Fruit and Vegetable Phytochemicals

Chemistry, Nutritional Value, and Stability

Laura A. de la Rosa
Emilio Alvarez-Parrilla
Gustavo A. González-Aguilar

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Edition first published 2010
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Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical, and Medical business to form Wiley-Blackwell.

Editorial Office
2121 State Avenue, Ames, Iowa 50014-8300, USA

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Library of Congress Cataloging-in-Publication Data

de la Rosa, Laura A.
Fruit and vegetable phytochemicals : chemistry, nutritional value and stability /
Laura A. de la Rosa, Emilio Alvarez-Parrilla, Gustavo A. González-Aguilar. – 1. ed.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-8138-0320-3 (hardback : alk. paper)
1. Phytochemicals. 2. Polyphenols. 3. Carotenoids. 4. Fruit–Analysis. 5. Vegetables–Analysis. I. Alvarez-Parrilla, Emilio. II. González-Aguilar, Gustavo A. III. Title.
QK898.P764R67 2009
615'.321–dc22

2009031846

A catalog record for this book is available from the U.S. Library of Congress.

Set in 10/12pt Times by Aptara® Inc., New Delhi, India
Printed in Singapore

1 2010

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Preface

There has been increasing interest in the nutritional properties of fruits and vegetables as sources of health-promoting phytochemical compounds, due to epidemiological data that correlate a high consumption of these compounds with a lower risk of several cardiovascular and degenerative diseases. Phytochemicals are a heterogeneous group of chemical compounds with numerous biological actions. The aim of this book is to provide scientists in the areas of food technology and nutrition with accessible and up-to-date information about the chemical nature, classification, and analysis of the main phytochemicals present in fruits and vegetables: polyphenols and carotenoids. Special care is taken to analyze the health benefits of these compounds and their interaction with fiber, antioxidants, and other biological activities, as well as the degradation processes that occur after harvest and minimal processing.

This book was possible thanks to the valuable collaboration of many scientists who agreed to dedicate part of their time to participate in this project, with valuable contributions from their different fields of expertise. To them we are sincerely thankful.

Dr. Laura A. de la Rosa
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Fruit and Vegetable Phytochemicals

Chemistry, Nutritional Value, and Stability

1 The Contribution of Fruit and Vegetable Consumption to Human Health

Elhadi M. Yahia

Introduction

Increasing incidences of some chronic diseases, including cancer and cardiovascular disease, especially in industrial countries, have raised awareness regarding the importance of diet (Erbersdobler 2003). It is estimated that one-third of the cancer cases and up to half of cardiovascular disease cases are thought to be diet related (Goldberg 1994). Numerous epidemiological studies have shown an inverse association between fruit and vegetable consumption and chronic diseases, including different types of cancer and cardiovascular disease (Hirayama 1990; Block and others 1992; Howe and others 1992; Steinmetz and Potter 1991, 1996; World Cancer Research Fund 1997; Joshipura and others 2001; Bazzano and others 2002; Kris-Etherton and others 2002). These studies have shown mounting evidence that people who avoid fruit and vegetables completely, or who consume very little, are indeed at increased risk of these diseases. Therefore, interest in the health benefits of fruit and vegetable consumption is increasing, and the interest in understanding the type, number, and mode of action of the different components in fruits and vegetables that confer health benefits is also increasing.

Fruits and vegetables have historically been considered rich sources of some essential dietary micronutrients and fibers, and more recently they have been recognized as important sources for a wide array of phytochemicals that individually, or in combination, may benefit health (Stavric 1994; Rechkemmer 2001). Therefore, some people have conferred on fruits and vegetables the status of "functional foods." There are many biologically plausible reasons for this potentially protective association, including the fact that many of the phytochemicals act as antioxidants.

Phytochemicals present in fruits and vegetables are very diverse, such as ascorbic acid, carotenoids, and phenolic compounds (Liu 2004; Percival and others 2006; Syngletary and others 2005; Yahia and others 2001a, 2001b). Plant polyphenols are ubiquitous in the diet, with rich sources being tea, wine, fruits, and vegetables; they demonstrate considerable antioxidative activity *in vitro*, which can have important implications for health (Duthie and others 2000).

Naturally occurring compounds such as phytochemicals, which possess anticarcinogenic and other beneficial properties, are referred to as chemopreventers. One of the predominant mechanisms of their protective action is due to their antioxidant activity and the capacity to scavenge free radicals. Among the most investigated chemopreventers are some vitamins, plant polyphenols, and pigments such as carotenoids, chlorophylls, flavonoids, and betalains. Resolution of the potential protective roles of specific antioxidants and other constituents of fruits and vegetables deserves major attention.

