favorable interaction with AChE and IC_{50} value was in submicromolar range for 5B; nonetheless, it was less potent compared to reference drug Dnp (IC_{50} = 13.8 vs. 0.033 μM for 5B and Dnp, respectively). Intriguing, lead molecules provided neuroprotection against Aβ cytotoxicity except compounds 5A and the detail mechanistic analysis is under investigation.

A selective and potent metal chelating agent should be able to scavenge excessive amount of free redox metals, and cross BBB. 8-HQ and 3-hydroxypyridinones (HPO) moieties are reported in the literature as potential therapeutic agents for the treatment of NDDs [108]. The iron affinity constant (pM) should be ≥ 20 for the clinical application of a iron chelators. The designed analogs were found to exhibit good affinity for iron (pM = 18.9–21.5) as compared to reference drug deferiprone (pM value = 19.3). The lipophilicity of compounds (log D) was calculated using shake flask method and HPLC. All the compounds in the series have log D values in range of 0.90–1.52, and therefore, they were expected to cross BBB smoothly. The neuroprotection ability of the lead molecules against iron (FeNTA) and Aβ-induced toxicities were assessed in primary mouse cortical neurons by measuring LDH release and MTT assay. The lead molecule, 5C (Fig. 5), at concentration of 30 μM or higher was able to reverse the increased level of LDH-induced by toxins. In this series, compound 5C having benzyl substitution reduced formazan production by 50% as compared to FeNTA alone. The morphological examination of the 5C treated neurons revealed significant reduction in synaptophysin level and cell damage. The compound, at the dose of 10 μM and higher turned out to be effective modulator in the cell culture experiment against $A\beta_{1-40}$-induced toxicity. The demonstration of weak inhibitory activity of 5C against iron containing enzymes is an indicator of the selectivity against the toxin-induced neurodegeneration [108].

DFP and DFO are in clinic for the treatment of peripheral iron toxicity such as thalassemia major and sickle cell anemia [83, 109]. The high iron binding affinity, poor blood brain barrier crossing ability and molecular size render these agents unsuitable for the treatment of neurodegeneration [110]. Hydroxypyridin-4-ones are emerging siderophore for the treatment of NDDs by virtue of their suitable physiochemical properties, high affinity for Fe^{3+} and ability to form neutral iron complex. To explore such siderophores, a novel 1-hydroxypyridin-2-one (Fig. 5D) series of compounds were synthesized as potential therapeutic agents for PD [111]. The metal binding hydroxamic acid functional group is essential to provide neuroprotection in 6-OHDA-induced oxidative insult. It is also critical for the reduction in cytoplasmic labile iron pool (LIP) under iron over load condition. The acid dissociation constants (pKa) were found at lower end, in the range of 5–6, for designed compounds as compared to 9.9 for DFP. Still, the compounds were able prevent cell death against iron-induced oxidative stress.

