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Review

Iron supplements: the quick fix with long-term consequences

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Abstract

Co-supplementation of ferrous salts with vitamin C exacerbates oxidative stress in the gastrointestinal tract leading to ulceration in healthy individuals, exacerbation of chronic gastrointestinal inflammatory diseases and can lead to cancer. Reactive oxygen and nitrogen species (RONS) have been ascribed an important role in oxidative stress. Redox-active metal ions such as Fe(II) and Cu(I) further activate RONS and thus perpetuate their damaging effects. Ascorbic acid can exert a pro-oxidant effect by its interaction with metal ions via a number of established RONS generating systems which are reviewed here. Further studies are required to examine the detrimental effects of nutraceuticals especially in chronic inflammatory conditions which co-present with anaemia.

Introduction

A growing public awareness of the benefits of a healthy lifestyle has been accompanied by an explosive use of nutraceuticals over the past decade. This has afforded the opportunity for increased historical and planned trials of the benefits and risks involved in taking supplements. In particular, emphasis has been placed on the anti-oxidant arsenal, which is an area that has been well studied but ambiguous. A great many studies have been conducted on the effects of anti-oxidant consumption after absorption at the molecular level (for example in blood), but critically most have overlooked the initial deleterious effects on the GI Tract.

Recently, vigorous debate has ensued regarding the toxic side-effects of nutraceutical self-administration. The health advantages of vitamin C have been widely reported. Vitamin C has been shown to exhibit anti-oxidant effects at low doses but conversely at high doses it becomes a pro-oxidant [1]. Studies have shown that vitamin C intake above the RDA frequently occurs and is attributed to the increase in supplementation in addition to dietary sources. A recent report gave vitamin C intake levels with 1524% RDA (50 mg) in supplement users however even in non-supplement users the recommended levels were exceeded with an average intake of 210% [2].

A daily intake exceeding the RDA was also found for other key nutrients such as iron. The daily intake of iron was found to be 1874% of the published Korean RDA (18 mg) for supplement users in comparison to 62% RDA for non-supplement users. This dramatic finding pertained to some one third of the population. Elevated ingestion of ferrous iron leads to the generation of reactive oxygen and nitrogen species (RONS), lipid peroxidation and oxidative stress [3]. High tissue concentrations of iron are associated with a number of pathologies including some cancers, inflammation, diabetes, liver and heart disease [4].

Despite these alarming figures, iron supplementation is very common. It is often taken in conjunction with vitamin C to aid absorption. The damaging effects of a high intake of either iron salts or vitamin C alone warrants

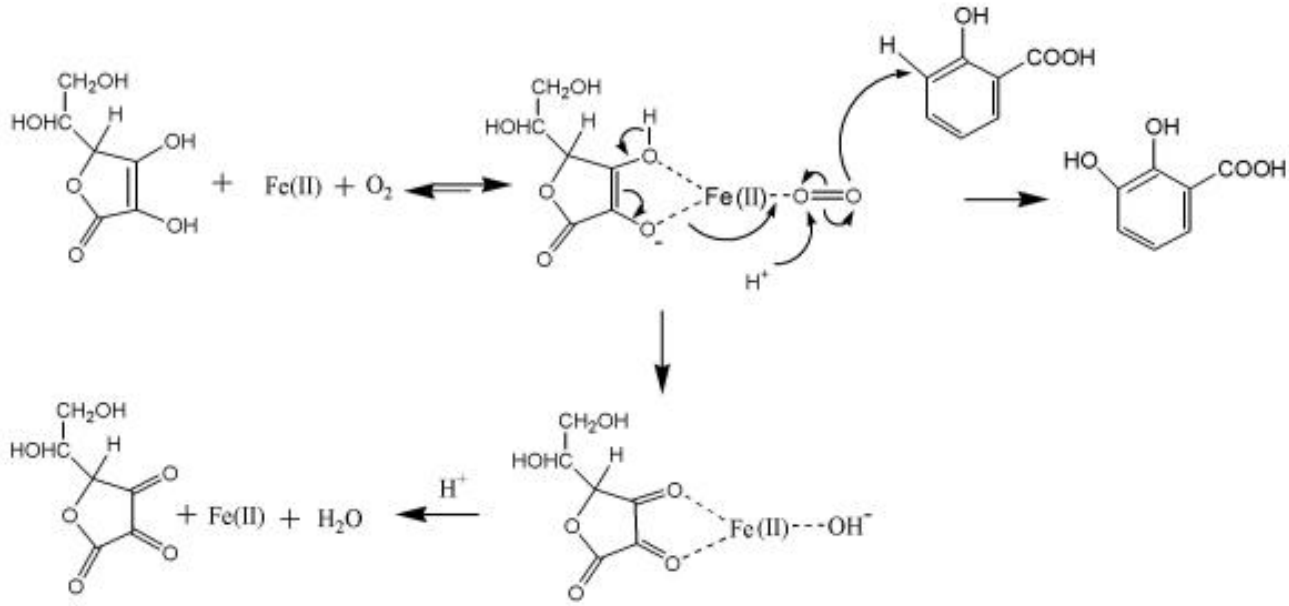

Figure 1
Proposed mechanism for the generation of H_2O_2 via the oxidation of ascorbic acid

