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Redox-Active Biofactors and their Possible Metabolic Relevance

Amandio Vieira[1*]

Some aspects of the prooxidative actions of iron and heme are presented, with the possible antioxidant (or prooxidant) activities of plant food components, phytochemicals. Perspectives for such redox metabolism are briefly discussed in a broader context of phytochemical bioactivity and pathophysiology. The references cited typically represent a few examples taken from a vast body of work on the topic, or examples of research on related topics for comparison purposes.

Phytochemicals, Iron Sequestration, and Iron Release

Excess levels of redox-active iron in the body contribute to a wide range of diseases, including major chronic diseases that afflict developed countries, e.g., some types of cancer, type 2 diabetes, and major cardiovascular diseases. The role of iron in these different pathologies is complex. A Fenton chemical reaction by which iron (ferrous) is likely to contribute to oxidative damage and some pathological processes is shown in the Figure 1. Forms of hereditary haemochromatosis are examples of iron-excess conditions, but other such conditions are also widespread; and they can differ greatly in the severity of iron-overload [1-4]. In this context, for example, iron-rich diets may increase the risk of colorectal carcinoma [5-7].

In contrast to this prooxidative context, there is much evidence that increased consumption of vegetables, fruits, and other plant foods (e.g., tea) leads to a decreased risk of some of the same chronic diseases, and is typically associated with lower indicators (end products) of oxidative damage [8,9]. The relatively low caloric density and content of possible beneficial factors-dietary fibre, vitamins, and other phytochemicals are likely to contribute to the health benefits of plant foods.

In terms of molecular mechanism that contribute to the health benefits of plant foods, sequestration of iron (and other transition metal ions) by phytochemicals and their metabolites, and prevention of excessive iron accumulation, may be of major importance. Chelation of iron by different classes of phytochemicals has been reported in various studies, reviewed in [3]. Polyphenols such as flavonoids and many others are known as scavengers of reactive chemical species, but their potential health benefits may involve more indirect antioxidant activities such as chelation of iron and other redox active elements. Such phytochemicals may lead both to decreased iron absorption in the gastrointestinal tract [10,11], and to

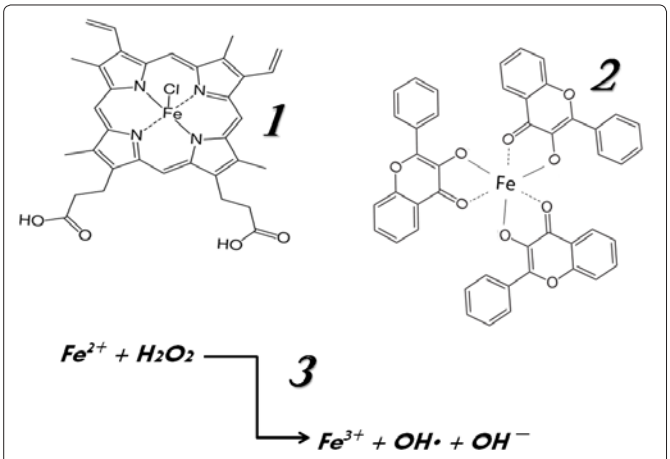

Figure 1:
1. Ferric iron bound by porphyrin; and **2.** by three flavonol core structures, 3-hydroxyflavanones, based on [24]; **3.** Ferrous iron can catalyze hydroxyl radical (OH •) production in a Fenton reaction.

sequestration of body iron (intracellular and extracellular) such that less redox-active-unliganded or poorly liganded [12] iron is available for production of hydroxyl radicals and other damaging reactive chemical species.

Plant foods are not sources of heme iron. This form of iron, abundant in red meats and other animal foods, has also been associated with some chronic diseases [7]. In terms of *in vivo* pathophysiology, heme proteins can release hemin which in turn can lead to oxidative damage. There is evidence that hemin may act as a pathological factor with potential relevance to neurodegenerative and other diseases, e.g., Alzheimer's disease [13]; and some biochemical oxidation assays involve hemin, e.g., [14]. Moreover, heme is a pro-inflammatory factor [15], and inflammation contributes to many chronic diseases including some cancers and CVD. Heme-related pathology may be an unrecognized factor in diabetes.