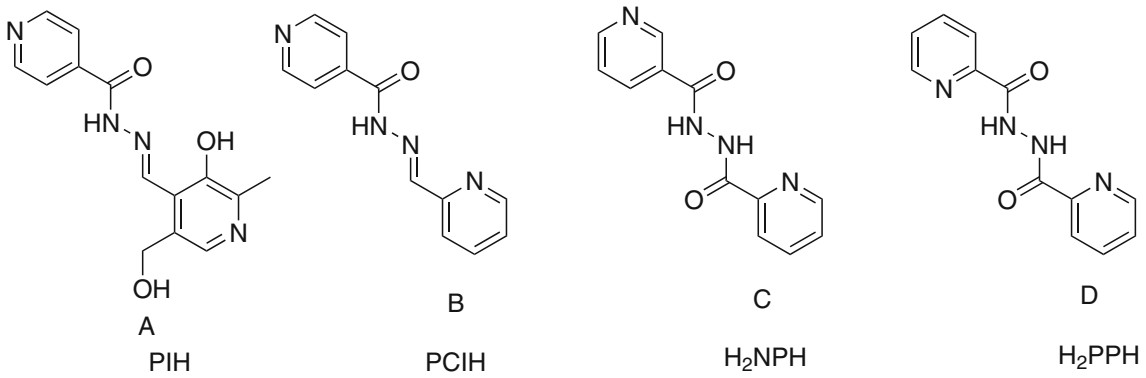


Fig. 6 Pyridoxal isonicotinoyl hydrazone (PIH) and related compounds

Arylhydrazones

The lipophilic nature of pyridoxal isonicotinoyl hydrazone (PIH) is responsible for its entry into mitochondrion and subsequent binding to iron accumulated into reticulocytes [112]. The unique properties of PIH make it suitable to serve as model drug for the treatment of Friedreich's ataxia (FA). Novel 2-pyridylcarboxaldehyde isonicotinoyl hydrazone (PCIH) analogs were synthesized (Fig. 6A–B) to address the patent-related issues associated with PIH series [113]. These compounds turn out to be promising in Fe overload disorders. Surprisingly, PCIH gets oxidized into charged species known as isonicotinoyl picolinoyl hydrazine (IPH).

To increase the activity of PIH series of compounds, several neutral diacylhydrazines were synthesized (Fig. 6C–D), which can get oxidized into hydrazine, thereby forming a neutral complex capable of crossing mitochondrial membrane.

H_2O_2-mediated prochelators

The existing metal chelators suffer from high metal binding affinity, uncontrolled metal binding property and ability to swoop up the intracellular iron pool, so novel H_2O_2-triggered prochelators were developed. As name indicates, these agents are inactive under normal physiological condition. The presence of excess H_2O_2 is responsible for their conversion into active chelator [114]. 2-boronobenzaldehyde isonicotinoyl hydrazone (BSIH) belongs to such prochelator class of compounds (Fig. 7). The selection of boronic acid as masking agent is based on its size, poor donor ability and sensitivity against H_2O_2. The oxidative stress-induced generation of H_2O_2 is responsible for the removal of protecting group and generation of phenolic compound salicylaldehyde isonicotinoyl hydrazone (SIH). At pH 7.4, SIH makes coplanar tridendate complexes Fe(SIH), and Fe(SIH)2 [115, 116]. Addition of Fe^{3+} to BSIH did not show any change in

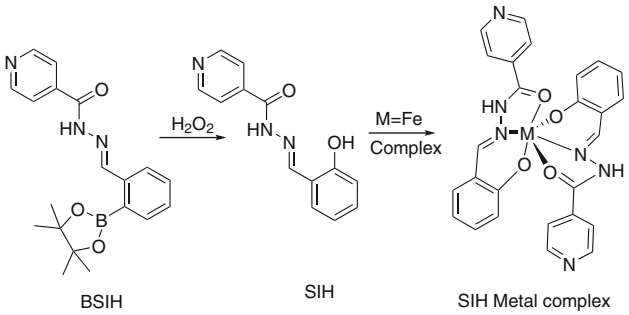


Fig. 7 2-Boronobenzaldehyde isonicotinoyl hydrazone (BSIH) prochelators

UV spectrum as compared to BSIH alone except the slight decrease at 300 nm which is an indicator of weak interaction with Fe^{3+}. The addition of H_2O_2 at low metal/ligand ratio could generate spectrum indicating the Fe(SIH), and $Fe(SIH)_2$ complexes. The free radical scavenging ability of BSIH was evaluated in *in vitro* deoxyribose assay. In this assay, significant decrease in absorbance (A/A0) was observed in the presence of BSIH which is an indicator of either radical scavenger activity or inhibition of Fenton reaction.

Multifunctional dopaminergic agonists

Hybrid drug design approach was adopted in order to develop bifunctional/multifunctional selective dopamine D3 agonists for the treatment of PD [117–122]. The known dopaminergic agonist moieties, i.e., aminotetraline or pramipexole, were merged with a fragment, N-arylpiperazine, derived from known D3 antagonist molecules. It was postulated that aminotetraline part of the molecules would interact at the agonist binding pocket, while antagonist fragment would fit into the accessory binding selectivity pocket. The major molecular modifications were centered on the accessory binding pocket responsible for D3 selectivity.

