Phytochemicals beyond Antioxidation

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EXPANDED ABSTRACT

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Fruits, vegetables, spices, and some grains provide thousands of phytochemicals to the human diet, and many of these are absorbed into the body. Although these commonly are antioxidants based on their ability to trap singlet oxygen, they have many documented functions beyond antioxidantiation. These phytochemicals can interact with the host to confer a preventive benefit by regulating enzymes important in metabolizing xenobiotics and carcinogens, by modulating nuclear receptors and cellular signaling of proliferation and apoptosis, and by acting indirectly through antioxidant actions that reduce proliferation and protect DNA from damage (1).

Current National Cancer Institute dietary recommendations emphasize increasing the daily consumption of fruits and vegetables from diverse sources such as citrus fruits, cruciferous vegetables, and green and yellow vegetables (2). Often in the scientific and lay press, a single phytochemical, such as lycopene from tomatoes, is featured for its antioxidant activities when the beneficial effects actually result from the ingestion of foods that contain families of compounds, including, in the case of tomatoes, lycopene, phytoene, phytofluene, vitamin E, and vitamin C. Tomato products, including soups, juices, pasta, and catsup, have received increased attention since Giovannucci and colleagues (3) reported that an increased dietary intake of lycopene is associated with a reduced risk of prostate cancer. Nonetheless, studies of lycopene exemplify the phytochemical functions beyond antioxidantiation manifested by many phytochemicals.

Lycopene has the highest antioxidant activity among all dietary carotenoids and is very efficient at quenching singlet oxygen and scavenging free radicals (4). Although the antioxidant activity of lycopene, as assayed by inhibition of formation of thiobarbituric acid–reactive substances in laboratory studies of multilamellar liposomes (5), is ranked as lycopene > α-tocopherol > α-carotene > β-cryptoxanthin > zeaxanthin = β-carotene > lutein, mixtures of carotenoids are more effective than the single compounds. This synergistic effect is most pronounced when lycopene or lutein is present. The superior protection of mixtures may be related to specific positioning of different carotenoids in membranes.

Although lycopene is a carotenoid without pro–vitamin A activity, it has potent effects on prostate cancer cell proliferation alone and in combination with α-tocopherol. Studies of the effects of lycopene and α-tocopherol (vitamin E) on the growth of 2 different human prostate carcinoma cell lines (the androgen-insensitive DU-145 and PC-3) found that lycopene alone is not a potent inhibitor of prostate carcinoma cell proliferation. However, the simultaneous addition of lycopene and α-tocopherol at physiological concentrations (<1 and 50 μmol/L, respectively) strongly inhibits prostate carcinoma cell proliferation, reaching values close to 90% (6). The effect of lycopene with α-tocopherol is synergistic and is not shared by β-tocopherol, ascorbic acid, and probucol. Furthermore, the combination of low concentrations of lycopene with 1,25-dihydroxyvitamin D3 synergistically inhibits cell proliferation and stimulates differentiation in the HL-60 promyelocytic leukemia cell line (7). Lycopene treatment induces a concentration-dependent reduction in HL-60 cell growth as measured by [3H]thymidine incorporation and cell counting. This effect is accompanied by inhibition of cell cycle progression in the G0/G1 phase as measured by flow cytometry. Lycopene alone induces cell differentiation as measured by phorbol ester–dependent reduction of nitro blue tetrazolium and expression of the cell surface antigen CD14. Additional gene-nutrient interactions also may be involved in the observed effects of carotenoids. Studies using human and animal cells have identified a gene, connexin 43, whose expression is upregulated by chemopreventive carotenoids and which allows direct intercellular gap junctional communication (GJC). GJC is deficient in many human tumors, and its restoration or upregulation is associated with decreased proliferation (8).

It is feasible to study the effects of mixtures of phytochemi-

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erals on serum biomarkers as demonstrated by a recent clinical trial (9) in which a mixed intake of fruits and vegetables (500 g/d meeting “5-a-day” guidelines vs. 100 g/d) increased folate by 15% and decreased plasma homocysteine by 11% in 47 normal volunteers. The fruit- and vegetable-rich diet provided 13.3 mg carotenoids, 173 mg vitamin C, and 228 μg folate compared to 2.9 mg carotenoids, 65 mg vitamin C, and 131 μg folate. Remarkably, plasma nutritional biomarkers increased by 46% for lutein, 45% for β-carotene, 64% for vitamin C, and 121% for α-carotene, demonstrating the ability to track such an intervention for cancer prevention.

The key research questions that need to be determined are:
a) Can biomarkers of these phytochemical effects be used to follow changes in cancer cell progression, morphology, or biochemistry useful in cancer prevention studies? b) Can methods be developed to simultaneously track the disposition of phytochemicals from fruits and vegetables, given the differences in volumes of distribution, pharmacokinetics of absorption, and the various pathways of metabolism and clearance of these substances? and c) Can synergistic interactions of phytochemicals from fruits and vegetables be demonstrated in vitro and in vivo that provide the scientific substantiation for the popular recommendation (10) to eat a variety of colorful fruits and vegetables for their cancer preventive benefits?

LITERATURE CITED