Evidence indicates that for the effect of fruit and vegetable consumption on health, the whole may be more than the sum of the parts; individual components appear to act synergistically where the influence of at least some of these is additive.

Consumption of a diet high in fruits and vegetables increases antioxidant concentration in blood and body tissues and potentially protects against oxidative damage to cells and tissues. Olmedilla and others (2001) described blood concentration of carotenoids, tocopherols, ascorbic acid, and retinol in well-defined groups of healthy nonsmokers, aged 25–45 years; the study included 175 men and 174 women from five European countries (France, Northern Ireland, Republic of Ireland, the Netherlands, and Spain). Analysis was centralized and performed within 18 months. Within-gender, vitamin C showed no significant differences between countries. Females in France, Republic of Ireland, and Spain had significantly higher plasma vitamin C concentration than their male counterparts. Serum retinol and α-tocopherol levels were similar, but γ-tocopherol showed great variability, being lowest in Spain and France and highest in the Netherlands. The ratio of provitamin A to non–provitamin A carotenoids was similar among countries, whereas the ratio of xanthophylls (lutein, zeaxanthin, and β-cryptoxanthin) to carotenes (α-carotene, β-carotene, and lycopene) was double in southern areas (Spain) compared to northern areas (Northern Ireland and Republic of Ireland). Serum concentration of lutein and zeaxanthin were highest in France and Spain and β-cryptoxanthin was highest in Spain and the Netherlands. *trans*-Lycopene tended to be highest in Irish males and lowest in Spanish males, whereas α-carotene and β-carotene were higher in the French volunteers. Because of the study design, concentration of carotenoids and vitamins A, C, and E represent physiological ranges achievable by dietary means and may be considered as "reference values" in serum of healthy, nonsmoking middle-aged subjects from the five European countries. Results suggest that lutein (and zeaxanthin), β-cryptoxanthin, total xanthophylls, γ-tocopherol, and the ratio of β-tocopherol to γ-tocopherol may be important markers related to the healthy or protective effects of a Mediterranean-like diet.

The epidemiological evidence indicates that avoidance of smoking, increased consumption of fruits and vegetables, and control of infections can have a major effect on reducing rates of several chronic diseases including cardiovascular disease and different types of cancer (Ames and others 1995; Graham and Mettlin 1981; Giovannucci 1999; Liu 2004; Syngletary and others 2005; Percival and others 2006). It is argued that increasing intake of 400 to 800 g/day of fruits and vegetables is a public health strategy of considerable importance for individuals and communities worldwide. For this reason the World Health Organization (WHO) recommends a daily intake of more than 400 g per person daily, and health authorities worldwide promote high consumption of fruits and vegetables. Many of the putative chemoprotective phytochemicals in fruits and vegetables are colored (due to various pigments). The guidelines are based on selecting one daily serving of fruits and vegetables from each of seven color classes (red, yellow-green, red-purple, orange, orange-yellow, green, white-green) so that a variety of phytochemicals is consumed. A study by Johnston and others (2000) during 1994–1996, a "continuing survey of food intakes by individuals," was used to examine the types of fruits and vegetables consumed in the US. The sample populations consisted of 4,806 men and women (25–75 years old) who completed two nonconsecutive 24-hr recalls, consumed 3.6–2.3 servings of vegetables and 1.6 ± 2.0 servings of fruit daily. Iceberg lettuce, tomatoes, French fried potatoes, bananas, and orange juice were the most commonly consumed fruits and vegetables, accounting for nearly 30% of all fruits and vegetables consumed. The most popular items, lettuce and tomatoes, were consumed by 39–42% of the sample population during the reporting period. Fewer respondents (16–24%) consumed French fried potatoes, bananas, or orange juice. Only 3% of the sample consumed broccoli during the reporting period. White potato consumption averaged 1.1 servings daily, with French fried potatoes representing 0.4 serving. Tomato product consumption averaged 0.5 serving daily, dark green vegetable consumption averaged 0.2 serving daily, and citrus, berries, or melon consumption amounted to nearly 0.8 serving daily. These data have indicated that people in the US are consuming more fruits and vegetables compared to previous years but that dark green and cruciferous vegetable intake is low. Many studies suggest that consumption of fruit and vegetables is still low in many countries (Naska and others 2000; Agudo and others 2002; USDA 2002; Blanck and others 2008), and efforts are still needed to increase it. This chapter will highlight the potential health benefits of fruit and vegetable consumption on several diseases, as well as the nutritional and health importance of some fruits and vegetables.

