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Natural Iron Chelators: An Orthomolecular Approach to Treat Iron Overload and Its Related Diseases

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Abstract: Despite its various vital roles in the different body's metabolisms, iron may have a hazardous impact on health when it exceeds its normal values. Iron overload is triggered by many genetic and behavioral factors. Furthermore, excessive iron levels have also been observed in many pathologies such as Alzheimer's, Parkinson's, cardiovascular and some cancerous diseases. This paper describes a set of natural iron chelators as an effective and a safe orthomolecular approach in chelating iron. Orthomolecular medicine is based on providing patients with nutritional supplementation at high doses to treat and prevent diseases. This paper describes the properties of a set of flavonoids and phenolic acids such as curcumin and ferulic acid that can be administered as supplements to patients suffering from iron overload since they are classified as strong chelators. Those natural iron chelators' supplements are mainly extracted from fruits, vegetables, and plants. As chelators, they are able to bind effectively to iron, inhibit the production of reactive oxygen species, and reduce the levels of oxidative stress. They can also play an effective therapeutic role in the treatment of neurodegenerative, cardiovascular, diabetic, and cancerous diseases thanks to their iron chelation, antioxidant, and anti-inflammatory properties.

Key words: Iron, natural iron chelators, iron overload, flavonoids, phenolic acids, neurodegenerative diseases, cancerous diseases, orthomolecular medicine.

1. Introduction

Iron is a trace metal that plays many vital roles in the human's body. It is the main factor in transporting oxygen from the lungs to the different body's tissues through the Hemoglobin protein. After delivering oxygen, iron binds carbon dioxide and transfers it to the lungs where it gets exhaled. Iron is also bound to oxygen in the myoglobin protein that is located in the muscles and that can be used as a source of oxygen when blood oxygen delivery becomes limited under intense muscular activities. Furthermore, iron is responsible of producing red blood cells through the haematopoiesis process and is a cofactor in many other enzymatic reactions such as the transfer of energy and electrons within the cells by the cytochrome enzyme [1].

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Iron is stored in cells bound to the ferritin molecule and in the blood bound to the transferrin protein. Serum ferritin is the most popular and cost-effective laboratory test applied to estimate body iron level. The normal iron range for males is between 10-220 μg/L, and for females is between 10-85 μg/L [2]. To ensure that the vital activities of iron are executed properly, normal iron levels are continuously preserved through a tight homeostasis process that inhibits any deficiency or excess in iron values [3]. However, a set of genetic, behavioral and pathological factors can dysregulate iron levels and lead to the accumulation of iron ions in excessive values in the organs [4]. Those elevated iron levels promote the production of free radicals, and increase the levels of oxidative stress. Under those morbid conditions, iron becomes a risk factor for many lethal pathologies such as Alzheimer's, Parkinson's, atherosclerosis, cancer, osteoporosis, cardiomyopathy, and diabetes [4].

Despite the effectiveness of phlebotomy and synthetic iron chelators in treating iron overload, many morbid side effects were reported such as thrombosis, hearing abnormalities, and renal failure [4, 5]. By applying one of the main principles of the orthomolecular medicine that is based on providing patients with nutritional supplementation at high doses to treat and prevent diseases, natural iron chelators' supplements may represent an effective and a safe alternative in treating iron overload. This paper presents the characteristics of a set of flavonoids and phenolic acids that are known for their strong iron chelation potential and that can be administered as supplements to patients suffering from iron overload. Furthermore, both of those natural iron chelators are mainly extracted from fruits, vegetables, and plants. Besides their chelation property, this article is also describing the antioxidant, anti-inflammatory, anti-carcinogenic, cardio-protective, and neuroprotective qualities of those chelators, which classify them as effective therapy agents in diseases that are characterized by excessive iron levels.

2. Flavonoids

2.1 Curcumin

Curcumin is a Flavonoid Polyphenol from the rhizome of *Curcuma longa*, the active ingredient in the Indian spice turmeric that is recognized for its iron-chelating properties. As an iron chelator, curcumin decreases the levels of the iron storage proteins ferritin and transferrin [6]. As a result, iron accumulation decreases within liver and spleen and reactive oxygen species are scavenged [7]. To activate its therapeutic benefits, the bioavailability of curcumin is boosted by combining it with other elements namely piperine, liposomes, phytosomes, polymeric micelles, peptide carriers, phospholipid complexes, micro-emulsions, and nanoparticles [8].

Through its chelation, antioxidation and anti-inflammatory properties, curcumin can also be part of the therapeutic strategies of a set of diseases that are characterized by high iron levels. For instance, curcumin shows a great potential in treating neurodegenerative pathologies such as Alzheimer's and Parkinson's diseases by preserving the structure and the function of the cerebral vessels and the mitochondria [9]. Furthermore, Parkinson's patients' locomotion is improved through oral and intravenous administration of curcumin [10]. Curcumin's drug delivery in the format of polymeric nanoparticles, liposomes, and peptides is also effective in targeting cancer cells in many cancer types such as breast cancer, lung cancer, head and neck squamous cell carcinoma, and prostate cancer [11]. Besides the inhibition of carcinogesis and brain tumors, curcumin is known for its great potential in treating other iron accumulation diseases such as type 2 diabetes [12].