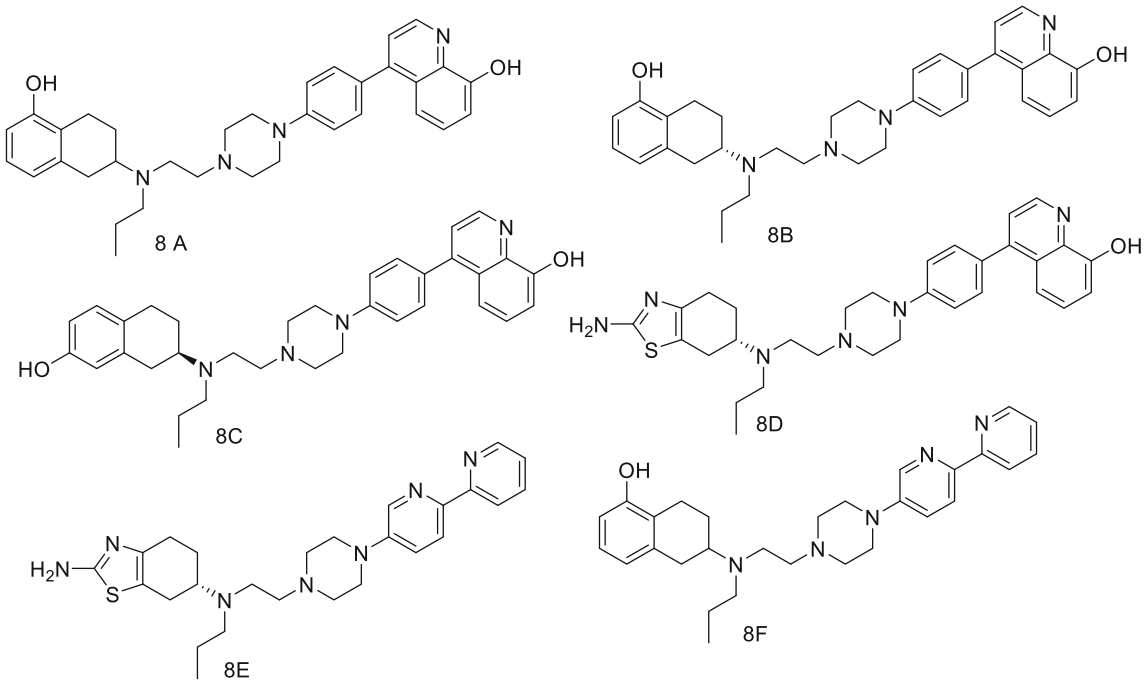


Fig. 8 Multifunctional dopamine D3 selective hybrid analogs for the treatment of PD 8HQ complex

Iron plays a very critical role in PD pathogenesis. Therefore, in vivo active polyfunctional selective D3 agonist molecules with an ability to chelate iron were developed by introducing the metal binding 8-HQ moiety into the piperazine fragment of the hybrid template [123]. It was rationalized that molecules with dopaminergic agonist (D2/D3) activity along with ability to chelate iron should provide not only symptomatic treatment but also be able to reduce the iron-induced oxidative stress. The enantiomerically pure compounds, 8B and 8C (Fig. 8) showed higher affinity at D2 and D3 receptors (Ki, D2 = 3.75, D3 = 1.28 nM for 8B; Ki, D2 = 4.55, D3 = 1.27 nM for 8C, respectively). Both the compounds displayed agonist activity at D2 and D3 receptors compared to natural agonist dopamine (EC_{50} D2 = 4.51 nM, D3 = 2.18 nM; D2 = 1.69 nM, D3 = 0.74 nM for 8B and 8C, respectively). The UV-based pH-dependent iron complexation study in the presence of 8B and $FeCl_3$ was carried out. Interestingly, 8B in the presence of $FeCl_3$ gave a different UV spectra compared to the 8B alone. Further, a bathochromic shift with increase in pH of the reaction mixture appeared due to complex formation. The mass spectrometric analysis of the solution produced the molecular ion peaks at M/z: 975, and M/z: 1434, 1435 which is corresponding to L2-Fe^{3+} and L3-Fe^{3+}, respectively. The Fe^{2+} and Fe^{3+} binding activity was monitored by ferrozine assay. This assay is based on measurement of absorption at 562 nm due to the ability of the lead molecules to liberate ferrozine from their iron complexes. At higher concentrations, 8D could solely make complex with Fe^{2+}. The lead compounds also exhibited potent in vivo activity in reserpine-induced hypolocomotion and 6-OHDA PD animal models. In another study, a multifunctional, in vivo active D3 selective agonist, along with ability to chelate iron and potent neuroprotective agent in MPTP mouse models, was discovered [124]. The lead compound, 8D, was found to have high affinity and efficacy toward D2 and D3 receptors (Ki, D2 = 27, D3 = 4.9 nM; EC_{50} D2 = 34 nM, D3 = 6.83 nM). The lead molecule, 8D, could form chelate with iron, and distinct shift in the λmax to the left was observed in UV-based pH complexation study. The compound was also tested for its ability to quench the free radicals using 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and deoxyribose assays. In addition, 8D could provide significant neuroprotection to animals against MPTP-induced dopaminergic cell death. The observation of this activity was rationalized on the basis of the ability of 8D to chelate iron and its antioxidant property in in vitro assays.

