



Polyphenols: antioxidants and beyond¹⁻³

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ABSTRACT

Research on the effects of dietary polyphenols on human health has developed considerably in the past 10 y. It strongly supports a role for polyphenols in the prevention of degenerative diseases, particularly cardiovascular diseases and cancers. The antioxidant properties of polyphenols have been widely studied, but it has become clear that the mechanisms of action of polyphenols go beyond the modulation of oxidative stress. This supplemental issue of *The American Journal of Clinical Nutrition*, published on the occasion of the 1st International Conference on Polyphenols and Health, offers an overview of the experimental, clinical, and epidemiologic evidence of the effects of polyphenols on health. *Am J Clin Nutr* 2005; 81(suppl):215S–75S.

KEY WORDS Polyphenols, flavonoids, antioxidants, health, cardiovascular diseases, cancers

Polyphenols are the most abundant antioxidants in the diet. Their total dietary intake could be as high as 1 g/d, which is much higher than that of all other classes of phytochemicals and known dietary antioxidants. For perspective, this is ~10 times higher than the intake of vitamin C and 100 times higher than the intakes of vitamin E and carotenoids (1, 2). Their main dietary sources are fruits and plant-derived beverages such as fruit juices, tea, coffee, and red wine. Vegetables, cereals, chocolate, and dry legumes also contribute to the total polyphenol intake.

Despite their wide distribution in plants, the health effects of dietary polyphenols have come to the attention of nutritionists only rather recently. Until the mid-1990s, the most widely studied antioxidants were antioxidant vitamins, carotenoids, and minerals. Research on flavonoids and other polyphenols, their antioxidant properties, and their effects in disease prevention truly began after 1995 (**Figure 1**). Flavonoids were hardly mentioned in textbooks on antioxidants published before that date (3). The main factor that has delayed research on polyphenols is the considerable diversity and complexity of their chemical structures.

Current evidence strongly supports a contribution of polyphenols to the prevention of cardiovascular diseases, cancers, and osteoporosis and suggests a role in the prevention of neurodegenerative diseases and diabetes mellitus (4). However, our knowledge still appears too limited for formulation of recommendations for the general population or for particular populations at risk of specific diseases. Evidence for a reduction of disease risk by flavonoids was considered “possible” for cardiovascular diseases and “insufficient” for cancers in a recent report

from the World Health Organization (5). The objectives of the 1st International Conference on Polyphenols and Health (Vichy, France, November 18–21, 2004) were to offer an overview of our current knowledge on the associations between polyphenol intake and disease and health and to discuss key issues awaiting resolution. More than 350 communications from > 30 countries were presented. The articles included in this volume correspond to the invited lectures presented at the conference.

Much of the evidence on the prevention of diseases by polyphenols is derived from *in vitro* or animal experiments, which are often performed with doses much higher than those to which humans are exposed through the diet. One purpose of the conference and of this volume was to review some of the evidence for health effects of polyphenols in humans, from both clinical trials and epidemiologic studies. Polyphenols clearly improve the status of different oxidative stress biomarkers (6). Much uncertainty persists, however, regarding both the relevance of these biomarkers as predictors of disease risk and the appropriateness of the different methods used (7). Significant progress has been made in the field of cardiovascular diseases, and today it is well established that some polyphenols, administered as supplements or with food, do improve health status, as indicated by several biomarkers closely associated with cardiovascular risk (8–10). Epidemiologic studies tend to confirm the protective effects of polyphenol consumption against cardiovascular diseases (11). In contrast, evidence for protective effects of polyphenols against cancers, neurodegenerative diseases, and brain function deterioration is still largely derived from animal experiments and *in vitro* studies (12, 13); we await the discovery of predictive biomarkers for such diseases or large intervention studies, similar to those performed with nonphenolic antioxidants (14).

