Whole Foods, Antioxidants and Health 12

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Introduction

The capacity of whole foods to improve antioxidant defences and our quality of life is poorly understood. Understanding how antioxidants from whole foods affect our health is very important in controlling the epidemic of heart disease and cancer observed today. The use of specific antioxidant supplements such as ascorbate, α-tocopherol and β-carotene has increased as the public has become more familiar with antioxidant concerns. Because their use has increased, the potential for increased risks associated with their misuse has also increased. For most persons in the developed nations, whole-food products remain the *primary* source of dietary antioxidants, but for poor persons in non-developed nations, whole foods are the *only* source of antioxidants.

For the purpose of this paper a whole food is considered to represent a foodstuff that undergoes no or minimal processing. The term 'whole food' is also meant to include beverages made from whole foods. This review will focus on the contribution of antioxidant activities to health promotion. Most whole-food antioxidant activity is derived from phenolic phytochemicals, including polyphenols and flavonoids. These molecules have antioxidant activity due to the strong reduction potentials of hydroxyls attached to their phenyl rings (Rice-Evans *et al*., 1996).

This review seeks to clarify some of the factors that are important in determining the value of a whole-food product to human antioxidant status. Specifically, this chapter seeks to describe whole-food antioxidants with respect to: (i) links between whole-food antioxidants and heart disease, cancer and vision loss; (ii) problems associated with dependence on any one antioxidant; (iii) factors influencing whole-food antioxidant content and bioavailability; and (iv) problems related to the evaluation of whole-food antioxidant consumption studies.

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Links Between Whole-food Antioxidants and Heart Disease, Cancer and Vision Loss

Antioxidant deficiencies have well-established links to the promotion of specific diseases. This is discussed more fully in other chapters. Antioxidant compounds are accumulated from the diet or synthesized in the body and prevent the chemical oxidation of proteins, lipids and other essential compounds. Industrialization has led to increased environmental pollutants in our air, food and water. Many of these pollutants have the capacity to deplete the body's antioxidant reserves. Antioxidant deficiencies resulting from dietary deficiencies and/or increased environmental oxidant stress may be linked to the development of many diseases including heart disease, cancer and vision loss.

Red wine is a whole-food product that has been widely associated with antioxidant effects (Renaud and de Lorgeril, 1992; Frankel *et al*., 1993). It was one of the first whole-food products shown to have measurable antioxidant effects *in vivo*, including increased resistance of low-density lipoproteins (LDL) to oxidation (Fuhrman *et al*., 1995; Whitehead *et al*., 1995; Miyagi *et al*., 1997). LDL oxidation can also be inhibited *in vitro* by many other whole-food products including: broccoli (Plumb *et al*., 1997), grape juice (Lanningham-Foster *et al*., 1995; Miyagi *et al*., 1997), soybean isoflavonoids (Tikkanen *et al*., 1998), garlic (Ide *et al*., 1997), blueberries (Laplaud *et al*., 1997) and cranberry extracts (Wilson *et al*., 1998).

Antioxidants may also promote arterial vasodilation and improve blood flow. In humans, antioxidants such as ascorbate have been suggested to promote arterial vasodilation *in vivo* (Heitzer *et al*., 1996; Solzbach *et al*., 1997). Vasodilation may be promoted by flavonoids from whole foods serving as antioxidants that increase the half-life of endothelially derived relaxing factor (EDRF), or these flavonoids may activate EDRF-activated receptors directly.

Damage to cellular regulatory proteins and DNA is central to the promotion of cancer in humans. Oxidation is a primary means by which this damage occurs and antioxidants from our food may have the ability to protect against cancer promotion. Analysis of antiproliferative effects of whole-food products also suggests that an anticancer role may exist. Genistein and other flavonoids derived from soybean products have been found to have antiproliferative effects on breast cancer cells *in vitro* (Tikkanen *et al*., 1998). Flavonoid-rich extracts from two members of the *Vaccinium* genus, cranberries and blueberries, have also been shown to have potent antiproliferative effects on cancer cells *in vitro* (Bomser *et al*., 1996).