Recently, the authors introduced bipyridyl moiety, a well-established iron chelating fragment possessing preferential affinity toward Fe^{2+} into the designed hybrid analogs [125]. The rationale behind the design of such analogs is based on observation that the majority of the iron exists as Fe^{2+} in PD patients. Also, Fe^{2+} is responsible for generation of free radicals via Fenton reactions. Therefore, Fe^{2+} preferring chelators should provide better neuroprotection in PD. The lead molecule, 8E (D-607), exhibited potent activity at D2 and D3 receptors (Ki, D2 = 674, D3 = 13.4 nM; EC_{50}, D2 = 51.6 nM, D3 = 13.5 nM). The specific binding constants were calculated using UV–visible technique. The dissoci-

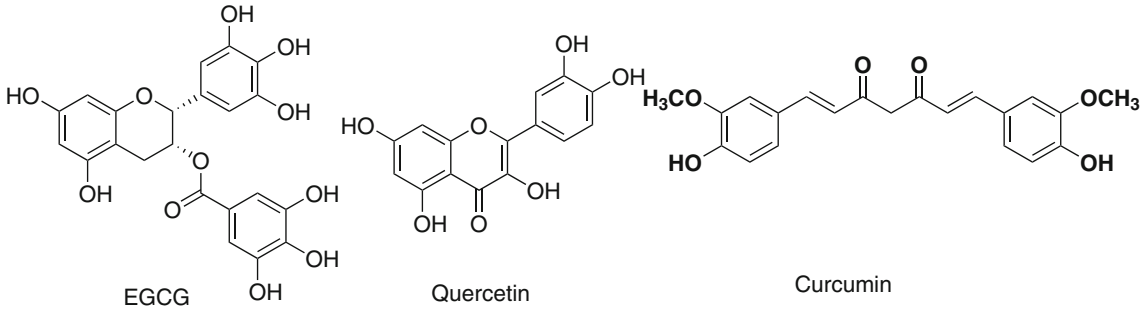
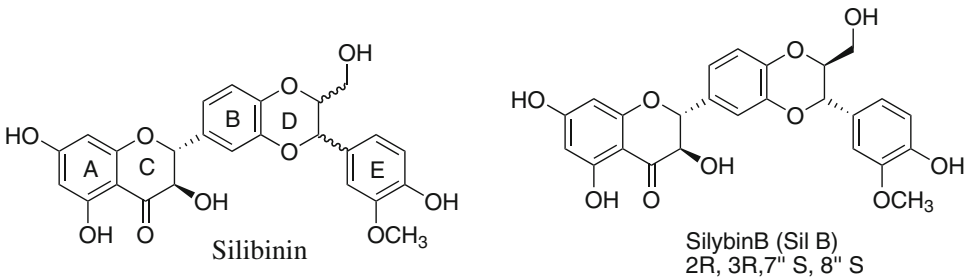


Fig. 9 Natural polyphenolic compounds possessing iron chelating property

Fig. 10 Chemical structures of Silibin and Silybin B



ation constant (K_d) was found to be 1.60×10^{-13} M for 8E. Further, it exhibited in vivo activity in reserpine-induced PD animal model and rescued PC-12 cells from toxicity of iron.

