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Iron overload disease is a group of heterogeneous disease, which is caused either due to hereditary or acquired condition. Excess of iron participate in redox reactions that catalyzes the generation of reactive oxygen species (ROS) and increases oxidative stress, which causes cellular damage and encourage the cell injury and cell death. The electronic databases of Scopus, PubMed and Google Scholar have been intensively searched for the research as well as review articles published with the full text available and with the key words such as natural iron chelating agent, synthetic iron chelating agents, iron overload disease, oxidative stress and antioxidant which were appearing in the title, abstract or keywords. In light of the literature review presented in this artial, based on meta-analyses, we suggest that iron chelating agents were used for the management of iron overload disease. These agents were having wide spectrum of activity, they were not only used for the management of iron overload disease but also used as anticancer and antioxidant in various oxidative stress mediated diseases. Last from many years Desferoxamine (DFO) was used as standard iron chelator but currently two new synthetic iron chelators such as Deferiprone (DFP) and Deferasirox (DFS) are available clinically. These clinically available synthetic iron chelators were having serious side effects and certain limitations. Phytochemicals such as flavonoids and polyphenols compounds were having iron chelating as well as antioxidant property with no or minimal side effects. Hence, this review provides an updates on natural iron chelation therapy for the safe and efficacious management of iron overload diseases.

Keywords: Natural iron chelating agents, synthetic iron chelating agents, iron overload disease, oxidative stress, antioxidant

1. Introduction

Iron is an essential element for all living organism. It participates in various biochemical reactions like oxygen transport, electron transfer, energy metabolism and DNA synthesis. The biological action of iron is largely due to its chemical properties as a transition metal, although these properties make it potentially toxic. Total body iron
content of an adult is 3–5 g (~ 55 mg/kg for male and ~ 45 mg/kg female). Majority of body iron is incorporated within hemoglobin (Hb) (60–70%) as circulating RBC; while about 20–30% of iron is present in the form of ferritin and hemosiderin as a spare iron in hepatocytes and reticuloendothelial (RE) macrophages. Remaining body iron is primarily located in myoglobin and enzymes such as cytochromes, peroxidases, catalases, xanthine oxidase and some mitochondrial enzymes. A healthy adult absorbs near about 1–2 mg/day of iron from the diet, which reimburses the non-specific loss of iron by exfoliation of intestinal epithelial cells. Moreover menstruating women additionally losses iron during the menstrual cycle. Erythropoiesis daily requires about 30 mg of iron, which is largely provided by the recycling of iron through RE macrophages.

The dietary iron is absorbed from the small intestine and the normal level of iron is regulated by feedback mechanism between its requirement and absorption. The dietary iron is present either as haeme or as inorganic ferric iron (Fe3+). Absorption of haeme iron takes place directly without the aid of active carrier transport. However, haeme iron is a minor source of dietary iron. The primary source of dietary iron is Fe3+ which has to be reduced to ferrous (Fe2+) form by acid reducing agents for efficient uptake. Iron is transported across the membrane by two distinct transporters. The divalent metal transporter 1 (DMT1) present at luminal membrane carries Fe2+ into the intestinal epithelial cell. This Fe2+ and iron released from the haeme is transported across the basolateral membrane by another iron transporter ferroportin (FP). Gut has a mechanism to prevent the entry of excess iron in the body. After reaching to the intestinal epithelial cell, iron is either transported to plasma or oxidized to Fe3+ and complexed with apoferritin to form ferritin, the cytosolic protein in which iron is stored. Ferritin usually remains stored in intestinal epithelial cells for 2–4 days after that the cells were shed off. This process is called as exfoliation. Whenever the body iron is low, the ferritin is either not formed or dissociates quickly to release iron. This released iron is transported to the blood [1].

The free form of iron is extremely toxic. The Fe2+ on entering into plasma it is rapidly oxidized to Fe3+ and complexed with apotransferrin (Apo-Tf) a glycoprotein to form transferrin (Tf). Two Fe3+ residues bound to one Tf molecule. This complex bound to membrane bound transferrin receptor 1 (Tfr1), present on erythropoietic and other cells. The Tf–Tfr1 complex is engulfed by receptor mediated endocytosis. The endosomes of erythropoietic and other cells become acidified through engulfed proton complex, which leads to conformational changes, which dissociates iron from the complex. The released Fe3+ is reduced to Fe2+ and transported out of the endosomes by DMT1. This released Fe2+ is utilized for hemoglobin synthesis or other biochemical process; Apo-Tf and Tfr1 are return to the cell surface for further cycles. In iron deficiency and haemolytic anemia, Tfr1 receptors up regulation take place at erythropoietic cells, but not at other cells. Under physiological conditions, all circulating iron is bound to transferrin. Nontransferrin bound iron (NTBI) can increase in a pathological condition like iron overload disease (Figure 1) [2, 3, 14].