2.2 Kolaviron, Floranol, and Pycnogenol

Other natural chelators' supplements from different origins are also known for their iron chelation and therapeutic benefits. Kolaviron, which is a garcinia biflavonoid extracted from the seeds of *Garcinia kola* and originally found in West African countries, is another iron chelator that blocks the oxidation of lipoproteins [13].

Another flavonoid that is known for chelating iron is floranol, which is extracted from the roots of *Dioclea grandiflora* located in the coastal plain of north-eastern Brazil. Floranol has the ability to bind effectively to iron and to reduce the atherosclerosis plaque by inhibiting the production of free radicals and the oxidation of the low-density lipoproteins [14].

Pycnogenol is among the flavonoids that are distinguished by their high bioavailability and high solubility. It is extracted from the French maritime pine tree and can combine strongly with ferric iron, which classifies it as a potential iron chelator and a free radicals scavenger [15]. Pycnogenol is also recognized for its neuro-protective benefits and improvements of sustained attention, memory, and executive functioning [16]. In addition, pycnogenol

can prevent cardiovascular diseases by stimulating antioxidant enzymes such as glutathione and blocking the production of free radicals [17].

2.3 Baicalein, Quercetin, and Catechins

Baicalein is a Chinese flavonoid whose supplements are composed of herbal extracts from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflor* [18]. Through the active metabolite baicalin, iron is chelated and the OH radical production is inhibited [19]. Baicalein is also characterized by its anti-inflammatory property, and by inducing apoptosis in cancer cells, which makes it an ideal candidate in the treatment and the prevention of many neurological and cancerous diseases such as Alzheimer's, Parkinson's, and leukemia [20, 21].

Besides its iron chelation property, quercetin is another flavonoid that is known for its therapeutic benefits. It can be extracted from vegetables and fruits especially onions, broccoli, apple, and berries. It can also be found in bee hives, olive oil, nuts, and tea [22]. When administered to thalassemia patients, quercetin reduces ferritin and inflammation [23]. It can also protect from UV radiation and certain types of cancer such as hepatic cancer [24, 25].

Catechins are classified as flavanols from the Flavonoid family that is characterized by its proven iron chelation and its role in treating various pathologies. Catechins can be found in many fruits and vegetables such as apples, blackberries, cherries, black grapes, pears, raspberries, black grapes, strawberries, apricots, and broad beans. Chocolate and rock-rose leaves are also a rich source of catechins [26]. However, the highest concentration of catechins is found in green tea leaves that are mostly composed of the epigallocatechin-3-gallate. Green tea catechins are effective in reducing the risk of stroke and coronary heart disease. Moreover, catechins have a great potential in blocking carcinogenesis, tumor growth, cancer cell invasion, and tumor angiogenesis [26]. To improve the bioavailability of catechins, their supplements are produced by applying nanotechnology [27].

3. Phenolic Acids

Besides chelating iron, many phenolic acids can be applied in treating various diseases. Phytic acid or inositol hexaphosphoric acid is a phenolic acid found mainly in cereals, legumes, oil seeds and nuts [28]. It is an anti-nutrient component since it inhibits the absorption of some minerals such as iron, which makes it a potential chelator in the case of iron overload [29]. Under excessive iron concentrations in the body and high oxidative stress levels, Parkinson's patients can benefit from Phytic acid in preserving their dopaminergic neurons from apoptosis [30].

Ferulic is another phenolic acid that is widely found in fruits and wheat bran [31]. Through its sodium salt, sodium ferulate, ferulic acid blocks the production of free radicals that are induced by iron excess and increases hepatic cells viability [32].

Known for its antioxidant and iron chelation properties, caffeic acid is a phenolic compound found mainly in coffee beans [33]. Caffeic acid can also reduce toxicity and inflammation especially in the neurons of Alzheimer's patients [34].

The combination of caffeic acid with quinic acid, which is also a strong iron chelator, leads to the creation of chlorogenic acid (CGA) [35]. CGA is a strong antioxidant and chelator found widely in fruits, vegetables, and coffee [36]. It can block the production of reactive oxygen species or scavenge them directly [37]. In addition, CGA protects neurons from glutamate excitotoxicity and ischemia [35]. CGA can also be part of the treatment of diabetes, cardiovascular diseases, obesity, inflammation, and cancerous tumors [38].

4. Conclusion

Iron chelation through supplementation that is based on flavonoids and phenolic acids is a promising alternative in the treatment of iron overload. In

addition, flavonoids and phenolic acids take part effectively in the therapies of many carcinogenic, cardiovascular, neurodegenerative and diabetic diseases as it was described in this paper. Nonetheless, more clinical studies are required to emphasize the efficacy of those natural chelators, and to define their effective therapeutic doses. In addition, combination of chelators in iron overload cases could represent an interesting research issue. Finally, iron supplementation should be monitored carefully especially when there is no medical evidence of iron deficiency such as in the case of pregnant women where systematic administration of iron should be reviewed to avoid any iron excess that may lead to gestational diabetes [39].

Conflict of Interest

The authors have declared no conflict of interest.

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