Effect of Consumption of Fruit and Vegetables on Some Diseases

Cancer

Epidemiological evidence of cancer-protective effects of fruits and vegetables, as well as the basic mechanisms by which phytochemicals in fruits and vegetables can protect against cancer development, has been previously surveyed by Wargovich (2000). Sometimes it was difficult to associate total fruit and vegetable consumption and cancer prevention, but it could be associated with some specific families or types of fruits and vegetables (Steinmetz and Potter 1996; Voorips and others 2000). For example, a high consumption of tomato or tomato-based products is consistently associated with lower risk of different cancer types as shown by meta-analysis, with the highest evidence found for lung, prostate, and stomach cancer (Giovannucci 1999). The metabolism of chemical carcinogens has been shown to be influenced by dietary constituents (Wattenberg 1975). Naturally occurring inducers of increased activity of the microsomal mixed-function oxidase system are present in plants; cruciferous vegetables are particularly potent in this regard. From Brussels sprouts, cabbage, and cauliflower, three indoles with inducing activity have been identified: indole-3-acetonitrile, indole-3-carbinol, and 3,3′-diindolylmethane. A second type of dietary constituent that affects the microsomal mixed-function oxidase system is added phenolic antioxidants, butylated hydroxyanisole (BHA), and butylated hydroxytoluene. The feeding of BHA has resulted in microsomal changes in the liver. Spectral characteristics of cytochrome P450 were changed, and the aryl hydrocarbon hydroxylase system of these microsomes demonstrated increased sensitivity to inhibition by α-naphthoflavone. A decrease in the binding of metabolites of benzo[*a*]pyrene to DNA was noted upon incubation of these microsomes with benzo[*a*]pyrene. BHA and butylated hydroxytoluene exert a protective effect against chemical carcinogens. Therefore, it seems that the constituents of the diet could be of consequence in the neoplastic response to exposure to carcinogens in the environment.

Several *in vitro* studies have shown that phenolic compounds in fruits and vegetables have antiproliferative effect in different cancer cell lines (Eberhardt and others 2000; Chu and others 2002; Sun and others 2002; Liu and others 2005; Mertens-Talcott and others 2005; Percival and others 2006).

Quercetin, a flavonoid found in many fruits and vegetables, has been shown to affect the metastatic potential of mouse tumor cells (Suzuki and others 1991). Mutagenicity of quercetin was examined by means of DNA fingerprint analysis using the Pc-1 probe that efficiently detects mutations due to recombination. Treatment of BMT-11 and FM3A tumor cells with quercetin resulted in gain and loss of bands in the fingerprints in both cell lines. The frequencies of the clones having undergone mutation were 3/11 and 6/26, respectively. This suggests that quercetin is mutagenic and induces recombination, and the results seem to provide a molecular basis for the phenotypic variations of BMT-11 tumor cells induced by quercetin. It is important to mention, however, that although *in vitro* quercetin has consistently tested positive for mutagenic activity in prokaryotic and eukaryotic cells, *in vivo* experiments have not confirmed these findings, supporting the toxicological safety of quercetin (Harwood and others 2007). Other flavonoids also show mutagenic activity (Takahashi and others 1979).

Chlorophyllin (CHL), a food-grade derivative of the ubiquitous fruit and vegetable pigment chlorophyll, has been shown to be a potent, dose-responsive inhibitor of aflatoxin B_1 DNA adduction and hepatocarcinogenesis in the rainbow trout model when fed with carcinogen (Breinholt and others 1995). Chlorophyllins are derivatives of chlorophyll in which the central magnesium atom is replaced by other metals, such as cobalt, copper, or iron. The relative efficacy of chlorophyll and chlorophyllin has been shown to modify the genotoxic effects of various known toxicants (Sarkar and others 1994). CHL neither promoted nor suppressed carcinogenesis with chronic postinitiation feeding. By molecular dosimetry analysis, reduced aflatoxin B_1-DNA adduction accounted quantitatively for reduced tumor response up to 2000 ppm dietary CHL, but an additional protective mechanism was operative at 4000 ppm CHL. The finding of potent inhibition (up to 77%) at CHL levels well within the chlorophyll content of some green fruits and vegetables may have important implications in intervention and dietary management of human cancer risks.

