Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals[1–4]

Rui Hai Liu

ABSTRACT Cardiovascular disease and cancer are ranked as the first and second leading causes of death in the United States and in most industrialized countries. Regular consumption of fruit and vegetables is associated with reduced risks of cancer, cardiovascular disease, stroke, Alzheimer disease, cataracts, and some of the functional declines associated with aging. Prevention is a more effective strategy than is treatment of chronic diseases. Functional foods that contain significant amounts of bioactive components may provide desirable health benefits beyond basic nutrition and play important roles in the prevention of chronic diseases. The key question is whether a purified phytochemical has the same health benefit as does the whole food or mixture of foods in which the phytochemical is present. Our group found, for example, that the vitamin C in apples with skin accounts for only 0.4% of the total antioxidant activity, suggesting that most of the antioxidant activity of fruit and vegetables may come from phenolics and flavonoids in apples. We propose that the additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods. *Am J Clin Nutr* 2003;78(suppl):517S–20S.

KEY WORDS Phytochemicals, antioxidant, phenolics, fruit, vegetables, diet and cancer, cardiovascular disease

INTRODUCTION

Food provides not only essential nutrients needed for life but also other bioactive compounds for health promotion and disease prevention. Previous epidemiologic studies have consistently shown that diet plays a crucial role in the prevention of chronic diseases (1, 2). Consumption of fruit and vegetables, as well as grains, has been strongly associated with reduced risk of cardiovascular disease, cancer, diabetes, Alzheimer disease, cataracts, and age-related functional decline (1–3). Heart disease, cancer, and stroke are the top 3 leading causes of death in the United States and most industrialized countries. It is estimated that one third of all cancer deaths in the United States could be avoided through appropriate dietary modification (3, 4). This convincing evidence suggests that a change in dietary behavior such as increasing consumption of fruit, vegetables, and grains is a practical strategy for significantly reducing the incidence of chronic diseases.

In its 1982 report on diet and cancer, the National Academy of Sciences included guidelines emphasizing the importance of fruit and vegetables in the diet (5). The value of adding citrus fruit, carotene-rich fruit and vegetables, and cruciferous vegetables to the diet for reducing the risk of cancer was specifically highlighted. In 1989, a National Academy of Sciences report on diet and health recommended consuming 5 or more servings of fruit and vegetables daily for reducing the risk of both cancer and heart disease (6). The 5-a-Day program was developed as a tool to increase public awareness of the health benefits of fruit and vegetable consumption and promote adequate intake of known vitamins. Prevention is a more effective strategy than treatment of chronic diseases. Plant-based foods, such as fruit, vegetables, and whole grains, which contain significant amounts of bioactive phytochemicals, may provide desirable health benefits beyond basic nutrition to reduce the risk of chronic diseases.

HEALTH BENEFITS OF PHYTOCHEMICALS

Phytochemicals—the bioactive nonnutrient plant compounds in fruit, vegetables, grains, and other plant foods—have been linked to reductions in the risk of major chronic diseases. It is estimated that more than 5000 phytochemicals have been identified, but a large percentage still remain unknown (7) and need to be identified before their health benefits are fully understood. However, more and more convincing evidence suggests that the benefits of phytochemicals in fruit and vegetables may be even greater than is currently understood because oxidative stress induced by free radicals is involved in the etiology of a wide range of chronic diseases (8).

Cells in humans and other organisms are constantly exposed to a variety of oxidizing agents, some of which are necessary for life. These agents may be present in air, food, and water, or they may be produced by metabolic activities within cells. The key factor is to maintain a balance between oxidants and antioxidants to sustain optimal physiologic conditions in the body. Overproduction of oxidants can cause an imbalance, leading to oxidative stress, especially in chronic bacterial, viral, and parasitic infections (9). Oxidative stress can cause oxidative damage to large biomolecules

[1] From the Department of Food Science and the Institute of Comparative and Environmental Toxicology, Cornell University, Ithaca, NY.

[2] Presented at the Fourth International Congress on Vegetarian Nutrition, held in Loma Linda, CA, April 8–11, 2002.