Block *et al*. (1992) evaluated the cancer protection linked to fruit and vegetable consumption. The relative risk ratios of 128 of the 158 studies reviewed suggest that consumption of low amounts of fruits and vegetables is associated with an approximate doubling of the risk for several types of cancer.

Because fruits and vegetables remain the primary source of antioxidants, it is probable that the protective effects are due to the antioxidant activities associated with the fruits and vegetables we consume (Block *et al.*, 1992). Compared with today's diet the Paleolithic diet was relatively rich in fruits and vegetables. That diet was evaluated by Eaton *et al.* (1997), who estimated that it contained 604 mg ascorbate and 33 mg α-tocopherol; this is much more than the typical American diet, which contains 77–109 mg ascorbate and 7–10 mg α-tocopherol. In the developed nations, the relatively high incidence of oxidation-related diseases such as heart disease and cancer may reflect a deficiency in total dietary antioxidants relative to the diet of our ancestors.

Vision loss can result from oxidative damage to the macula of the eye (Seddon *et al.*, 1994). Consumption of foods rich in antioxidants may slow or prevent the development of age-related macular degeneration (see Chapter 22). By reducing oxidative damage to the macula, antioxidants from red wine apparently delay or prevent vision loss at consumption levels as low as one glass per month (Obisesan *et al.*, 1998). Similar processes may prove to be useful for preventing oxidation of proteins in the lens of the eye. Future studies will certainly yield interesting developments in this field because with increased life expectancies we need to maintain quality vision for longer. If antioxidants from whole foods can be shown to be effective in this regard, the quality of life for millions of the elderly could be improved worldwide.

Problems Associated with Dependence on One Antioxidant

Over 4000 flavonoids from plant sources have been identified (Kandaswami and Middleton, 1994), in addition to countless non-flavonoid compounds with antioxidant capacities. Indeed, in the 1930s investigators suggested that flavones might be essential to the human diet and they were termed vitamin P (Rusznyak and Szent-Gyorgyi, 1936). The substances that make up this bewildering variety of compounds differ widely in their antioxidant activities and their ability to affect both enzyme function and blood clotting activities. Synergistic effects of a balanced mixture of different antioxidants obtained from the diet may be required by the body for optimal health maintenance.

About half of the plasma antioxidant capacity comes from albumin and urate, the remainder represents the antioxidant gap (Miller and Rice-Evans, 1996). This gap is filled by the activities of single molecules, for example the vitamins α-tocopherol and ascorbate, flavonoids such as quercetin, isoflavonoids such as diadzein, and by the activity of antioxidant enzymes including superoxide dismutase and peroxidase. Furthermore, within the antioxidant system constant recycling of antioxidants such as α-tocopherol also occurs (Bieri, 1972). The importance of whole-food antioxidants in terms of promoting antioxidant recycling in the body is poorly understood.

Supplementation of diets with any single molecule showing *in vitro* antioxidant capacity does not necessarily promote health improvement. Recent studies of β-carotene have revealed that there may be risks associated with antioxidant supplementation. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1994) and the CARET study (Omenn *et al*., 1996) the risk ratio for lung cancer in smokers receiving β-carotene increased. Protective effects of a diet rich in fruit and vegetable have recently been shown to reduce lung cancer independently of the effects of single-vitamin supplements (Yong *et al*., 1997).

Problems with single supplements have also been observed in animal models. Resveratrol is a polyphenolic compound from red wine with an antioxidant capacity *in vitro* (Siemann and Creasy, 1992) and has received much attention. Resveratrol may inhibit cancer in mice (Jang *et al*., 1997), however dietary supplementation with it is not associated with reduced lipid peroxidation in rats (Turrens *et al*., 1997) and may even be associated with increased atherogenesis (Wilson *et al*., 1996).

