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Hydrophilic Phytochelators in Iron Overload Condition

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ABSTRACT

Background: Iron overload can cause many complications and damage many organs as well as physiologic functions. Consumption of phetochemicals and flavonoids with iron chelating ability, instead of synthetic iron chelators, can be less harmful and more effective. The aim of this review is to investigate hydrophilic phytochelators in iron overload condition. **Methods**: In this review, the possible natural iron chelators including quercetin, rutin, bailcalin, silymarin, resveratrol, mimosine, tropolone, curcumine, catechin, kojic acid, and caffeic acid were investigated. Furthermore, the mechanisms through which they chelate iron were discussed. **Results:** The mentioned antioxidants eliminated excessive iron, decreased iron absorption, exerted antioxidant and anti-inflammatory activity without causing adverse effects and other metal deficiencies in iron overload condition. **Conclusion:** The combination of synthetic chelators with these antioxidants or their replacement with natural chelators could be possible treatments for iron overload.

Keywords: *Iron overload; Iron chelation; Iron chelator; Antioxidant, Flavonoid; Polyphenol.*

Introduction

The important role of iron in human body is undeniable. Iron is an essential cofactor for hundreds of proteins and enzymes that participates in oxidation and reduction reactions. It is also involved in red blood cell function, myoglobin activity, immune function, cognitive performance, brain function, as well as function and synthesis of neurotransmitters. Therefore, iron deficiency can cause multiple organ malfunctions. However, iron overload can be as destructive and dangerous as its deficiency (Barton, 2007).

Hemochromatosis is a hereditary condition with excessive iron absorption. Hemosiderosis is an iron storage condition that develops in individuals who consume abnormally large amounts of iron or in those with a genetic defect resulting in excessive iron absorption. Iron overload is also observed in thalassemia, cycle cell disease, and myelodysplasia, which is due to blood transfusion therapy transmitting 200 to 250 mg of iron to the patient's body per unit. Iron overload is attributed to a distinct gene that favors excessive iron absorption and absorbs the iron that exists in the

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diet. In other words, these patients experience severe iron toxicity (Gallagher, 2012).

Iron must be bound to proteins such as ferritin, hemosiderin, and transferrin to prevent its destructive effects, but by increase in the amount of iron, the liver fails to produce enough protein to store iron. Therefore, excessive free iron will be produced as a result. Since body cannot deal with this large amount of excessive iron, it deposits iron into organs such as the heart, liver, and endocrine organs, which leads to dysfunction of these organs. The consequences of this disease represent as liver dysfunction, cardiomyopathy, diabetes, and even death. Chemically, free iron is a highly reactive element that can interact with oxygen to form intermediates with the potential of damaging cell membranes, degrading DNA, oxidating LDL cholesterol, and finally damaging the cardiovascular system. It also helps to generate excessive amounts of free radicals that attack cellular molecules and develop carcinogenic molecules within cells (Hershko *et al.*, 2003, Shander *et al.*, 2009).

Chelation therapy removes excessive iron effectively. Desferrioxamine (DFO), deferiprone (L1), and deferasirox (1CL670) are currently available chelating drugs, which bind with Fe^{+} molecules from organs and eliminate them through urine or feces. However, regardless of their iron-removing characteristic, these drugs' serious adverse effects overshadow the patient's life. Desferrioxamine causes reactions at infusion sites, inducing hearing, vision, growth, and skeletal abnormalities, and Yersinia infection. Agranulocytosis, transient neutropenia, arthralgia, mild gastrointestinal symptoms, and mild aminotransferase elevation are caused by L1. Deferasirox induces skin rash, elevation of serum creatinine, mild gastrointestinal symptom, mild aminotransferase elevations, as well as hearing and vision abnormalities. Another problem of using such drugs is that they remove iron as well as other two valence metals such as zinc and cause micromineral deficiency (Barton, 2007).