One of the major difficulties of elucidating the health effects of polyphenols is the large number of phenolic compounds found in food (15), yielding differing biological activities, as shown in several *in vitro* studies (16, 17). Major differences in bioavailability are now well established, and the influence of structural factors is better understood (18). This issue was discussed at length during the conference. The active compounds may not be

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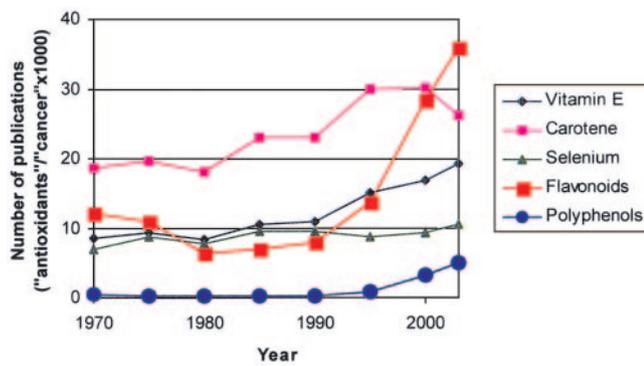


FIGURE 1. Increase in the number of publications regarding various antioxidants in the past 30 y. Publications were those registered in the Medline database. Values were determined as follows: number of results from the query “compound X” AND “year n”/number of results from the query “cancer” AND “year n” \times 1000. The key word cancer was used as a reference, to take into account the general increase in the number of publications.

the native polyphenols found in food, which are most often tested in *in vitro* studies; they are more likely to be metabolites (19). The importance of microbial metabolites has been emphasized in some recent studies, as exemplified by equol, the major metabolite of daidzein (20). Polyphenols are extensively conjugated in the body, and nonconjugated metabolites most often account for a minor fraction of the circulating metabolites. Very little is currently known regarding the biological activities of these conjugated metabolites (1). Glucuronides of isoflavones and epicatechin were shown to have much weaker estrogenic activity and provided no protection against oxidative stress in cells grown *in vitro* (21, 22). These findings suggest that many of the *in vitro* studies published to date must be reevaluated, in light of the new data on polyphenol bioavailability.

A considerable body of literature supports a role for oxidative stress in the pathogenesis of age-related human diseases and a contribution of dietary polyphenols to their prevention. The complex relationships between antioxidant status and disease are still poorly understood and have been studied intensively. For many years, polyphenols and other antioxidants were thought to protect cell constituents against oxidative damage through scavenging of free radicals. However, this concept now appears to be an oversimplified view of their mode of action (23). More likely, cells respond to polyphenols mainly through direct interactions with receptors or enzymes involved in signal transduction, which may result in modification of the redox status of the cell and may trigger a series of redox-dependent reactions (24–26). Both antioxidant and prooxidant effects of polyphenols have been described, with contrasting effects on cell physiologic processes. As antioxidants, polyphenols may improve cell survival; as prooxidants, they may induce apoptosis and prevent tumor growth (12). However, the biological effects of polyphenols may extend well beyond the modulation of oxidative stress. One of the best-known examples involves the interaction of soy isoflavones with estrogen receptors and the effects of these compounds on endocrine function. These effects could explain the prevention by isoflavones of bone resorption among postmenopausal women (27). A detailed understanding of the molecular events underlying these various biological effects is essential for evaluation of the overall impact on disease risk and progression.

The current evidence for protective effects of polyphenols against diseases has generated new expectations for improvements in health, with great interest from the food and nutritional supplement industry regarding promotion and development of polyphenol-rich products. However, it is still impossible to evaluate the individual and societal benefits that increases in polyphenol intake could have for the general population or for particular groups at specific disease risk. Furthermore, a significant increase in the consumption of polyphenols, as for many other phytochemicals, may not be without risks (28). Some hazards associated with the consumption of polyphenols are documented, but evaluation among humans is still very limited. Lastly, we should not forget that many polyphenols have a taste and/or a color (29); food must be not only good for health but also acceptable to consumers.

Integration of the results of past and future experiments in various disciplines, including biochemistry, cell biology, physiology, pathophysiology, epidemiology, and food chemistry, will be needed to identify the most effective polyphenols and to determine the optimal levels of intake for better health. The present research efforts will coordinate with current efforts to identify more accurate biomarkers of risks for nutrition-related diseases and should lead to dietary recommendations and the formulation of new food products contributing to good health.

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