Monoterpenes are natural plant products found in the essential oils of many commonly consumed fruits and vegetables and have been widely used as flavor and fragrance additives in food and beverages. Monoterpenes have been shown to possess antitumorigenic activities (Kelloff and others 1996). Limonene, the simplest monocyclic monoterpene, which is found in some citrus fruits, and perrillyl alcohol, a hydroxylated limonene analog, have demonstrated chemopreventive and chemotherapeutic activity against mammary, skin, lung, pancreas, and colon tumors in rodent models (Crowell and Gould 1994; Wattenburg and Coccia 1991; Stark and others 1995).

Experimental studies (Sugie and others 1993; Dashwood and others 1989; Tanaka and others 1990) have shown that indoles and isothiocyanates (found in *Brassica* vegetables) given to animals after a carcinogen insult reduced tumor incidence and multiplicity at a number of sites including the liver, mammary gland, and colon. A possible inhibitory activity of isothiocyanates and indoles against tumorigenesis apparently stems from their ability to influence Phase I and Phase II biotransformation enzyme activities (Zhang and Talalay 1994; Boone and others 1990; McDannell and McLean 1988). Sulforaphane, which is present in broccoli, is a potent inducer of the Phase II detoxification enzymes quinine reductase and glutathione transferase and an inhibitor of the carcinogen-activating cytochrome P450 2E1 (Zhang and others 1992; Barcelo and others 1996).

Numerous studies (Rungapamestry and others 2007) have indicated that the hydrolytic products of at least three glucosinolates, 4-methylsulfinylbutyl (glucoraphanin), 2-phenylethyl (gluconasturtiin), and 3-indolylmethyl (glucobrassicin), have anticarcinogenic activity. Indole-3-carbinol, a metabolite of glucobrassicin, has shown inhibitory effects in studies of human breast and ovarian cancers. *S*-Methylcysteine sulfoxide and its metabolite methylmethane thiosulfinate were shown to inhibit chemically induced genotoxicity in mice. Thus, the cancer chemopreventive effects of *Brassica* vegetables that have been shown in human and animal studies may be due to the presence of both types of sulfur-containing phytochemicals (i.e., certain glucosinolates and *S*-methylcysteine sulfoxide).

Stomach

Reports on an inverse relationship between the consumption of fresh vegetables and human gastrointestinal cancer have been followed by screening for the protective activity of a large number of plant extracts, including leafy vegetables (Botterweck and others 1998; Larsson and others 2006).

Protection for all sites of digestive-tract cancers (oral cavity and pharynx, esophagus, stomach, colon, rectum) was associated with an increased intake of tomato-based foods and an increased supply of lycopene (Franceschi and others 1994). People who ate at least one serving of tomato-based product per day had 50% less chance of developing digestive tract cancer than those who did not eat tomatoes (Franceschi and others 1994). The intake of lycopene has also been associated with a reduced risk of cancers of sites other than the digestive tract, such as the pancreas and the bladder (Gerster 1997). Older subjects who regularly ate tomatoes were found to be less likely to develop all forms of cancer (Colditz and others 1985). A significant trend in risk reduction of gastric cancers by high tomato consumption was also observed in a study that estimated dietary intake in low-risk versus high-risk areas in Italy (Buiatti and others 1990). A similar regional impact on stomach cancer was also observed in Japan (Tsugani and others 1992), where out of several micronutrients including vitamins A, C, and D and β-carotene, only lycopene was strongly inversely associated with stomach cancer. Franceschi and others (1994) have shown a consistent pattern of protection for many sites of digestive tract cancer associated with an increased intake of fresh tomatoes.

Habitual consumption of garlic has been reported to correlate with a reduction in gastric nitrite content and reduction in gastric cancer mortality (Mei and others 1982; You and others 1989). *Allium* compounds present in garlic have been reported to inhibit the synthesis of *N*-nitroso compounds (Mei and others 1989). In a human study, 5 g of fresh garlic consumption has shown to markedly suppress urinary excretion of *N*-nitrosoproline in individuals given supplemental nitrate and proline (Mei and others 1989). In addition, two ecological studies (World Cancer Research Fund Food 1997) showed that in areas where garlic or onion production is very high, mortality rates from stomach cancer are very low.