[3] Supported by USDA Federal Formula Funds.

[4] Address reprint requests to RH Liu, Department of Food Science, Stocking Hall, Cornell University, Ithaca, NY 14853-7201. E-mail: rl23@cornell.edu.

such as proteins, DNA, and lipids, resulting in an increased risk for cancer and cardiovascular disease (8, 10). To prevent or slow down the oxidative stress induced by free radicals, sufficient amounts of antioxidants need to be consumed. Fruit and vegetables contain a wide variety of antioxidant compounds (phytochemicals) such as phenolics and carotenoids that may help protect cellular systems from oxidative damage and lower the risk of chronic diseases.

Role of phytochemicals in the prevention of cancer

Evidence suggests that dietary antioxidants can reduce cancer risk. Block et al (11) established this in an epidemiologic review of ≈200 studies that examined the relationship between fruit and vegetable intake and cancers of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas, and ovary. In 128 of 156 dietary studies, the consumption of fruit and vegetables was found to have a significant protective effect. The risk of cancer for most cancer sites was twice as high in persons whose intake of fruit and vegetables was low compared with those with high intake. Significant protection was found in 24 of 25 studies for lung cancer. Fruit was significantly protective in cancers of the esophagus, oral cavity, and larynx. In 26 of 30 studies, there was a protective effect of fruit and vegetable intake with respect to cancers of the pancreas and stomach and in 23 of 38 studies for colorectal and bladder cancers.

A prospective study involving 9959 men and women (age 15–99 y) in Finland showed an inverse association between the intake of flavonoids and the incidence of all sites of cancer combined (12). After a 24-y follow-up, the risk of lung cancer was reduced to 50% in the highest quartile of flavonol intake. Consumption of quercetin in onions and apples was found to be inversely associated with lung cancer risk in Hawaii (13). The effect of onions was particularly strong against squamous cell carcinoma. Boyle et al (14) showed that increased plasma levels of quercetin following a meal of onions were accompanied by increased resistance to strand breakage by lymphocyte DNA and decreased levels of some oxidative metabolites in the urine.

Carcinogenesis is a multistep process, and oxidative damage is linked to formation of tumors through several mechanisms (9, 10). Oxidative stresses induced by free radicals cause DNA damage, which, when left unrepaired, can lead to base mutation, single and double strand breaks, DNA cross-linking, and chromosomal breakage and rearrangement. This potentially cancer-inducing oxidative damage might be prevented or limited by dietary antioxidants found in fruit and vegetables. Studies to date have demonstrated that phytochemicals in common fruit and vegetables can have complementary and overlapping mechanisms of action, including modulation of detoxification enzymes, scavenging of oxidative agents, stimulation of the immune system, regulation of gene expression in cell proliferation and apoptosis, hormone metabolism, and antibacterial and antiviral effects (15, 16).

Role of phytochemicals in the prevention of cardiovascular disease

Numerous investigations have been undertaken that suggest a strong link between dietary intake of phytochemicals and reduced risk of cardiovascular disease. Dietary flavonoid intake was significantly inversely associated with mortality from coronary artery disease and inversely related (more weakly but still significantly) with incidence of myocardial infarction (17). In a study in Finland, intake of apples and onions, both high in quercetin, was inversely correlated with total mortality and coronary mortality (18). In a recent Japanese study, the total intake of flavonoids (quercetin, myricetin, kaempferol, luteolin, and ficetin) was inversely correlated with the plasma total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations (19). Intake of quercetin alone was inversely related to total cholesterol and LDL plasma levels. Joshipura et al (20) reported that total fruit intake and total vegetable intake were both individually associated with decreased risk for coronary artery disease; the inverse association between total consumption of fruit and vegetables and coronary artery disease was observed when the dietary intake was > 4 servings/d.