Once the iron enters the cell, the fraction that is not needed for immediate use is stored by ferritin and haemosiderin in RE cells of liver, spleen and bone marrow. Iron status of the body regulates the synthesis of apoferritin. When the iron status is low, the iron regulating element (IRE) at DNA is blocked and synthesis of apoferritin is not taken place, whereas more Tf is produced. Moreover excess of apoferritin is synthesized to trap iron when the iron store is high [4, 5].

The plasma iron obtained from three primary sources, firstly from constant degradation of older RBC (lifespan ~120 days), secondly from stored iron from RE cells in liver, spleen and bone marrow while thirdly from intestinal absorption. The conservation and recycling of iron are necessary to reload the iron contained within Hb. The recycling takes place at macrophage, which phagocytes the RBC and liberates iron in haeme form by haeme oxygenase-1 [6].
Daily excretion of iron in an adult male is approximately 1–2 mg, mostly as exfoliated intestinal epithelial cells, some RBCs and in bile. The primary route of excretion of iron is feces, while skin, urine and sweat are minor routes. In menstruating women, monthly menstrual loss of iron is about 0.5–1 mg/day. Excess of iron is required during last two trimesters of pregnancy for expansion of RBC mass, transfer to the fetus and to compensate the loss during delivery [7].

The iron homeostasis maintained by its controlled absorption, recycling and storage. The iron is regulating peptide hormone, hepcidin produced mainly by the liver, whereas a smaller amount is produced in other organs like lung and heart plays a vital role in this regards. Hepcidin act by degradation of FP, an iron efflux transporter, concerned about transportation of iron across the basolateral membrane in the intestine. Iron overload increases whereas anemia and hypoxia decrease the synthesis of hepcidin [8]. Hepcidin synthesis is regulated by bone morphogenetic protein (BMP)/SMAD pathway via activation of hepcidin transcription. The loss of hepatic SMAD4 gene results in iron overload due to the failure of hepcidin-mediated degradation of FP [9].

2. Determination of serum iron

The biochemical estimation of body iron status depends on serum based indicators, as follows:

1. Serum iron (SI)
2. Serum ferritin (SF)
3. Transferrin saturation
4. Soluble transferrin receptor (sTfR)
5. Erythrocyte protoporphyrin
These indicators present challenges for clinical practice and national nutrition surveys, and often iron status interpretation is based on the combination of several indicators (Figure 2). The diagnosis of iron deficiency through SF concentration, the most commonly used indicator, is complicated by concomitant inflammation. The sTfR concentration is an indicator of functional iron deficiency that is not an acute phase reactant, but challenges in its interpretation arise because of the lack of assay standardization, common reference ranges, and common cutoffs. However it is unclear which indicators are best suited to assess excess iron status. The value of hepcidin, non–transferrin-bound iron, and reticulocyte indexes is being explored in research settings. Serum based indicators are generally measured on fully automated clinical analyzers. Although international reference materials have been available for years, the standardization of immunoassays is complicated by the heterogeneity of antibodies used and the absence of physicochemical reference methods to establish “true” concentrations. The assessment of iron status in NHANES was based on the multi-indicator ferritin model. However, the model did not indicate the severity of iron deficiency and produced categorical estimates. Recently, iron status assessment in NHANES has used the total body iron stores (TBI) model, in which the log ratio of sTfR to SF is assessed. Together, sTfR and SF concentrations cover the full range of iron status. The TBI model better predicts the absence of bone marrow iron than SF concentration alone, and TBI can be analyzed as a continuous variable. Additional consideration of methodologies, interpretation of indicators and analytic standardization is important for further improvements in iron status assessment [10].