Part of the reason for these confusing results may be related to the fact that supplementation studies often use antioxidant amounts that are larger than could be encountered in a normal diet. Occasionally, when very high concentrations of antioxidants are reached, an antioxidant can promote oxidation; this observation has been called a pro-oxidant effect (Otero *et al*., 1997; Podmore *et al*., 1998). The popularity of antioxidant neutraceuticals coupled with a 'more is better' mentality may make pro-oxidant considerations important.

Factors Influencing Whole-food Antioxidant Content and Bioavailability

Differences in the distribution of flavonoids within a particular type of plant or fruit affect the antioxidant capacity of whole foods. In grapes, polyphenolic compounds are distributed unequally in the different tissues. The skin is generally much richer in flavonoid content than the pulp (Creasy and Coffee, 1988). As a result, wine can be produced from an antioxidant-rich grape and still be relatively poor in antioxidant content if the skin is not included in the fermentation process. This observation becomes important in describing the wide range observed in wine polyphenol content and antioxidant capacity (Siemann and Creasy, 1992; Frankel *et al*., 1995). This observation may also be important for interpreting the outcomes of food consumption surveys, as may arise, for example, if apples were eaten after being peeled.

Environmental factors affect plant tissue growth and complicate the study of whole-food antioxidant capacities; for example by altering the antioxidant content of a fruit from year to year or from field to field (Siemann and Creasy, 1992). Polyphenols such as resveratrol are invariably present in grape skin. However, plant exposure to fungal attack and ultraviolet (UV) radiation is associated with dramatic increases in the production of resveratrol and other polyphenolic compounds as part of the immune defence strategy of grapes (Creasy and Coffee, 1988). In foods such as the cranberry, UV exposure is also associated with increased production of flavonoid pigments and potentially with antioxidant capacity.

Whole-food antioxidant content is also modified by a wide range of factors related to the processing of the food prior to consumption. Food processing can reduce antioxidant value by dilution and exposure of the contents to oxidative stress. Antioxidants in food can be oxidized by chemicals used as food preservatives, such as nitrites, intended to inhibit bacterial growth. Conversely, antioxidant capacity can be increased by the food preservative butylated hydroxytoluene (BHT), which is used to prevent the peroxidation of food lipids and the development of rancidity.

Flavonoid absorption and bioavailability is an important concern regarding whole-food antioxidant studies. In humans, the flavonoid catechin has been shown to be absorbed intact from the gastrointestinal tract, with complete clearance at around 48 h (Das, 1971). In plants, flavonoids are typically conjugated to sugars. Both conjugated and unconjugated forms of the flavonoid quercetin are absorbed following consumption of onions by humans (Hollman *et al.*, 1995; Papanga and Rice-Evans, 1997). Absorption appears to be greatest for quercetin conjugated to sugars due to transport by sugar-dependent transporters (Hollman *et al.*, 1996). Absorption of other flavonoids such as phloridzin and anthocyanins has also been detected (Papanga and Rice-Evans, 1997). Quercetin absorption from the gut and plasma concentrations are similar to those observed for β-carotene (Hollman *et al.*, 1996). Accordingly, flavonoids such as quercetin are probably also physiologically active antioxidants in the body.

Problems with the Evaluation of Whole-food Antioxidant Consumption Studies

Evaluation of *in vivo* study outcomes is complicated by many factors that are difficult to objectively address. Given the low baseline incidence of heart disease, cancer and macular degeneration, large long-term interventional studies may be required to fully appreciate whole-food effects on these diseases. Furthermore, the same whole-food products can differ widely in their antioxidant content because of environmental influences and food processing techniques, so surveys of antioxidant intake may not reflect true intake levels. Possible genetic differences influencing human antioxidant status have not been investigated but may also be found to play a role in explaining why individual effects of whole-food antioxidants vary. One of the greatest problems surrounding the study of whole-food effects on *in vivo* antioxidant capacity has been the lack of assays for complete quantification of plasma antioxidant capacity.