Mechanisms for the prevention of arteriosclerosis by antioxidants have been proposed. In the LDL oxidation hypothesis, oxidized LDL cholesterol has been suggested as the atherogenic factor that contributes to heart disease (21, 22). Oxidized LDL is typically taken up by macrophage scavenger receptors, thus promoting cholesterol ester accumulation and foam cell formation, which promotes atherosclerotic disease. Dietary antioxidants that are incorporated in LDL are themselves oxidized when these LDL are exposed to prooxidative conditions before any extensive oxidation can occur in the sterol or polyunsaturated fatty acids (23). In addition, phytochemicals have been shown to have roles in the reduction of platelet aggregation, modulation of cholesterol synthesis and absorption, and reduction of blood pressure. Recently, C-reactive protein, a marker of systemic inflammation, has been reported to be a stronger predictor of cardiovascular disease than LDL cholesterol (24), suggesting that inflammation is a critical factor in cardiovascular disease. Inflammation not only promotes initiation and progression of atherosclerosis but also causes acute thrombotic complications of atherosclerosis. Therefore, the anti-inflammatory activity of phytochemicals may play an important role in the prevention of cardiovascular disease.

WHOLE FOODS OR DIETARY SUPPLEMENTS?

The hypothesis that dietary antioxidants lower the risk of chronic disease has been developed from epidemiologic studies that consistently show that consumption of whole foods, such as fruit and vegetables, is strongly associated with reduced risk of chronic diseases. Therefore, it is reasonable for scientists to identify the bioactive compounds responsible and hope to find the “magic bullet” to prevent those chronic diseases. The key question here is whether a purified phytochemical has the same health benefit as the phytochemical present in whole food or a mixture of foods. It is now believed that dietary supplements do not have the same health benefits as a diet rich in fruit and vegetables because, taken alone, the individual antioxidants studied in clinical trials do not appear to have consistent preventive effects. The isolated pure compound either loses its bioactivity or may not behave the same way as the compound in whole foods. For example, numerous investigations have shown that the risk of cancer is inversely related to the consumption of green and yellow vegetables and fruit. Because β-carotene is present in abundance in these vegetables and fruit, it has been extensively investigated as a possible cancer-preventive agent. However, the role of carotenoids as anticancer supplements has recently been questioned as a result of several clinical studies (25–28). In one study, the incidence of nonmelanoma skin cancer was unchanged in patients receiving a β-carotene supplement (25). In other studies, smokers gained no benefit from supplemental β-carotene (26) with respect to lung cancer incidence and possibly even suffered a deleterious effect, with a significant increase in lung cancer and total mortality (27, 28). Vitamin C supplementation also has been shown not to lower the incidence of cancer and heart disease (29, 30).

We recently reported that phytochemical extracts from fruit have strong antioxidant and antiproliferative effects and proposed that the combination of phytochemicals in fruit and vegetables is critical to powerful antioxidant and anticancer activity (31–33). For example, the total antioxidant activity of phytochemicals in 1 g of apples with skin is equivalent to 83.3 μmol vitamin C equivalents—that is, the antioxidant value of 100 g apples is equivalent to 1500 mg of vitamin C. This is much higher than the total antioxidant activity of 0.057 mg of vitamin C (the amount of vitamin C in 1 g of apples with skin). In other words, vitamin C in apples contributed only $<0.4\%$ of total antioxidant activity (31). Thus, most of the antioxidant activity comes from phytochemicals, not vitamin C. The natural combination of phytochemicals in fruit and vegetables is responsible for their potent antioxidant activity. Apple extracts also contain bioactive compounds that inhibit tumor cell growth in vitro. Phytochemicals in 50 mg apple with skin per milliliter (on a wet basis) inhibit tumor cell proliferation by 42%. Phytochemicals in 50 mg apple without skin per milliliter inhibit tumor cell proliferation by 23%. The apple extracts with skin significantly reduced the tumor cell proliferation when compared with the apple extracts without skin.