**3. Iron overload disease**

Iron overload disease is also known as haemochromatosis is a group of heterogeneous disease which is caused either due to hereditary or acquired condition. Iron overload disease is characterized by the accumulation of iron in the body with or without organ dysfunction [11, 12]. Iron overload is unavoidable since there is no physiologically regulated mechanism for excretion of excess iron. During iron overload, the low molecular weight iron can play an essential catalytic role in the initiation of free radical reactions. These free radicals have the potential to damage cellular macromolecules like lipids, proteins, carbohydrates and nucleic acids resulting in cell injury, impaired cell function and integrity or cell death. The rate of free radical generation determines the intensity of cell injury [13].

*Figure 2. Laboratory measurement of iron indicators needed to calculate transferrin saturation.*
3.1 Types of iron overload disease (haemochromatosis)

The haemochromatosis is classified into two main categories, namely primary and secondary haemochromatosis [14].

A. Familial or hereditary haemochromatosis (Primary iron overload).

a. Hereditary haemochromatosis (HH, HFE1).

i. C282Y homozygosity.

ii. C282Y, H63D heterozygosity.

iii. Other HFE gene mutations.

a. Juvenile haemochromatosis (HFE2).

b. Transferrin receptor 2 mutation (HFE3).

c. Ferroportin mutation (HFE4).

d. Aceruloplasminemia.

e. Atransferrinaemia.

f. Neonatal iron overload.

g. Autosomal dominant haemochromatosis (Solomon Islands).

B. Acquired haemochromatosis (Secondary iron overload).

a. Iron loading anemia’s.

b. Transfusional iron overload.

c. African iron overload.

d. Iron overload in chronic liver disease.

3.1.1 Familial or hereditary haemochromatosis (primary iron overload)

Hereditary haemochromatosis (HH, HFE1) is the most prevalent form of primary iron overload disease. HFE1 is an autosomal recessive disorder caused due to a mutation in HFE gene on chromosome 6, that resulting in iron overload and variable multiorgan dysfunction. More than 20 mutations of HFE gene were identified, but the most clinically significant mutations, however, are the C282Y and H63D. The C282Y mutation is a missense mutation that causes the tyrosine to replace cysteine at position 282, whereas H63D mutation is characterized by a histidine to aspartic acid substitution at position 63 in the HFE protein [15]. The H63D mutation may add to minor increases in serum iron levels, but in the absence of C282Y, there was no clinical significance of the H63D mutation. Approximately 85–90% of HFE patients were C282Y homozygotes while 3–5% of subjects with HFE may be C282Y/H63D compound heterozygous [16]. Another mutation of HFE gene is S65C
that leads to substitution of serine for cysteine, this kind of mutation also results into mild iron overload in the compound to heterozygous type HFE1 [17].

The C282Y mutation leads to disruption of a disulfide bridge that decreases the affinity of HFE gene towards β2 microglobulin and TfR1. This type of HFE gene mutation is retained in the Golgi complex [18]. This mutation resulted in decreased uptake of plasma transferrin-bound iron (TBI) by the duodenal crypt cells. This decreased uptake of iron would result into false iron deficiency even increasing total body iron stores that results into upregulation of iron regulating protein (IRP), DMT1 and ferroportin 1 (Fpn1) expression and increased iron absorption from the intestine [19, 20].

Mutation of a gene other than HFE gene is a rare genetic disorder of iron metabolism, also responsible for the development of the iron overloaded disease. Juvenile haemochromatosis, a type 2 haemochromatosis (HFE2) is a rare autosomal recessive disorder resulting in iron overload during the second and third decades of life. Some patients with HFE2 have mutations in hepcidin or hemojuvelin genes [21, 22]. Mutations of transferrin receptor-2 gene situated on chromosome 7q22 responsible for the development of transferrin receptor 2 mutations (HFE3) type of haemochromatosis. HFE3 is inherited in an autosomal recessive fashion [23]. HFE4 is caused due to mutations in ferroportin gene (IREG1, MTP1 or SLC11A3). It is inherited in an autosomal dominant fashion. These mutations are rare and should not routinely be screened for diagnosis purpose, but should be considered if HH cannot be diagnosed by conventional HFE gene mutations [24]. Other forms of hereditary haemochromatosis like aceruloplasminemia, atransferrinaemia, neonatal iron overload and autosomal dominant haemochromatosis (Solomon Islands) are rare conditions and they comprise of the very negligible proportion of inherited haemochromatosis [25].