Colon

Consumption of fruits and vegetables, and the associated vitamin C, carotene, and fiber, has been reported to reduce risk of colon cancer (Ziegler and others 1981). Since plant sterols are plentiful in vegetarian diets, the effect of β-sitosterol on colon tumor formation in rats treated with the carcinogen *N*-methyl-*N*-nitrosourea was studied by Raicht and others (1980). They have demonstrated that β-sitosterol nullified in part the effect of this direct-acting carcinogen on the colon. They suggest that plant sterols may have a protective dietary action to retard colon tumor formation, and therefore the beneficial effects of vegetarian diets may be enhanced because of the presence of these compounds.

An increased risk of colon cancer has been associated with decreases in the frequency with which vegetables were eaten in a study of 214 females with cancer of the colon, and 182 females with cancer of the rectum yielded similar results (Graham and others 1978). The decrease in risk was found to be associated with frequent ingestion of vegetables, especially cabbage, Brussels sprouts, and broccoli, and it is consistent with the decreased numbers of tumors observed in animals challenged with carcinogens and fed compounds found in these same vegetables.

Associations between fruit, vegetable, and dietary fiber consumption and colorectal cancer risk were investigated in a population that consumes relatively low amounts of fruit and vegetables and high amounts of cereals (Terry and others 2001). Data were examined from a food-frequency questionnaire used in a population-based prospective mammography screening study of women in central Sweden. Women with a diagnosis of colorectal cancer were identified by linkage to regional cancer registries, and Cox proportional hazards models were used to estimate relative risks; all statistical tests were two-sided. During an average 9.6 years of follow-up of 61,463 women, 460 incident cases of colorectal cancer were observed. In the entire studied population, total fruit and vegetable consumption was inversely associated with colorectal cancer risk, but subanalyses showed that this association was largely due to fruit consumption. The association was stronger and the dose–response effect was more evident among individuals who consumed the lowest amounts of fruit and vegetables; individuals who consumed less than 1.5 servings of fruit and vegetables/day had a higher relative risk of developing colorectal cancer compared with individuals who consumed greater than 2.5 servings.

Diets containing citrus fiber have been reported to reduce the risk of intestinal cancer. The effect of dietary dehydrated citrus fiber on carcinogenesis of the colon and small intestine was studied in male F344 rats by Reddy and others (1981). Weanling rats were fed semipurified diets containing 5% fat and 15% citrus fiber; at 7 weeks of age, all animals, except vehicle-treated controls, received weekly injections of 8 mg azoxymethane (AOM)/kg body weight for 10 weeks, and the AOM- or vehicle-treated groups were necropsied 20 weeks after the last injection of AOM. The animals fed the citrus fiber diet and treated with AOM had a lower incidence (number of animals with tumors) and multiplicity (number of tumors/tumor-bearing animal) of colon tumors and tumors of the small intestine than did those fed the control diet and treated with

AOM. The number of adenomas but not the number of adenocarcinomas was reduced in rats fed on the citrus pulp diet.

The effect of a diet containing 10–40% lyophilized cabbage or broccoli as cruciferous vegetable or 10–40% lyophilized potato as noncruciferous vegetable fed for 14 days on the colon mucosal glutathione (GSH) level was studied in male rats (Chen and others 1995). The GSH levels of the duodenum mucosa and the liver were also measured. Cabbage and broccoli enhanced the colon and duodenum mucosal GSH levels in a dose-related manner, but potato had no effect. All three vegetables had no effect on the liver GSH level. The effect of GSH on colon tumorigenesis induced by 1,2-dimethylhydrazine (DMH) was also examined in rats. Male Sprague-Dawley rats were injected weekly with DMH (20 mg/kg body wt) for 20 weeks (Chen and others 1995). DMH lowered the colon mucosal GSH level. GSH (100 mg/day/rat) dissolved in the drinking water and given to rats during and after DMH injections had little or no effect on tumor incidence and total number of colon tumors. Tumors were larger in rats that received GSH than in those that received water. Therefore, it seems likely that the colon mucosal GSH level can be enhanced by feeding rats a diet high in cabbage or broccoli and that GSH added to the drinking water did not affect DMH-induced colon tumorigenesis under the experimental conditions used.

Steinmetz and others (1994) have shown that risk of cancer in the distal colon was 50% lower in women with the highest consumption of garlic than in women who did not consume garlic.

However, some large cohort studies (Michels and others 2000; Voorips and others 2000) showed no appreciable association between fruit and vegetable intake and colon and rectal cancer.