We also studied the total antioxidant activity and synergy relationships between different fruit combinations, with results showing that plums had the highest antioxidant activity and that combinations of fruit resulted in greater antioxidant activity that was additive and synergistic. We proposed that the additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods (31–33). This partially explains why no single antioxidant can replace the combination of natural phytochemicals in fruit and vegetables in achieving the health benefits. There are ≈8000 phytochemicals present in whole foods. These compounds differ in molecular size, polarity, and solubility, and these differences may affect the bioavailability and distribution of each phytochemical in different macromolecules, subcellular organelles, cells, organs, and tissues. Pills or tablets simply cannot mimic this balanced natural combination of phytochemicals present in fruit and vegetables.

Our work suggests that to improve their nutrition and health, consumers should be getting antioxidants from a diverse diet and not from expensive nutritional supplements, which do not contain the balanced combination of phytochemicals found in fruit and vegetables and other whole foods. More important, obtaining antioxidants from dietary intake by consuming a wide variety of foods is unlikely to result in consumption of toxic quantities because foods originating from plants contain many diverse types of phytochemicals in varying quantities. Furthermore, the health benefits of the consumption of fruit and vegetables extend beyond lowering the risk of developing cancers and cardiovascular diseases; this consumption also has preventive effects on other chronic diseases such as cataracts, age-related macular degeneration, central neurodegenerative diseases, and diabetes.

Dose issues related to dietary supplements

Research progress in antioxidant and bioactive compounds has boosted the dietary supplement and nutraceutical industries. The use of dietary supplements is growing, especially among baby boomers. However, many of these dietary supplements have been developed based on the results from chemical analysis, in vitro studies, and animal experiments, without human intervention studies. For a thorough understanding of the efficacy and long-term safety of many dietary supplements, further investigation is needed.

What dose of a single antioxidant should be used as a dietary supplement? Natural phytochemicals at the low levels present in fruit and vegetables offer health benefits, but these compounds may not be effective or safe when consumed at higher doses, even in a pure dietary supplement form. Generally speaking, taking higher doses increases the risk of toxicity. The basic principle of toxicology is that any compound can be toxic if the dose is high enough. Dietary supplements are no exception to this basic principle.

It is also important to differentiate the pharmacologic dose from the physiologic (or nutritional) dose. Pharmacologic doses are used clinically to treat specific diseases and need a doctor's prescription; physiologic (or nutritional) doses are used to improve or maintain optimal health, such as in dietary supplements. In the case of antioxidant nutrients, the proper physiologic dose should follow the recommended dietary allowance (RDA) (34). The pharmacologic dose is not equal to the physiologic dose and in some cases can be toxic. In a human study, 30 healthy individuals whose diets were supplemented with 500 mg vitamin C/d showed an increase of oxidative damage in the DNA isolated from lymphocytes (35). This study suggests that vitamin C at a high dose (500 mg) may act as a prooxidant in the body. We do not have an RDA for phytochemicals. Therefore, it is not wise to take megadoses of purified phytochemicals as supplements before strong scientific evidence supports doing so.

CONCLUSIONS

Increasing the consumption of fruit and vegetables, whole grains, and soy is a practical strategy for consumers to optimize their health and to reduce the risk of chronic diseases. Use of dietary supplements, functional foods, and nutraceuticals is increasing as industry is responding to consumers' demands. However, there is a need for more information about the health benefits and possible risks to ensure the efficacy and safety of dietary supplements. It is recommended that consumers follow the US Department of Agriculture dietary guidelines to meet their nutrient requirements for health improvement and disease prevention. We believe that the evidence suggests that antioxidants are best acquired through whole-food consumption, not as a pill or an extract.

The author had no conflict of interest.

REFERENCES

1. Temple NJ. Antioxidants and disease: more questions than answers. Nutr Res 2000;20:449–59.
2. Willett WC. Diet and health: what should we eat? Science 1994;254: 532–37.
3. Willett WC. Diet, nutrition, and avoidable cancer. Environ Health Perspect 1995;103(8):165–70.
4. Doll R, Peto R. Avoidable risks of cancer in the United States. J Nat Cancer Inst 1981;66:1197–265.
5. National Academy of Sciences, Committee on Diet, Nutrition, and

