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How good is chocolate?[1,2]

Paul J Nestel

Many thousand polyphenolics in the plant world contribute importantly to the human food supply. Probably the most abundant are the flavonoids, which comprise the isoflavones in soybean, the flavonol catechins and epicatechins in grapes and tea, quercetin in onions and apples, naringin in citrus, and others. The role of flavonoids as likely mediators of the health benefits of eating fruit and vegetables and the potential of flavonoids in promoting health as individual nutrients has stimulated substantial research as well as speculation. On occasion, epidemiologic associations and preliminary research have led to overly simplistic extrapolations; eg, the Japanese paradox is based on soy and green tea, the French paradox is based on red wine, and the benefits of the Mediterranean diet are based on olive oil. In each instance, single polyphenolics such as genistein, epicatechins, resveratrol, or hydroxytyrosol have been claimed to have powerful antioxidant activity. However, essential information such as the bioavailability, pharmacokinetics, and plasma concentrations of these compounds is generally lacking in clinical studies.

Joining the lengthening list of candidate flavonoids are the procyanidins found in grape seeds, tea, and cocoa. Procyanidins are present in several oligomeric forms that are by no means equipotent (1) and are complex molecules in which catechins, epicatechins, and their gallic esters are linked (2). Like other polyphenols, procyanidins display strong antioxidant activity in vitro as well as other biological properties that have led to possibly premature claims for cardiovascular protection. The antioxidant activity of procyanidins has a linear relation to their concentration in tests such as the oxygen radical absorbance capacity (ORAC) assay (3). In vitro, procyanidins are powerful inhibitors of tyrosine nitration by peroxynitrite (4).

Rein et al (5) recently published in this Journal a study of the inhibition by cocoa of platelet activation ex vivo. Several indexes of platelet activation were diminished between 2 and 6 h after a cocoa beverage was consumed. ADP-stimulated P-selectin expression, an important biomarker of thrombogenicity, and epinephrine-induced fibrinogen binding conformation of glycoprotein IIb-IIIa, a target of modern antiplatelet therapy, were both lessened.

In the current issue of the Journal, Wan et al (6) report a study of similar design, although the outcomes may be less persuasive. Their interest was in the effects of the combined consumption of cocoa and dark chocolate, which delivered a substantial 466 mg procyanidins/d. Plasma epicatechin concentrations rose quickly to a peak within 2 h of consumption and then declined rapidly. The peak concentration was only in the low nanomolar range. Ex vivo antioxidant activity was measured by LDL oxidizability, and serum antioxidant capacity was assessed with use of the ORAC assay. LDL oxidizability and serum antioxidant capacity both changed significantly, although the LDL oxidation lag time was only 8% greater and ORAC was only 4% greater after the subjects consumed 466 mg procyanidins/d compared with an average American diet. Although the conclusion would have been more convincing had the concentration of epicatechins in plasma correlated with an index of antioxidant activity, the results indicate support for beneficial biological activity of cocoa procyanidins. Kondo et al (7) reported similar prolongation in lag times after cocoa consumption. Another reported effect of cocoa procyanidins in humans is immunomodulatory; ie, interleukin 2 expression in circulating mononuclear cells was found to be suppressed (1).

The study by Wan et al raises several issues that are common to several recent published effects of flavonoids: their bioavailability, the robustness of their biomarkers, and the clinical relevance of the findings. Recent improvements in analytic methods have enabled measurements of flavonoids and their metabolites in plasma and urine. It is clear that the absorption and pharmacokinetics of these compounds vary widely among individuals, reflecting conjugation, oligomeric forms, and the degree of conversion to metabolites. Absorption and excretion of some of these flavonoids is rapid. We found that, on average, only ≈25% of isoflavones are absorbed (8), and because daidzein is excreted more rapidly than is genistein, the apparent bioavailability of the 2 isoflavones may be misjudged. Reviewing the subject, Duthie and Crozier (9) point out that the reported absorption of quercetin ranges between 0% and 50% and may depend on its different glucosides.

The robustness of biomarkers is critical to nutritional interventions. Results of such studies rank lower in the hierarchy of evidence than do large clinical trials that are the hallmark of drug-based therapeutic trials. Hence, the credibility of outcomes derived from diet-based or nutrient-supplemented experimental designs depends critically on biomarkers that serve as surrogates of disease outcome. The robustness of the much used ex vivo oxidizability of LDL has been questioned in recent years. A major conference on the subject concluded that

[1] From the Baker Medical Research Institute, Melbourne.

[2] Reprints not available. Address correspondence to PJ Nestel, Baker Medical Research Institute, PO Box 6492, St Kilda Road, Central Melbourne 8008, Australia. E-mail: paul.nestel@baker.edu.au.

this assay be replaced by measurements of plasma concentrations and excretion of isoprostanes, of hydroxy fatty acid concentrations, and of the emerging monoclonal antibodies that target various epitopes of oxidized lipid-linked lipoprotein (10). Furthermore, indexes of total antioxidant capacity, such as ORAC, should be limited to assays of foods and should not be used for biological fluids.

The clinical relevance of antioxidant assays needs to take into account that tissue and cellular effects are not necessarily reflected in events measured in plasma. Do the concentrations in tissues reach biological potency? How small an effect is still clinically useful; is an 8% prolongation in the ex vivo lag time of LDL meaningful? In many studies of several flavonoids, changes of this order were interpreted as being clinically relevant because the differences were statistically significant.

The emerging data on procyanidins in cocoa are interesting and likely to be nutritionally relevant. However, would healthy adults necessarily benefit from further antioxidant supplementation in the form of dark chocolate? One lesson from the negative findings of several vitamin E trials is that in the absence of biomarker measurements, it is impossible to conclude whether the test population was already replete with antioxidants before the interventions began and, therefore, unlikely to benefit from supplementation. What weighting should nutritionists place on each piece of evidence relating to the biological efficacy of single flavonoids? Given that there are thousands of flavonoids in the foods that we eat at one time or another, or daily of the more common ones, should each new finding be greeted as an encouragement to eat that particular source because it contains a specific flavonoid? Is it not more purposeful to view the evidence on individual flavonoids as integral to our understanding of the potential of a diversified food supply and the mechanisms through which that potential is mediated?

These issues lend support to those who argue for the consumption of greater varieties of plant foods, the evidence for which is derived from large prospective cohort studies.

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