Natural products as iron chelators for NDDs

Secondary metabolites constitute one of the most important groups of natural products among the different plant species. The neuroprotective effects of dietary natural flavonoids are well documented in literature [81, 126]. The metal chelation property of flavonoids depends on their chemical structure, number of hydroxyl groups and their position. Natural antioxidants such as polyphenols and vitamins are potent chelators of ROS [127]. Polyphenols are excellent hydrogen donors that are accepted by reactive radical to yield much less reactive species. The antioxidant property of natural polyphenols is dependent on the presence on iron binding motif. The iron chelation ability of the natural products is predominating over radical scavenging which is responsible for antioxidant property [128]. Further, the prooxidant and antioxidant properties of flavonoids are depended on nature and concentration of flavonoids and metal species [129]. Epigallocatechin gallate (EGCG, Fig. 9), a metal chelators and antioxidant polyphenols from green tea, is able to provide neuroprotection activity in PD animal models [130, 131]. It is a potent metal chelator compared to other natural polyphenolic compounds. The Aβ aggregates formed in the presence of EGCG exhibited less cytotoxicity toward PC12 cells compared to Aβ alone [132]. The presence of 3′4′-dihydroxyl group in the B ring and 4-keto and 5-hydroxy in C ring are the pharmacophoric features required for the activity. It also regulates APP processing via IRE and reduces toxic Aβ species [133]. It has been shown that 6-OHDA-mediated neurotoxicity via upregulation of DMT1 through IRE/IRP could be reversed upon EGCG treatment [134]. The HIF-1 and IRP2-mediated iron-dependent proteasomal degradation becomes also inactivated by EGCG treatment [10]. EGCG can do two pronged attack on APP: first it reduces α secretase activity, thereby Aβ production goes down, and second, it decreases the amount of secreted Aβ peptides [131].

Quercetin (Fig. 9), a natural polyphenols, reduces intestinal iron transport through four different mechanisms [135]. 3-hydroxyl and 4-carbonyl groups of quercetin play a major role in iron chelation [136]. The neuroprotection mechanism of quercetin was attributed to its impact on various cellular pathways [137]. In a study focused on identification of polyphenols with potent iron chelating ability, quercetin demonstrated its ability to chelate both intracellular and extracellular iron [138]. Isothermal titration calorimetry (ITC) experiment indicated that quercetin binds with Fe^{2+} and Fe^{3+} with binding constants 8.3×10^5 and 3.86×10^6, respectively. Co-treatment of colonic epithelial cells with iron and quercetin for 24 h resulted in significant decrease in ferritin level compared to iron treatment alone presumable by chelating extracellular iron and inhibiting intracellular iron transport. Pretreatment with quercetin followed by co-treatment with iron to the cells reversed the increase in labile iron pool and ferritin expression, and decrease in the TfR1 and IRP proteins expression compared to iron treatment alone.

Table 1 Summary on the role of the iron chelators, pathology/mode of action in neurodegenerative disorders

S. no.	Name	Pathology/mode of action	References
1	Deferoxamine	Improves PD symptoms in MPTP-treated mice. Reduced $FeSO_4$-induced oxidative stress in SK-N-SH cell line	[77]
2	Deferiprone	MPTP and 6-OHDA animal models of PD. Rescue mitochondria from iron accumulation	[79]
3	Clioquinol (CQ)	MAO inhibitory activity, reverses iron-induced toxicity in MPTP-induced PD animal model	[88]
4	VK-28	Protect neuronal cells against 6-ODA-induced toxicity. Inhibits iron-induced lipid peroxidation	[94]
5	M30	MAO inhibitory activity in 6-OHDA, MPTP and lactacystin PD animal models	[97]
6	HLA 20	Selective MAO-B inhibitor Protect P19 cells against 6-OHDA-induced toxicity. Membrane lipid peroxidation inhibitory activity	[101]
7	PBT2	Reduces oligomeric Aβ in double-transgenic mice APP/PS1	[104]
8	Q1	Decreases mitochondrial iron accumulation and oxidative stress in animal models of PD	[105]
9	Q4	Rescues dopaminergic cells line, SHSY-5Y, against rotenone-induced oxidative damage	[105]
10	Hydroxypyridone (HP)	Antioxidant activity (free radical quenching agent) Decreases level of LDH and reduces formazan production	[108]
11	1-hydroxypyridin-2-one (HOPO)	Hydroxamic acid group provide neuroprotection in 6-OHDA-induced oxidative insult	[111]
12	PIH	Potent iron binding property	[112]
13	PCIH and H2NPH	PCIH gets oxidized into charged species known as IPH which binds with iron accumulated into reticulocytes Forms a complex and cross mitochondrial membrane and bind with iron accumulated into reticulocytes	[113]
14	SIH	Protecting group get removed by H_2O_2 and generation of phenolic compound SIH into active form	[115]
15	8B	Affinity toward D2 and D3 receptors (EC_{50} D2 = 4.51 nM, D3 = 2.18 nM)	[123, 124]
16	D-607 (8E)	Potent D2 and D3 receptors activity (Ki, D2 = 674, D3 = 13.4 nM; EC_{50}, D2 = 51.6 nM, D3 = 13.5 nM)	[125]
17	EGCG	Neuroprotection activity in PD animal models. Regulates APP processing via IRE and reduces toxic Aβ species	[130]
18	Quercetin	Ability to chelate both intracellular and extracellular iron. Decreases intracellular ferritin and inhibit intracellular iron transport	[135, 137]
19	Curcumin	Reverses iron-induced necroptosis in primary cortical neurons	[139]
20	Silybin	Neuroprotective in $Aβ_{25–35}$-induced mice model of AD. Metal chelating property	[145]
21	Silybin B	Promotes clearance of Aβ aggregates	[147]