Recently, biochemical studies highlighted the possible iron-chelating properties of flavonoids and polyphenolic compounds with at least two iron binding sites. These flavonoids are divided into two categories of lipophilic and hydrophilic chelators. Lipophilic chelators represent the opposite effect to L1 and DFO, increase iron absorption, minimize iron excretion, and increase deposition of excess iron in tissues. Therefore, they are considered to be a possible treatment for iron deficiency anemia. On the other hand, hydrophilic chelators are different. They eliminate excessive iron and decrease iron absorption in addition to exerting antioxidant and anti-inflammatory activity without causing adverse effects and other metal deficiencies (Kontoghiorghe *et al.*, 2015). The combination of synthetic iron chelators with these antioxidants or even replacing them with natural chelators would be a possible treatment for iron overload. Here are some natural hydrophilic iron chelators:

Quercetin

Quercetin is a member of flavones that mainly exists in apples, onions, tea, red wines, and berries. As experimental studies demonstrated, it possesses numerous beneficial effects on human health, many of which are correlated to its antioxidant capability. Quercetin can scavenge free radical species and has synergistic effects with enzymes and physiological antioxidants (Dolatabadi *et al.*, 2014). The catechol moiety is a possible site on Quercetin for the iron chelation and the high binding energy values indicate that Quercetin is a powerful chelating agent that can sequester iron to prevent its involvement in oxidation reaction (Leopoldini *et al.*, 2006).

Studies in iron-dextran induced iron overloaded mice showed that the injected Quercetin could reduce the hepatic iron overload, decrease serum ferritin, and increase the fecal excretion of iron (Zhang *et al.*, 2006). In another study hepatic and renal iron contents significantly decreased after Quercetin supplementation in a dose-dependent manner (Zhang *et al.*, 2011). Tang Y. et al found that quercetin alleviated ethanol-mediated suppression of hepcidin expression in mice (Tang *et al.*, 2014). Lesjack M. et al. also claimed that

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Quercetin could limit the rate of intestinal iron absorption and decreased subsequent basolateral iron efflux into the blood circulation in rats (Lesjak *et al.*, 2014).

Rutin

Rutin is a glycoside form of quercetin found in citrus fruit (Leopoldini *et al.*, 2006). Since rutin has two binding sites for iron (Guo *et al.*, 2007), it exerts its antioxidant effects by chelating ferric ions (Shimoi *et al.*, 1997). Rutin has a potent iron chelating activity in a dose dependent manner (Oke-Altuntas *et al.*, 2016), However, studies focused more on its free radical scavenging ability rather than iron chelation. Rutin was more effective in inhibition of free radical formation than L1 (Afanas'ev *et al.*, 2000). It also protects kidney by scavenging reactive oxygen species (Ferrali *et al.*, 1997).

Baicalin/ Baicalein

Baicalin and its aglycone, baicalein are the main effective components in the plants of genus Scutellaria (Lamiaceae) namely the root of S. Baicalensis Georgi and Xiao-chaihu-tang (Sho-saiko-to), a hepato-protective Chinese traditional herb medicine mixture (Ohta *et al.*, 1997). Most of the pharmacological activities of baicalin and baicalein are associated with their antioxidant and anti-inflammatory efficacies (Dinda *et al.*, 2017). Zhang Y. et al. found that baicalin could release iron from ferritin and increased its excretion through feces (Zhang *et al.*, 2006). Baicalin can also gradually combine with hepatic non-heme iron, take it into blood stream, and finally excrete it from body (Zhao *et al.*, 2005). However, it is hard to segregate the iron chelation and free radical scavenging activity of baicalin. Furthermore, scarce studies have been conducted on its iron chelating ability; so, this hypothesis needs further experimental support (Yoshino and Murakami, 1998).

Silymarine/ Silibin

Silymarin and its main component, silibin are polyphenols found in milk thistle (Borsari *et al.*, 2001). Silymarin is known to be a powerful iron chelator, which is capable of depleting iron stores and reducing serum ferritin (Hagag *et al.*, 2013). It also reduces intestinal iron absorption by reducing serum level of hepcidin. In other words, lower ferritin levels inhibit the release of extra hepcidin (Moayedi *et al.*, 2013). Although silymarin can effectively reduce serum iron level, it cannot decrease iron deposition in kidney, heart, and liver, even when coadministered with DFO (Adibi *et al.*, 2012). Combined therapy with silymarin and DFO can be more effective in serum ferritin reduction than DFO alone, but combination of L1 and silymarin is not different from L1 alone (Hershko, 2010).

Some studies investigated silibin's affinity for ferric iron. The bioavailability of silibin is higher than silymarin. It can form iron complexes at acidic PH and reduce non heme iron absorption (Borsari *et al.*, 2001, Loguercio and Festi, 2011).