3.1.2 Acquired haemochromatosis (secondary iron overload)

The ineffective erythropoiesis like thalassaemia, hereditary sideroblastic anemia and certain myelodysplastic syndromes, the hyperplastic erythroid marrow stimulate the iron absorption to a level that leads to the clinical iron overloaded condition. There is a direct relationship between erythropoiesis and iron absorption [26]. Each unit of blood contains 200–250 mg of iron. Chronic blood transfusion therapy is required in a condition like β thalassaemia, bone marrow failure and sickle cell anemia. Excess of transfusion, the iron load, initially accumulates in the RE macrophages but iron may deposit later in the parenchymal cells of the liver, heart, pancreas and endocrine tissue. Phlebotomy is not a treatment alternative because of the underlying anemia. Iron chelation therapy with Desferoxamine (DFO) administered continuous infusion is often the only option. Another oral iron chelator, Deferiprone (DFP) and Deferasirox (DFS) has been studied but has limitations in their efficacy [27].

Iron overload in sub-Saharan Africa was believed initially due to ingestion of large amounts of iron obtained from traditional home brewed beer fermented in non-galvanized steel drums. Moreover, only a few numbers of these beer drinkers acquire iron overload, suggesting that a genetic predisposition may be involved in the development of iron overload. This indicates that the gene locus is not related to the HFE gene, but maybe specific putative locus has not been identified [28]. Whereas heterozygosity for a common polymorphism (Q248H) in Fpn1 gene was identified in African and African-American person with iron overload [29].

Liver cirrhosis may increase the hepatic iron deposition. It seen in non-biliary cirrhosis likes alcoholic liver disease, chronic viral hepatitis and non-alcoholic steatohepatitis [30]. Very few cases were reported to have iron overload due to liver cirrhosis. The mechanism is not known, heterozygosity for the C282Y mutation in the HFE gene may play an important role [31]. In cirrhosis, there is a decrease in the
synthesis of Tf whereas an increase in the plasma NTBI levels, which may contribute to hepatic iron overload [32]. Reduced incorporation of iron into the RBC as well as reduced RBC lifespan in liver cirrhosis related hypersplenism, combined with portocaval shunting may also contribute to the liver iron overload [33].

3.2 Complications of iron overload disease

Iron overload may lead to produce organ complications such as liver failure (fibrosis and rarely carcinoma), cardiac abnormalities (cardiomyopathy, arrhythmias and heart failure), and hepatosplenomegaly. The other symptoms include chronic abdominal pain, weakness, fatigue, joint pain, arthritis, osteoporosis, arthralgia, loss of libido, impotence, infertility, hyperpigmentation of the skin, cutaneous atrophy, flattening of nails and loss of hair [12]. Endocrine abnormalities like diabetes mellitus, hypothyroidism, hypoparathyroidism, hypocortisolism, adrenal insufficiency, hypothalamic–pituitary dysfunction, pancreatic dysfunction, amenorrhea, delayed puberty and hypogonadism seen with iron overloaded patients [34]. Iron overload also leads to kidney damage [35]. Accumulation of iron in the brain may lead to neurodegenerative diseases like Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, corticobasal degeneration and superficial siderosis [36].

4. Iron chelator: pharmacology and toxicology

4.1 Concept and chemistry of iron chelator

Iron chelators typically contain donor atoms like oxygen, nitrogen or sulfur which form coordinate bonds with the bound iron. The donor atoms determine the preference of the chelator for either the Fe2+ or Fe3+ oxidation states [37]. Chelators that contain nitrogen and sulfur as donor atoms can prefer not only Fe2+ but also other divalent metals such as Cu2+ and Zn2+ [38]. Iron chelators may be classified by their binding structures. Bidentate iron chelator such as DFP requires three molecules each with two iron binding sites Fe3+ (3:1 ratio). A tridentate iron chelator DFS requires two molecules for Fe3+ (2:1 ratio); whereas hexadentate iron chelator, DFO binds Fe3+ in a 1:1 ratio [39]. Iron can coordinate six ligands in an octahedral arrangement. Hence DFO has the highest affinity for iron. The effectiveness of iron chelator determine by how wholly and efficiently it form the complex; thus affinity and stoichiometry of iron chelator play an essential role for its therapeutic effectiveness [40].

