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Commentary

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Inhibition of iron absorption by polyphenols as an anti-cancer mechanism

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It is well known that cancer might be considered in part to be a preventable disease, highly susceptible to modulation by dietary factors. Polyphenol compounds, which are abundant in fruits, vegetables, seeds and drinks, have been shown to play a potential role as chemopreventive agents.[1] The mechanisms underlying this beneficial effect are not fully understood. Assessing the real impact of such constituents on human health is difficult, as in many cases the exact composition of foods and the bioavailability of active molecules are not known. However, there is evidence that polyphenol compounds can prevent the DNA damage caused by free radicals or carcinogenic agents. The mechanisms can be direct radical scavenging, chelating divalent cations involved in Fenton reaction and modulating enzymes related to oxidative stress.[1] We suggest that some of the involved mechanisms might be related to inhibition of iron absorption by polyphenols present in the diet.

Iron is an essential nutrient in humans and both iron deficiency and iron excess can result in deviation from the optimal health. Although the absolute amount of iron extracted from the diet is small, its absorption is highly regulated in humans since there is no physiologic pathway for active iron excretion. Haem and non-haem iron enter intestinal mucosal cells by two independent pathways, haem iron being more efficiently absorbed (25–30%) from the diet than non-haem iron (5–15%).[2] Although non-haem iron is not absorbed as well as haem iron, it is an important source because haem iron comprises only about 15% of total iron in the typical western diet.[3] Beyond its chemical form, the availability of iron for absorption is determined by the presence of enhancers and inhibitors in the meal. Among the latter, polyphenols represent important compounds.

The phenolic compounds are released from food or beverages during digestion, and can combine with iron in the intestinal lumen making it unavailable for absorption. The polyphenols are such powerful inhibitors of non-haem iron that substantial changes in the amount of iron absorbed are more likely to occur if the timing of consumption is altered, rather than the quantity.[2] For example, a serving of yod kratin (leaves of the lead tree, *Leucaena glauca*, a vegetable with a high content of polyphenols and widely consumed in Thailand) reduced iron absorption from a composite meal of rice, fish and vegetables by almost 90%.[4] Among elderly participants in the Framingham Heart Study, each cup of coffee (236 ml) consumed in a week was associated with 1% lower serum ferritin, a good measurement of body iron stores.[5]

Interestingly, all major types of food polyphenols can strongly inhibit dietary non-haem iron absorption, and a dose-dependent inhibitory effect of polyphenol compounds on iron absorption has been demonstrated. In particular, it has been reported that any beverage providing 20–50 mg total polyphenols reduce iron absorption from a bread meal by 50–70%, whereas beverages containing 100–400 mg total polyphenols reduce iron absorption by 60–90%.[6] It was noticed that a single serving of instant coffee contains 120 mg of polyphenols.[6]

Because this study used a simple bread meal, extrapolation of the results to more complex meals might be difficult. However, it should be noted that sufficiently prolonged use of polyphenol compounds has been found to cause iron depletion or iron deficiency in populations with marginal iron stores.[7,8] Furthermore, the consumption of polyphenol-containing beverages has been suggested as a useful strategy to reduce iron absorption in patients with iron overload disorders.[9,10]

The effect of regular tea-drinking during meals on accumulation of storage iron was evaluated in patients with genetic haemochromatosis,[10] and the inhibitory effect of black tea on intestinal iron absorption was confirmed. Body iron stores were evaluated quantitatively by exhaustive phlebotomy, the assessment of body iron status being haemoglobin, saturation of serum iron binding capacity and serum ferritin. A significant reduction in iron absorption was observed when the test meal was accompanied by drinks of tea instead of water. In the tea-drinking group, the increase in storage iron was reduced by about one-third compared with that of the control group.

An effect of iron loss in reducing cancer risk has been confirmed in the Iron (Fe) and Atherosclerosis STudy (FeAST) with subjects randomized to reduction in iron stores or observation.[11] The FeAST study is the first randomized trial of the effects of reduction of stored iron on cancer mortality. In the iron reduction group, mean serum ferritin declined from 122.5 ng/ml to 79.7 ng/ml, a 35% decrease. This reduction is within normal reference ranges for serum ferritin, and although it does not equate to iron depletion, it is noteworthy that in the FeAST trial it is of the same order of magnitude of the decrease of storage iron as reported with the regular consumption of a polyphenol-rich tea with meals in the population with genetic haemochromatosis.[10]