Considering the antioxidant and free radical scavenging abilities of silymarin and silibin alongside iron chelation, they can be a possible chelation therapy for chronic iron overload (Borsari *et al.*, 2001).

Resveratrol

Resveratrol is a flavonoid found in red wine and is mostly popular for its antioxidant effects especially on cardiovascular diseases. However, very little is known about its iron chelating ability. Recent studies suggested that the resveratrol's antioxidantive function might be due to its iron chelation (Imam *et al.*, 2017) since resveratrol and its analogs contain catechol moiety (Mazzone *et al.*, 2013). Resveratrol has been known to reduce bone loss (Zhao *et al.*, 2015) and protect liver (Das *et al.*, 2016) in iron overload condition. A study showed that oral administration of resveratrol could attenuate cardiac iron overload in hemochromatosis patients (Das *et al.*, 2015). Therefore, it may be able to reduce iron deposit in organs. More investigations can clarify the metal binding ability of this flavonoid and its possible role in iron overload diseases.

Mimosine

Mimosine is produced in Leucaena, a legume growing in tropical region (Barros-Rodríguez *et*

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al., 2014). Human clinical studies showed that leucaena could be well tolerated up to 5g twice daily, but many toxic side effects were reported in animals feeding on leucaena leaves and seeds. It is believed that mimosine and its goitrogen metabolites are responsible for the side effects; therefore, mimosine has not been used in human studies (Hegarty *et al.*, 1979). However, it has been identified to be effective in animal models for the treatment of iron overload and inhibition of free radical formation (Kontoghiorghes *et al.*, 1986a).

Mimosine has an α-ketohydroxypyridine binding site, which has high affinity for iron and can form stable iron complex in the case of oral consumption (Kontoghiorghes *et al.*, 1987). Different studies suggested different mechanisms for mimosine affecting iron metabolism. A study in rabbits showed that mimosine could excrete iron through urine (Kontoghiorghes *et al.*, 1993). Another study in mice showed that hydrophilic phytochelators such as mimosine reduced iron absorption and inhibited the transfer of iron in many cell types (Kontoghiorghes, 1990a). Some studies compared mimosine to synthetic iron chelators. Kontoghiorghes showed that the ability of mimosine in mobilizing and removing iron from human transferrin was just slightly lower than L1, while DFO and deferasirox were not effective in mobilizing iron (Kontoghiorghes and Evans, 1985). The amount of iron excreted through urine using mimosine was the same as the amount of L1 at the same dose (Kontoghiorghes *et al.*, 1993). The mimosine's ability to reduce iron absorption was also the same as DFO (Kontoghiorghes, 1990a).

Tropolone and its derivatives

Tropolone is another phytochemical found in plants including Red Cedar, Cupressus Llusitanica, Thuja Plicata, etc., but it is not used as a food product (Saniewski *et al.*, 2007). Its oral activity was mostly studied in animal models. Tropolone has a high affinity for iron and forms insoluble iron complexes in oral administration, which decreases iron absorption (Kontoghiorghes, 1990b). It also transfers iron across the cell membrane and increases the uptake and incorporation of iron in cells and haem (Kontoghiorghes *et al.*, 2004).

The toxicity and convulsion observed in animals consuming tropolone hampered further human studies on its iron chelating property. Tropolone was more effective than L1 and DFO in iron excretion. In one study, tropolone was used in a dose, which was 10 times lower than its natural amount found in its dietary sources (20 mg/kg). The results showed that it could excrete iron at equivalent amount as L1 and DFO, but it remained toxic (Kontoghiorghes *et al.*, 1993). Therefore, tropolone is still determined as an effective treatment in iron overload condition.

Purpurogallin is a red pigment with the tropolone ring in its molecule; in other words, it is a biologically active homologus of tropolone. It also can be obtained by oxidation of pyrogallol, which is an antioxidant found in plants like Myriophyllum Spicatum (Inamori *et al.*, 1997). Both purpurogallin and pyrogallol can increase iron excretion and inhibit noxious effects of free radicals induced by iron overload (Kontoghiorghes *et al.*, 1986b). Hinikitol is another tropolone derivative found in the farms of cupressaceous plants that has been widely used in food as an antimicrobial agent (Nakano *et al.*, 2006). Hinikitol is known to play its antioxidant, anti-inflammatory, and anticancer roles by chelating iron (Jayakumar *et al.*, 2013).