Iron chelators were mainly focused on the management of iron overload conditions due to multiple blood transfusions as the supportive treatment of disease like β-thalassaemia, sickle cell disease and myelodysplasia [41]. An iron chelator is having a broad spectrum of activity, they were not only used for the management of iron overload disease, but also as in the treatment of cancer due to their ability to sequester metals essential to tumor growth [42]. Other than the iron chelation, they also play an essential role as antioxidant in various oxidative stress mediated diseases like liver disease [43], ischemic reperfusion injury [44], atherosclerosis [45], diabetes mellitus [46], inflammation [47], infectious disease [48] and neurologic disease [49].

4.2 Current iron chelator

In current medicine, iron chelators include natural compounds derived from microorganisms such as siderophores and synthetic iron chelators were clinically used for the treatment of iron overloaded conditions.
4.2.1 Siderophores

Siderophores are the low molecular mass with high affinity iron chelating compounds that are secreted by the iron dependent microorganisms such as bacteria and fungi. They serve primarily as iron transport across the cell membrane. Wide range of siderophores is available such as Ferrichrome, DFO, Fusarinine, Ornibactin, Enterobactin, Bacillibactin, vibriobactin and Azotobactin. The commonly used siderophore is DFO [50].

4.2.1.1 Desferoxamine (DFO)

DFO is the most common clinically used siderophore. It has been used for the treatment of iron overloaded diseases last for decades and it remains the current standard for the iron chelation therapy [51]. The toxic effect of an excess of iron in iron overloaded disease is majorly due to NTBI; iron has both redox activity as well as ability to concentrate in highly vascular tissues such as hepatic, cardiac and endocrine tissue [52]. DFO is a hexadentate iron chelator, which can bind Fe3+ in a 1:1 ratio as shown in Figure 3. DFO is a multifunctional therapeutic agent, which can detoxify NTBI by its chelation property and heme proteins by ferryl reduction as well as free radical scavenging action. DFO also acts as a reducing agent, which prevent the oxidation of membrane lipids by removing high-oxidation states of heme iron, like ferryl myoglobin (Mb) or Hb [53].

Because of its high molecular weight (656.79), DFO is not orally bioavailable. Hence it is administered via subcutaneous injection at a dose of 50 mg/kg/day as a 10% solution in sterile water (0.50 or 2.0 g vials). Additionally, DFO has a short half-life of about 5–10 min, therefore to improve its efficacy; the required dose is injected over a period of 4–12 hrs via a small portable peristaltic pump. DFO is poorly metabolized by transamination, β-oxidation, decarboxylation and N-hydroxylation. DFO is excreted as its 1:1 complex with iron mostly in the urine and a small amount in feces [54].

4.2.2 Synthetic iron chelator

4.2.2.1 Deferiprone (DFP)

DFP is a synthetic oral iron chelator that has shown comparable efficacy to DFO and is more effective than DFO in the removal of excess iron from the heart. An advantage of DFP is that Fe3+ chelate of DFP carries no net charge and therefore, DFO-iron complex can easily penetrate the membrane. Additionally, the combination of DFO and DFP is widely used now a day without any new toxic effects [51].
The clinical DFP is used limited in thalassemia major; however, its use in agranulocytosis and arthropathy [55]. Bidentate iron chelator such as DFP requires three molecules each with two iron binding sites Fe³⁺ (3:1 ratio) as shown in Figure 4.

4.2.2.2 Deferasirox (DFS)

DFS is another synthetic oral chelator that has recently approved by US-FDA for the use in the treatment of iron overload diseases. DFS is effective in removing excess of iron from the liver. DFS has good tolerance, though monitoring is required for renal function [56]. DFS is as effective as DFO in maintaining the iron balance. The combinations of DFO and DFS or the combination of two orally active iron chelator DFP and DFS have been suggested as a treatment option for transfusional iron overload. DFS is used in the treatment of uncommon anemia like aplastic anemia, Diamond–Blackfan anemia and Fanconi’s anemia, which are associated with iron overload [57]. DFS is tridentate iron chelator DFS requires two molecules for Fe³⁺ (2:1 ratio) as shown in Figure 5.