In the FeAST study, during 4.5 years of follow-up, the risk of new malignancy was significantly lower in the iron reduction group than in controls. Among patients with new cancers, those with iron reduction had highly significant lower cancer-specific and all-cause mortality. The FeAST trial results suggest that reduction of stored iron may have a broad anti-tumour effect. These findings are plausible in view of the mounting evidence on the role of iron in cancer.[10–15]

Iron reduction may have multiple anti-cancer actions, which might include depriving neoplastic cells of a key required nutrient,[13] thereby producing an anti-angiogenic effect from reduction of ferritin,[14] inhibition of the formation of 8-hydroxydeoxyguanosine[15] and influencing cell cycle regulation at multiple sites.[16] Finally, tumour suppressor genes may have specific vulnerability to the iron-catalyzed Fenton reaction.[17]

It is therefore plausible that increased intake of polyphenol compounds may, among other beneficial effects, maintain a relatively low iron status and, as a result, reduce the risk of cancer. It is important in future studies of polyphenols action to include assessments of the effects of the intervention on iron status.

Conflict of interest: None declared.

References

1. Ramos S. Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways. *Mol Nutr Food Res* 2008; **52**:507–26.
2. Heath AL, Fairweather-Tait SJ. Clinical implications of changes in the modern diet: iron intake, absorption and status. *Best Pract Res Clin Haematol* 2002; **15**:225–41.
3. Burgess L, Hackett AF, Kirby S, Maxwell S, Nathan I. A reassessment of the fat intake of children from meat and meat products and an estimate of haem iron intakes. *J Hum Nutr Diet* 2001; **14**:55–61.
4. Tuntawiroon M, Sritongkul N, Brune M, Rossander-Hultén L, Pleehachinda R, Suwanik R, *et al*. Dose dependent inhibitory effect of phenolic compounds in foods on nonheme-iron absorption in men. *Am J Clin Nutr* 1991; **53**:554–7.
5. Fleming DJ, Jacques PF, Dallal GE, Tucker KL, Wilson PW, Wood RJ. Dietary determinants of iron stores in a free-living elderly population: the Framingham Heart Study. *Am J Clin Nutr* 1998; **67**:722–33.
6. Hurrell RF, Reddy M, Cook JD. Inhibition of non-haem iron absorption in man by polyphenolic-containing beverages. *Br J Nutr* 1999; **81**:289–95.
7. Hallberg LF, Hulthén L. Prediction of dietary iron absorption: an algorithm for calculating absorption and bioavailability of dietary iron. *Am J Clin Nutr* 2000; **71**:1147–60.
8. Mennen LI, Walker R, Bennetau-Pelissero C, Scalbert A. Risks and safety of polyphenol consumption. *Am J Clin Nutr* 2005; **81(Suppl. 1)**:326S–9S.
9. de Alarcon PA, Donovan ME, Forbes GB, Landaw SA, Stockman JA III. Iron absorption in the thalassemia syndromes and its inhibition by tea. *N Engl J Med* 1979; **300**:5–8.
10. Kaltwasser JP, Werner E, Schalk K, Hansen C, Gottschalk R, Seidl C. Clinical trial on the effect of regular tea drinking on iron accumulation in genetic haemochromatosis. *Gut* 1998; **43**:699–704.
11. Zacharski LR, Chow BK, Howes PS, Shamayeva G, Baron JA, Dalman RL, *et al*. Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial. *J Natl Cancer Inst* 2008; **100**:996–1002.
12. Mascitelli L, Pezzetta F, Sullivan JL. Aspirin-associated iron loss as an anticancer mechanism. *Med Hypotheses* 2010; **74**:78–80.
13. Hann HW, Stahlhut MW, Blumberg BS. Iron nutrition and tumor growth: decreased tumor growth in iron-deficient mice. *Cancer Res* 1988; **48**:4168–70.

14. Coffman LG, Parsonage D, D'Agostino R, Torti FM, Torti SV. Regulatory effects of ferritin on angiogenesis. *Proc Natl Assoc Sci USA* 2009; **106**:570–5.

15. Yoshiji H, Nakae D, Mizumoto Y, Horiguchi K, Tamura K, Denda A, *et al*. Inhibitory effect of dietary iron deficiency on inductions of putative preneoplastic lesions as well as 8-hydroxydeoxyguanosine in DNA and lipid peroxidation in the livers of rats caused by exposure to a choline-deficient L-amino acid defined diet. *Carcinogenesis* 1992; **13**: 1227–33.

16. Yu Y, Kovacevic Z, Richardson DR. Tuning cell cycle regulation with an iron key. *Cell cycle* 2007; **6**:1982–94.

17. Toyokuni S. Iron and carcinogenesis: from Fenton reaction to target genes. *Redox Rep* 2002; **7**:189–97.