Curcuminoids

Curcuminoids are the phenolic yellowish pigment of turmeric or Curcuma longa L. that has been widely used as a coloring agent and spice in many foods. Curcuminoids and its structurally related compound, curcumin, has been known to possess antioxidant and anti-inflammatory properties (Asai and Miyazawa, 2000). Recently, its ferric iron binding capacity has been focused because it is a possible treatment for thalassemia and other iron overload diseases (Srichairatanakool *et al.*, 2007, Thephinlap *et al.*, 2009).

In vitro studies have shown that curcumin is able to reduce hepatic ferritin synthesis and decrease iron level in bone marrow, splin, and liver. It can reduce

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hepcidin expression, which means that curcumin exerts its iron chelating properties independent of hepcidin. Curcumin could also activate iron-responsive element-binding protein (IRP) and transferrin receptor 1(TfR1) in mice and induce iron deficiency (Jiao *et al.*, 2009). These properties in addition to its modulating redox state and attenuating oxidative stress-induced inflammation (Niu *et al.*, 2016) makes curcumin a potent remedy for iron overload condition.

Catechin and its derivatives

Catechins are strong antioxidants with metal binding capacity, mostly found in green tea and cocoa bean (Yang *et al.*, 2014). They have a catechol moiety metal chelating site through which they bind iron and make insoluble iron complexes (Zijp *et al.*, 2000). Epigallocatechin gallate (EGCG) is a member of catechin family with an extra gallate chelating site, which makes it a stronger iron chelator than catechin and other substituents on the catechol ring that increases its stability (Kontoghiorghe *et al.*, 2015).

The iron chelating activity of EGCG was studied in a few investigations. The results showed that this flavonoid not only helps to restore balanced redox status in patients with iron overload, but also reduces the basolateral iron export in caco-2 cells. So, it reduces iron absorption through gut lumen (Ferlazzo *et al.*, 2016, Ma *et al.*, 2011). Another study reported that EGCG did not impair non-heme iron absorption in women with iron deficiency (Ullmann *et al.*, 2005). It clarifies that EGCG reduces iron absorption only in iron overload condition.

Caffeine/ Caffeic acid

Caffeine is a well-known plant alkaloid found in leaves, seeds, and nuts of a number of plants. It is a major constituent of coffee, cocoa, tea, cola drinks, and chocolate (Ding *et al.*, 2014). Caffeine does not have any metal binding activity, but is conjugated to DFO to improve its cell permeability. DFO-caffeine complex has both iron-scavenging ability and antioxidant properties (Alta *et al.*, 2014, Huayhuaz *et al.*, 2017). Conversely, caffeic acid is known to be an iron chelator, apart from its antioxidative and anti-inflammatory activity (Perron and Brumaghim, 2009, Srichairatanakool *et al.*, 2006). Caffeic acid is a caffeine's derivative found in many plants and occurs in diet as part of fruits, vegetables, tea, and wine (Clifford, 2000).

Caffeic acid has iron binding affinity due to its catechol moiety (Kontoghiorghe *et al.*, 2015). It inhibits free radical formation through both iron chelation and antioxidant activity (Ikeda *et al.*, 2011). Nevertheless, investigations demonstrated that caffeic acid is less effective than catechin in inhibiting the reactive oxygen species formation (Matsui *et al.*, 2017). It also did not cause much increase in iron incorporation in red blood cells in comparison to tropolone (Kontoghiorghes, 1988).

Kojic acid

Kojic acid is a by-product in the fermentation process of malting rice to be used in the production of Sake, the Japanese rice wine (Bentley, 2006). Its phenolic hydroxyl group makes it a bidendate metal chelator and it is considered as a potent iron chelator (Kotyzova *et al.*, 2004, Nurchi *et al.*, 2011, Ochiai *et al.*, 2012). Kojic acid is also a potent antioxidant and is potentially capable to target oxidative stress pathways (Mohammadpour *et al.*, 2013).