serious consideration. However, in tandem this cocktail is potent. Uncontrolled interaction between vitamin C and iron salts leads to oxidative stress. Many patients suffering from diseases of the GI tract such as Crohn's disease and ulcerative colitis often also present with iron deficiency anaemia requiring co-supplementation of vitamin C and iron. A great deal of interest has been shown in the effects of iron supplementation on gastric function in patients suffering from inflammatory diseases and in healthy individuals. Numerous studies have demonstrated iron-induced increases in oxidative damage and disease severity in animal models of gastric inflammation [5-7]. In particular, studies have highlighted the induction of gastric ulcers in rats by the injection of ferrous iron and ascorbic acid [8]. However, ferrous iron or ascorbic acid, when injected alone into the gastric wall did not produce penetrating ulcers. The authors propose that lipid peroxidation mediated by oxygen radicals plays a critical role in ulcer pathogenesis as treatment with superoxide dismutase significantly decreased ulceration in tandem with peroxidation. In a long-term study, an iron enriched diet affected an increase in colorectal carcinoma in induced colitis in mice [7].

In humans, a single clinical dose of ferrous sulfate has been shown to induce oxidative damage in healthy individuals [9]. This study extends previous reports showing iron induces enhanced lipid peroxidation in rats [8]. Using a double-lumen perfusion tube, perfusion with saline containing ferrous sulphate resulted in some fifty fold increases in lipid peroxidation as measured by thiobarbituric acid reactive substances. Intriguingly, antioxidant capacity increased some three-fold with iron administration. In patients with Crohn's disease, treatment with ferrous sulphate (120 mg for 7 days), increased clinical symptoms of disease activity [10]. These results clearly indicate that the unnatural concentration of iron salts in a bolus dose accompanied by excess reducing vitamin C can seriously compromise the epithelial lining of the GI tract.

Mechanisms of Redox-Active Metal Ion Mediated RONS Formation

Ascorbic acid has a number of known interactions with metal ions. These interactions involve redox reactions including i) activation of molecular oxygen leading to oxidation of endogenous aromatic moieties [Udenfriend's system] [11,12], ii) the reduction reactions of Fe(III) to Fe(II) facilitating their involvement in the activation of peroxides [the Fenton reaction] [13], iii) metal ion catalysis of the oxidation of ascorbic acid with concomitant formation of hydrogen peroxide (H_2O_2) and potential hydroxyl radical ($^{\bullet}OH$) generation [from Weissberger *et al.*] [14-16].

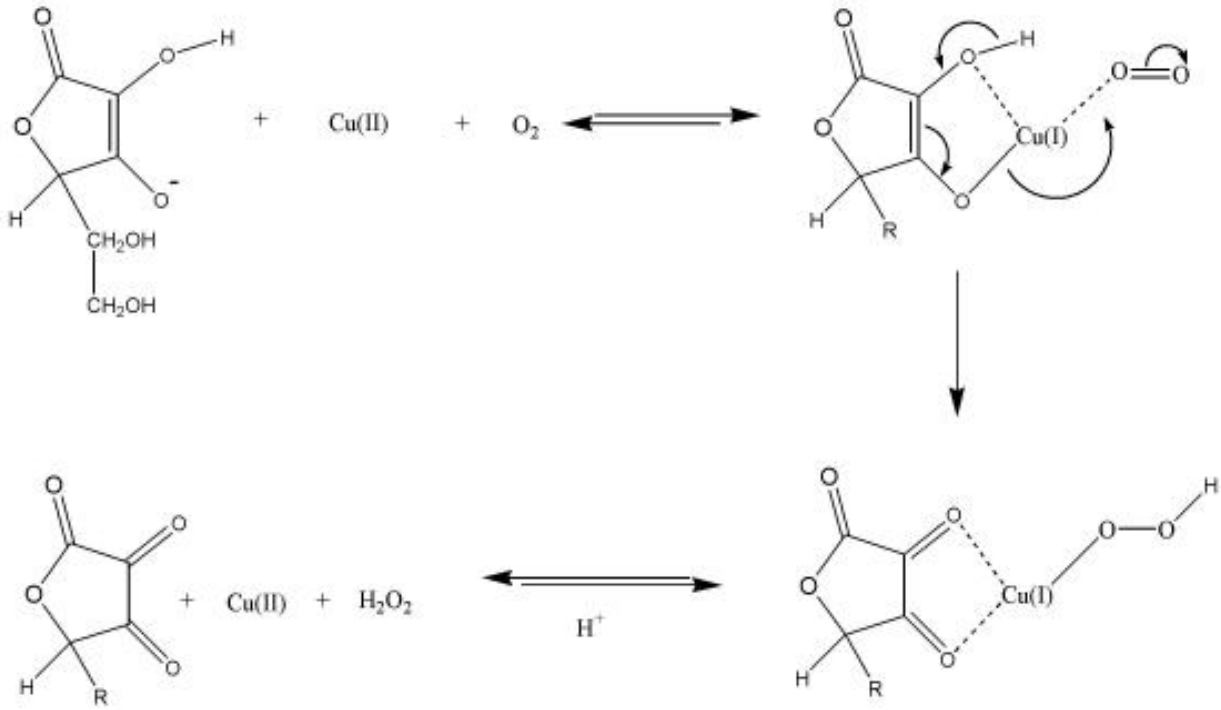

Figure 2
Proposed mechanism for the hydroxylation of aromatic moieties by iron ascorbate binding