A problem with testing the concentrations of individual antioxidants is the amount of labour required. While the chemical antioxidant potential of many flavonoid and phenolic compounds has been determined, the relative physiological importance of each individual antioxidant has not been determined. Given that over 4000 flavonoids are known to exist, and given that flavonoid metabolites also have the potential to serve as antioxidants, it will clearly not be practicable to assay the relative concentrations and activities of all the antioxidants in the body.

Tests have been developed which compare the oxidative resistance of plasma to α-tocopherol analogues. The test rates the antioxidant capacity of a plasma sample as being greater, equal to or less than a given concentration of standard. Problems with the method are reproducability and equipment needs (Cao and Prior, 1997). Plasma antioxidant capacity can be estimated by exposing the plasma to an oxidant followed by measurement of thiobarbituric acid-reactive substances (TBARS) produced by oxidative stress. This method has been applied to studies of red wine and suggests that it has the ability to increase the oxidative resistance of plasma lipids (Fuhrman *et al*., 1995), although the results are not universally accepted (de Rijke *et al*., 1996). Finally, isoprostanes are produced as a result of LDL lipid peroxidation (Morrow *et al*., 1990). Recently developed immunoassays for isoprostane may become useful for evaluating long-term changes in antioxidant protection from whole-food consumption (see Chapter 28).

Discussion

Our understanding of connections between antioxidants in whole foods, antioxidant capacity, and the body's ability to resist oxidative damage is poorly understood (Fig. 12.1). We are beginning to understand that deficiencies in antioxidants are often associated with the promotion of disease. The development of techniques for objective plasma oxidant assessment will increase our ability to understand how whole-food antioxidants affect our health.

The nutraceutical industry has popularized single-supplement antioxidants. While they may indeed provide measurable health benefits, the cost of supplements and their inaccessibility to poor persons in developing countries poses a problem to their utility. Considered individually, antioxidants differ from one to another with respect to their individual and possible synergistic effects. Whole foods, by contrast, have the potential to provide humans with a broad range of antioxidant compounds. It is probable that we will determine that consumption of such a mixture of antioxidants with their diverse physiological activities is associated with the best promotion of health.

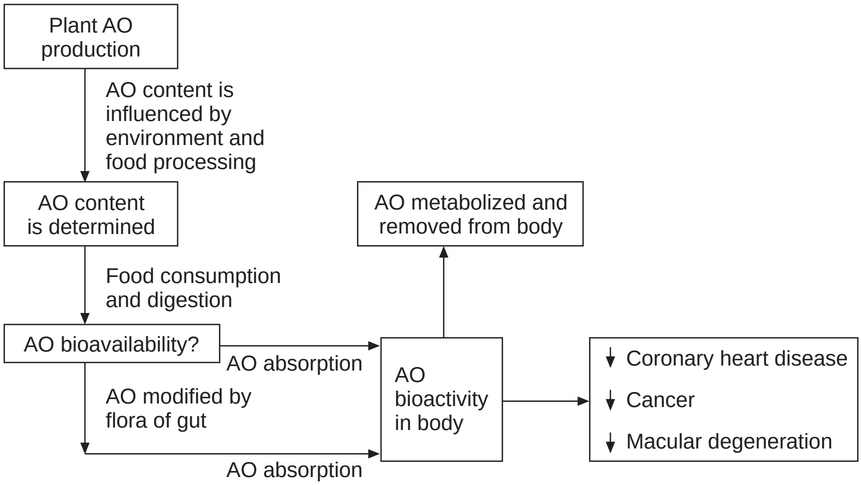

Fig. 12.1. Review of the factors determining the effect of whole-food antioxidants on health. AO, antioxidants from whole food.

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