Different studies investigated the antioxidant and iron removal activity of kojic acid in comparison with other natural and synthetic iron chelators. Kojic acid is found to be less effective than catechol in inhibition of oxidative damage (Kontoghiorghes *et al.*, 1986b). It was also less effective than L1 and mimosine in iron mobilization and inhibition of lipid peroxidation (Mostert *et al.*, 1987). Kojic acid could not reinforce iron incorporation in red blood cells (Kontoghiorghes, 1988). So, kojic acid is a powerful iron chelator, although it is less powerful and effective than other chelators.

Discussion

The body iron should be kept in its normal range. Extra iron can contribute to detrimental Reactive oxygen species (ROS) generating process and cause inflammation. It also causes many

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complications by precipitating in different organs, especially heart, liver, and endocrine organs. Hence, chelation therapy is used in iron overload condition to bind excess iron within the system and remove it from the body. Although thalassemic patients can survive up to the age of 70 years by management of synthetic iron chelators, it should be noted that synthetic iron chelators are still toxic in high doses. A proper iron chelator must be orally active with the lowest toxicity and cost. Nowadays, a large number of patients do not receive any chelation treatment considering the high cost, toxicity, and unpleasant complications of treatments with synthetic iron chelators. In this study, orally active antioxidants were introduced with their possible iron chelating and free radical scavenging capabilities besides their lower cost, toxicity, and complications compared to the synthetic drugs. These natural chelators make complexes with metals in concentrations higher than the physiologic concentration. Therefore, they treat iron overload without causing any other micromineral deficiency. This advantage is lacked in synthetic drugs.

Quercetin, rutin, bailcalin, silymarin, resveratrol, mimosine, tropolone, curcumine, catechin, kojic acid, and caffeic acid contain catechol or gallate moiety that are known as metal binding sites. Iron binds to these sites and eliminates from the body with the help of them. Few in vitro studies provided us with some limited knowledge on mechanisms of iron chelation. Some studies only investigated their antioxidant activity without clarifying whether this effect was due to scavenging reactive oxygen species or chelating excessive iron. Besides iron chelation and free radical scavenging, these antioxidants can be effective in iron overload condition by reducing liver iron load, increasing fecal and urinary excretion of iron, reducing serum ferritin, removing iron from ferritin and transferrin, increasing hepcidin expression, reducing intestinal iron absorption, increasing the uptake and incorporation of iron in haem, as well as inducing osteo- and cardio-protective effects. We should also keep in mind some of these antioxidants' toxic properties and the fact that they should be used in very low doses to be safe.

Some studies focused on foods, but not the antioxidants. African walnut (Olabinri *et al.*, 2010), wheat grass extract(Pole, 2006), and green tea extract (Al-Basher, 2019) showed iron chelating activity, which is probably caused by iron chelator antioxidants that they contain. Other natural compounds also exist with possible iron chelating activity, which have not been investigated yet. These compounds include citrate, nicotinamine, muginic acid, fulvic acid, and humic acid containing carboxylic acid metal binding site (Fang *et al.*, 2015, Korkina and Afanas'ev, 1997, Namba and Murata, 2010, Van Schaik *et al.*, 2008, Weber *et al.*, 2008, Yang and Van Den Berg, 2009). Considering the confined and incomplete knowledge on these compounds' iron chelating ability, we can only guess about the effectiveness of these natural chelators in iron overload conditions. Myrecitin, Ferulic acid, vitamin C, Mevidol, and Anthocyanins can also affect the iron metabolism by reducing hepcidin expression, releasing iron from its stores, increasing serum iron, and reducing the iron-induced inflammation. Yet, they have not shown any iron binding affinity (Imam *et al.*, 2017).

To determine the possible clinical application of these natural chelators in hemochromatosis, thalassemia, and other iron overload diseases, more investigations are needed to figure out their cellular mechanism of action and clarify the role that iron chelation plays in relation to their anti-inflammatory activity. Some appealing subjects for future studies can be on their bioavailability, safe dosage, most effective way of administration (oral or parenteral), best intervention period, and combined administration of these natural chelators together or with synthetic chelators.

Conclusions

Natural iron chelators are more reliable and safer than the synthetic ones. Application of natural iron chelators alone or with synthetic chelators in iron overload condition can be of less harm and more benefit for patients.

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Conflict of interest

The authors declare that they have no conflict of interest. They also did not receive any financial support for this study.

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Authors' contribution

Study concept, design, and drafting were prepared by Sajadi Hezaveh Z. Shidfar F did the critical revision of the manuscript for important intellectual contents.

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