Cancer, Assembly of Life Sciences, National Research Council. Diet, nutrition, and cancer. Washington, DC: National Academy Press, 1982.
6. National Academy of Sciences, Committee on Diet and Health, National Research Council. Diet and health: implications for reducing chronic disease risk. Washington, DC: National Academy Press, 1989.
7. Shahidi F, Naczk M. Food phenolics: an overview. In: Shahidi F, Naczk M, eds. Food phenolics: sources, chemistry, effects, applications. Lancaster, PA: Technomic Publishing Company Inc, 1995:1–5.
8. Ames BN, Gold LS. Endogenous mutagens and the causes of aging and cancer. Mutat Res 1991;250:3–16.
9. Liu RH, Hotchkiss JH. Potential genotoxicity of chronically elevated nitric oxide: a review. Mutat Res 1995;339:73–89.
10. Ames BN, Shigenaga MK, Gold LS. DNA lesions, inducible DNA repair, and cell division: the three key factors in mutagenesis and carcinogenesis. Environ Health Perspect 1993;101(suppl 5):35–44.
11. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 1992; 18(1):1–29.
12. Knekt P, Jarvinen R, Seppanen R, et al. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol 1997;146:223–30.
13. Le Marchand L, Murphy SP, Hankin JH, Wilkens LR, Kolonel LN. Intake of flavonoids and lung cancer. J Natl Cancer Inst 2000;92(2): 154–60.
14. Boyle SP, Dobson VL, Duthie SJ, Kyle JAM, Collins AR. Absorption and DNA protective effects of flavonoid glycosides from an onion meal. Eur J Nutr 2000;39:213–23.
15. Dragsted LO, Strube M, Larsen JC. Cancer-protective factors in fruits and vegetables: biochemical and biological background. Pharmacol Toxicol 1993;72:116–35.
16. Waladkhani AR, Clemens MR. Effect of dietary phytochemicals on cancer development. Int J Mol Med 1998;1:747–53.
17. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993;342:1007–11.
18. Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. Br Med J 1996; 312(7027):478–81.
19. Arai Y, Watanabe S, Kimira M, Shimoi K, Mochizuki R, Kinae N. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr 2000;131(9):2243–50.
20. Joshipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. Ann Intern Med 2001; 134:1106–14.
21. Berliner J, Leitinger N, Watson A, Huber J, Fogelman A, Navab M. Oxidized lipids in atherogenesis: formation, destruction and action. Thromb Haemost 1997;78:195–9.
22. Witztum JL, Berliner JA. Oxidized phospholipids and isoprostanes in atherosclerosis. Curr Opin Lipidol 1998;9:441–8.
23. Sanchez-Moreno C, Jimenez-Escrig A, Saura-Calixto F. Study of low-density lipoprotein oxidizability indexes to measure the antioxidant activity of dietary polyphenols. Nutr Res 2000;20(7): 941–53.
24. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347: 1557–65.
25. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with β-carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996;334: 1145–49.
26. Greenberg ER, Baron JA, Stuckel TA, Stevens MM, Mandel JS. A clinical trial of β-carotene to prevent basal cell and squamous cell cancers of the skin. N Engl J Med 1990;323:789–95.
27. The α-tocopherol, β-carotene Cancer Prevention Study Group. The effect of vitamin E and β-carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330: 1020–35.
28. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of β-carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150–5.
29. Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 1993;85(18):1483–92.
30. Salonen JT, Nyysonen K, Salonen R, et al. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. J Intern Med 2000;248: 377–86.
31. Eberhardt MV, Lee CY, Liu RH. Antioxidant activity of fresh apples. Nature 2000;405:903–4.
32. Sun J, Chu Y-F, Wu X, Liu RH. Antioxidant and antiproliferative activities of fruits. J Agric Food Chem. 2002;50:7449–54.
33. Chu Y-F, Sun J, Wu X, Liu RH. Antioxidant and antiproliferative activities of vegetables. J Agric Food Chem. 2002;50:6910–16.
34. National Research Council. Recommended Dietary Allowance. 10th ed. Washington, DC: National Academy Press, 1989.
35. Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P, Lunec J. Vitamin C exhibits pro-oxidant properties. Nature 1998;392:559.