Hydrogen peroxide can react with hemin to release redox-active, catalytic iron [16]. Superoxide can also contribute to oxidative damage by releasing iron from heme-proteins [17]. Another potential beneficial activity of phytochemicals (or phytochemical-iron complexes, above) is the conversion of superoxide radicals to hydrogen peroxide; this could help in moderating superoxide induced iron release. If the hydrogen peroxide generated can be rapidly scavenged (e.g., catalases, glutathione peroxidases), its subsequent reaction with the released hemin may be minimized.

Potential health benefits of dietary plant foods and phytochemicals, as well as harmful effects of excessive iron and other transition metals, must also be considered in the context of factors influenced by an individual's genetic composition: e.g. effectiveness and efficiency of damage repair, levels of endogenous antioxidant factors, and levels of prooxidants generated by basal metabolism.

From ROS Scavenging to a Plethora of Phytochemical Bioactivities

Many xenobiotic compounds can have antioxidative or

***Corresponding author:** Amandio Vieira, PhD, Nutrition and Metabolism Laboratory, Simon Fraser University, BPK9625-8888 University Drive, Burnaby, BC, V5A 1S6, Canada, Tel: +1-778-782-425; Fax: +1-778-782-3040; E-mail: avvieira@sfu.ca

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prooxidative activity depending on the experimental system used to study them. 'Antioxidant' phytochemicals (including vitamins) and their metabolites may have protective roles in vivo against some chronic diseases. Much has been reported on the *in vitro* antioxidant activities of phytochemicals; and radical scavenging activities have been proposed as a basis for their beneficial health effects. Possible *in vivo* relevance of such antioxidant activities, however, remains to be established in most cases. Some *in vivo* markers of oxidative damage are decreased after intake of specific phytochemicals or plant foods, e.g., [9,18,19]. It is also possible that antioxidant effects of a phytochemical (or phytochemical-rich plant foods/extracts, or their metabolites) contribute to protection against a very specific pathological reaction *in vivo* even if that phytochemical does not induce measurable changes in (or even slightly increases) more 'global' markers of oxidative damage.

Analogous to the possible benefits of regular physical activity in terms of an adaptive response to exercise-induced production of reactive chemical species [20-22], chronic low-level prooxidative effects of phytochemicals (or moderate levels of other dietary components, e.g., alcohol) may provide some benefit by up-regulating various endogenous antioxidant defenses. This putative beneficial effect is based on the assumption that the body reacts to such repeated challenge by 'setting' a higher basal level of its antioxidant defenses and a greater response capacity. A possible physiological mechanism that could 'set' and 'reset' such a redox adjustment is one based on epigenetic regulation, i.e., relatively stable redox-modulated chromatin modifications. In any case, a potential benefit of low-level prooxidative conditioning by dietary factors would have to be balanced against possible toxic effects.

In many cases, the actions of plant foods or phytochemicals and their metabolites against specific pathological reactions of chronic diseases *in vivo* may not directly involve redox mechanisms. Many other possible control mechanisms have been identified for these compounds, e.g., modulation of cell signaling and transport, membrane structure, genetic and epigenetic control. Interestingly, changes in cellular redox balance may influence some of these basic cell properties and functions through redox-sensitve effectors (and some reactive species such as hydrogen peroxide are themselves signaling effectors [23]). Thus, metabolic adjustments to the release of iron or heme, to the presence of redox-active phytochemicals, as well as from the changes in dietary nutrient energy sources to changes in cell membrane lipid composition etc., may influence these fundamental pathophysiological functions.

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Author Affiliation

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[1]*BPK Nutrition and Metabolism Laboratory, Simon Fraser University, Burnaby, BC, Canada*