Curcumin (Fig. 9), a polyphenolic traditional medicinally active compound, has been extensively investigated for its plethora of biological activities [139, 140]. The multitargeting ability of curcumin was attributed to its keto–enol tautomerization. Curcumin forms non-florescent 1:1 and 1:2 types of metal complexes [141]. It can reverse iron-induced necroptosis in primary cortical neurons [142]. The binding of curcumin with iron exhibited negativity cooperation with K_{d1} ~ of 0.5–1.6 μM and K_{d2} ~ of 50–100 μM [143]. Tremendous amount of efforts are going on to improve the bioavailability of curcumin; however, clinical efficacy is still remaining unclear [144].

Silymarin, active constitutes isolated from *Silybum marianum*, could provide significant neuroprotection in $A\beta_{25–35}$-induced mice model of AD [145]. Silymarin treatment drastically reduced the level of malondialdehyde, and 4-hydroxy-2-nonenal key markers of the oxidative stress. The polyphenolic nature of silymarin also imparts metal chelating property, thereby it provides relief from metal-induced toxicity [146]. Silibinin, a major component of silymarin exists as diastereoisomeric mixture of silybin A (Sil A) and silybin B (Sil B, Fig. 10) in equal proportion. The optical purity plays an important role in the biological activity (Table 1). So, the isolation, characterization and in-depth *in vtiro* and in vivo studies were carried out in AD models. Interestingly, Sil B was found to be most active in promoting clearance of Aβ aggregates and rescuing transgenic *C. elegans* from Aβ-induced toxicity [147]. Further, Silibin has been reported in the literature for anti-cancer and hematological disorders [148].

Challenges associated with iron chelators

A strong correlation is established between metal ions and onset of neurodegeneration; however, the clinic efficacy of such agents is still under investigation. The change in the biodistribution of metals with progression of the disease needs to be determined for the selection of specific metal chelators to be administered. Similarly, the metal selectivity and specificity of chelators are of paramount importance to avoid side effects associated with chelators [149]. The long-term safety, oral bioavailability, pharmacokinetic and pharmacodynamic properties are other unmet challenges in the development of such agents. Recent studies based on CQ treatment give an indication that metal redistribution might be an approach rather than metal chelation for treatment of NDD. Metal ions are key regulator involved in Aβ production and its mediated neurotoxicity. The ability to dissolve the existing Aβ aggregates should be reevaluated in preclinical and clinical studies. Several nanomaterials are under investigation to enhance the delivery of iron chelators in the brain [150, 151].

Conclusion

Iron plays a critical role in the NDDs via multiple mechanisms. It is vital for neurotransmitter synthesis and neuronal growth; however, excess amount of iron is responsible for the neurodegeneration. Therefore, several proteins and receptors are involved to regulate its concentration in peripheral and central nervous systems. Genetic and non-genetic factors also play a major role in regulation of iron homeostasis. It is also responsible for generation of toxic aggregates of proteins, which are causative agents for neurodegeneration. Currently, available treatments for NDDs focused to provide symptomatic relief without addressing the underlying pathogenetic factors such as iron accumulation. Therefore, there is urgent need for the development of novel treatment regimens addressing the symptomatic and basic factors involved in the disease process. In the last two decades, several small molecules possessing pharmacophoric features to chelate excess amount of iron are being investigated for effective management of neurodegeneration. Interesting, few such molecules have shown promising activity in preclinical and clinical trials. Further, these studies also provide an insight on pathogenesis and possible exploration of novel moieties to act as disease modifying agents. The development of multifunctional drugs for multifactorial diseases such as NDDs might open a new avenue in the drug development area. However, there are many unmet challenges associated with the iron chelation therapy. Current research in this field focused on the development of such agents which will hopefully add disease modifying properties to the current mostly symptomatic treatment regimen.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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