4.3 Limitations of current iron chelation therapy

All these iron chelators are having severe side effects and certain limitations. The side effects and limitations of DFO include irritation at the infusion site, growth retardation, skeletal changes, ocular and auditory disturbances, hypersensitivity reactions and systemic allergic reaction such as rash, urticaria, anaphylactic
reaction, with or without shock and angioedema. DFO is an expensive drug and cannot be afforded by the majority of patients. The primary in a challenge with DFO therapy is patient’s adherence. DFO is having poor oral bioavailability and short $t_{1/2}$, therefore it is administered by slow subcutaneous infusion over a period of 8–12 hrs for 5–7 days/week. This leads to lower patient compliance. The slow subcutaneous DFO infusion affect quality of life as the slow infusion can produce troublesome, time-consuming and painful. Patient’s poor compliance resulted in gaps during chelation therapy, which leads to increase the plasma iron level, which causes further damage.

The major side effect of DFP is that it produces agranulocytosis, which can be reversed by discontinuation of therapy. The other side effects of DFP include gastrointestinal discomfort, arthropathy, increased liver-enzyme levels, low plasma zinc level, the progression of hepatic fibrosis associated with an increase in iron overload or hepatitis C and joint pain [58].

DFS produces various side effects such as agranulocytosis, gastrointestinal discomfort, skin rash, loss of hearing and visual impairment. Especially in geriatric patients and other patients with high risk of myelodysplastic syndrome, hepatic or renal impairment and thrombocytopenia are prone to develop hepatic failure, kidney failure and gastrointestinal hemorrhage with the use of DFS. Also, these agents are not suitable for use during pregnancy [59].

5. Herbal iron chelators

Due to these side effects and limitations, the use of synthetic iron chelators is suboptimal. Taking into account the paucity of iron chelating agents, scientists are putting their efforts towards the finding of therapeutically potential iron chelator to get maximum possible benefits with fewer harmful effects. Plants containing flavonoids and polyphenolic compounds possess iron chelating and antioxidant property [60, 61]. Due to the specific chemical structure of flavonoids, they can chelate iron and forms the soluble as well as stable iron-flavonoids complex.
<table>
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<tr>
<th>Plant</th>
<th>Family</th>
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<th>Part used</th>
<th>Type of study</th>
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<td>Aqueous and Methanol</td>
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</table>

**Table 1.** Natural Iron chelating agents.
Flavonoids possess three possible sites for metal chelating that can bind metal ions as follows (Figure 6).

i. 3-hydroxy-4-ketone groups in the C-ring

ii. 5-hydroxy group in the A-ring and 4-carbonyl group in the C–ring

iii. 3′,4′-dihydroxy groups, located on the B-ring.

The complex is then excreted in urine and feces [62]. Flavonoids and polyphenolic compounds illustrate their antioxidant activity through various mechanisms, such as free radicals scavenging, transition metals chelation and inhibition of various enzymes [63].

Some medicinal plants were reported to have In-vitro iron chelating potential, while other medicinal plants have been screened for In-vivo iron chelation activity, whereas some plants were clinically evaluated for the treatment of iron overload in β thalassaemia patients as showed in Table 1.

6. Conclusion

Chelation therapy is the preferred medical treatment for reducing the toxic effects of metals. Chelating agents are capable of binding to toxic metal ions to form complex structures which are easily excreted from the body removing them from intracellular or extracellular spaces.

Presently, siderophore like DFO and synthetic iron chelators such as DFP and DFS were used for the treatment of iron overload diseases. These iron chelators have severe side effects and certain limitations. As compared to siderophores and synthetic iron chelators, natural iron chelators are usually less toxic and have minimum side effects. Additionally, these medicines possess antioxidant property, which plays an essential role in the treatment of iron overload disease and its complications associated with oxidative stress. Therefore, need to search for more safe and effective treatment of iron overloaded disease has become an area of current research interest.
Natural Iron Chelators as Potential Therapeutic Agents for the Treatment of Iron Overload...
DOI: http://dx.doi.org/10.5772/intechopen.98749

Author details

Naheed Waseem A. Sheikh*, Satish B. Kosalge, Tusharbindu R. Desai, Anil P. Dewani, Deepak S. Mohale and Alok S. Tripathi
1 Hi-Tech College of Pharmacy, Chandrapur, Maharashtra, India
2 School of Pharmacy, RK University, Rajkot, Gujarat, India
3 P. Wadhwani College of Pharmacy, Yavatmal, Maharashtra, India
4 Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India

*Address all correspondence to: wsheikh2@gmail.com

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