Udenfriend's system

In chemical model systems, the Udenfriend system has been demonstrated to hydroxylate aromatic compounds, saturate hydrocarbons to alcohols and olefins to epoxides [17]. It has been distinguished from the Weissberger system in both the mechanism and type of oxidation products produced [17]. Udenfriend's system involves ascorbic acid as a two-electron donor complexed to a transition metal such as Fe(II) [11]. It is speculated that in the presence of O_2, complexation between Fe(II) and ascorbic acid results in the formation of an active oxygen species speculated to be •OH [18]. The proposed mechanism (Figure 1) shows the oxidation of ascorbic acid to dehydroascorbic acid, by electron transfer through Fe(II), and subsequent hydroxylation of an aromatic compound [19]. This reaction has been shown to be enhanced when iron is coupled with a chelator for example in iron-citrate complexes found within biofluids [20].

Fenton chemistry

The Fenton reaction involves the transition metal catalyzed reduction of H_2O_2 to generate a powerful oxidizing species. Transition metals have varying oxidation states, and therefore they are able to catalyze oxidation and reduction reactions. In the blood, circulating iron is tightly bound to the protein transferrin, which reduces its reduction potential, and subsequently its reactivity with H_2O_2. In chronic inflammatory diseases low molecular mass metal ion deposits can result from i) compromised vasculature, ii) the activation of heme oxygenase and iii) release from storage proteins via superoxide [21]. The Fenton system can generate hydroxyl radicals from the metal ion activation of H_2O_2 (eq. 1) [22]. Ascorbic acid can then recycle Fe(III) to Fe(II) facilitating further generation of •OH by subsequent Fenton cycles.

$$Fe(II) + H_2O_2 \rightarrow {}^{\bullet}OH + Fe(III) + OH^- \quad (1)$$

Weissberger system

Metal ion catalysis of the oxidation of ascorbic acid has long been an established process for the formation of H_2O_2. The reaction was studied in detail initially by Weissberger *et al*. (Figure 2) [14] and subsequently by Martell *et al* [15]. Although the reaction between ascorbic acid and oxygen proceeds slowly in the absence of metal ions, the introduction of redox active metal ions in cata-

lytic amounts greatly enhances the rate of reaction. The very low rate constant for the ascorbic acid auto-oxidation is reported as $5.87 \times 10^{-4}\ M^{-1}sec^{-1}$ [15]. The catalytic rate in the presence of Fe(III) is greatly enhanced to $6.4 \times 10^{3}\ M^{-1}sec^{-1}$. Importantly, in the presence of metal ion chelators other than ascorbic acid the reaction proceeds to give a Fe(II) complex which would react rapidly with H_2O_2 to generate $^{\bullet}OH$ [17]. This generation of toxic $^{\bullet}OH$ from a simple system containing metal ions, ascorbic acid and oxygen has potentially deleterious consequences owing to the ubiquitous nature of these components in diseased tissues. Under these conditions it is imperative to restrict ascorbic acid intake to recommended daily intake levels.

Conclusions

Co-supplementation of ferrous salts with vitamin C exacerbates oxidative stress in the gastrointestinal tract, predisposing individuals to ulceration, inflammatory disorders, and exacerbation of existing chronic disorders and may cause cancer.

Iron and ascorbic acid form a potentially toxic cocktail. Ascorbic acid has been shown to exhibit both anti-oxidant and pro-oxidant effects in a dose related fashion. The chemical mechanisms given above have been established demonstrating the potential for these compounds to interact and oxidatively damage surrounding tissues. Even in healthy subjects a positive or negative deviation from the optimal plasma ascorbic acid level results in oxidative damage [23]. The detrimental effects of large quantities of ascorbic acid and iron in healthy subjects and patients with GI inflammatory diseases warrant further investigation. In addition dietary supplements containing iron and ascorbic acid may be deleterious as these components do not naturally come in concentrated form (as in supplementation tablets).

The evidence for inflammation resulting from the interaction of ferrous ions and ascorbate in animals already exists. These studies can be extended to humans by exploiting some of the many studies undertaken on vitamin and mineral supplementation. A recent study conducted by the Food Standards Agency (UK) is the largest to date and could be exploited in a follow up to assess the long term effects of iron and ascorbic acid co-supplementation [24]. As iron uptake in the GI tract is regulated by plasma iron levels [25], analysis of plasma iron should dictate the requirement for iron and vitamin C supplementation to avoid residual iron damaging the GI tract.

Competing interests

None declared.

Authors' contributions

The authors contributed equally to this work.

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