Breast

A meta-analysis of 26 prospective and retrospective studies (Gandini and others 2000) confirmed the reduction of the risk of breast cancer with enhanced intake of fruit and vegetables, in contrast to a pooled analysis of eight prospective studies that indicated that fruit and vegetable consumption did not significantly reduce the risk of breast cancer (Smith-Warner and others 2001). A Europe-wide prospective EPIC study (European Prospective Investigation into Cancer and Nutrition) with 285,526 women has demonstrated that a daily intake of 370 g fruit or 246 g vegetables is not associated with a reduced breast cancer risk (van Gils and others 2005). Shannon and others (2003) reported a protective effect of vegetable and fruit intake at the highest quartile of consumption, suggesting a threshold effect in reducing breast cancer risk. However, reports indicated that 100 g of fresh apples have an antioxidant activity equivalent to 1700 mg of vitamin C and that whole apple extracts prevent breast cancer in a rat model in a dose-dependent manner at doses comparable to human consumption of one, three, and six apples a day (Liu and others 2005). Whole apple extracts were reported to effectively inhibit mammary cancer growth in the rat model; thus consumption of apples was suggested as an effective means of cancer protection. Female Sprague-Dawley rats treated with the carcinogen 7,12-dimethylbenz[*a*]anthracene (DMBA) at 50 days of age developed mammary tumors with 71% tumor incidence during a 24-week study, but a dose-dependent inhibition of mammary carcinogenesis by whole apple extracts was observed, where application of low, medium, and high doses of whole apple extracts, comparable to 3.3, 10, and 20 g of apples/kg of body weight, reduced the tumor incidence by 17, 39 ($p < 0.02$), and 44% ($p < 0.01$), respectively; this is comparable to human consumption of one (200 g/60 kg), three, and six apples per day.

Garcia-Solis and others (2008, 2009) studied the antineoplastic properties of some fruits and vegetables using *in vivo* and *in vitro* models. The effect of "Ataulfo" mango fruit consumption was studied on chemically induced mammary carcinogenesis and plasma antioxidant capacity (AC) in rats treated with the carcinogen *N*-methyl-*N*-nitrosourea (MNU) (Garcia-Solis and others 2008). Mango was administered in the drinking water (0.02–0.06 g/mL) during both short-term and long-term periods to rats, and plasma antioxidant capacity was measured by ferric reducing/antioxidant power and total oxyradical scavenging capacity assays. Rats treated with MNU had no differences in mammary carcinogenesis (incidence, latency, and number of tumors), nor differences in plasma antioxidant capacity. On the other hand, they (Garcia-Solis and others 2009) used a methylthiazolydiphenyltetrazolium bromide assay to screen the antiproliferative activity of aqueous extracts of avocado, black sapote, guava, mango, cactus stems (cooked and raw), papaya, pineapple, four different prickly-pear fruit, grapes, and tomato on the breast cancer cell line MCF-7. Only the papaya extract had a significant antiproliferative effect, and there was no relationship between total phenolic content and AC with antiproliferative effect. These results suggested that each plant food has a unique combination in quantity and quality of phytochemicals that could determine its biological activity.

Indole-3-carbinol, 3,3′-diindolylmethane, and indole-3-acetonitrile, three indoles occurring in edible cruciferous vegetables, have been studied for their effects on 7,12-dimethylbenz[*a*]anthracene-induced mammary tumor formation in female Sprague-Dawley rats and on benzo[*a*]pyrene-induced neoplasia of the forestomach in female ICR/Ha mice (Wattenberg and Loub 1978). When given by oral intubation 20 hr prior to 7,12-dimethylbenz[*a*]anthracene administration, indole-3-carbinol and 3,3′-diindolylmethane had an inhibitory effect on mammary tumor formation, but indole-3-acetonitrile was inactive. Indole-3-carbinol, when added to the diet for 8 days prior to challenge with 7,12-dimethylbenz[*a*]anthracene, inhibited mammary tumor formation, whereas indole-3-acetonitrile did not. Dietary administration of all three indoles inhibited benzo[*a*]pyrene-induced neoplasia of the forestomach in ICR/Ha mice.

The consumption of a mixture of phenolic compounds presented in apple or purple grape juice inhibited mammary carcinogenesis in 7,12-dimethylbenzo[*a*]anthracene (DMBA) treated rats (Liu and others 2005; Jung and others 2006). However, the individual antioxidants of these foods studied in clinical trials, including β-carotene, vitamin C, and vitamin E, do not appear to have consistent preventive effects comparable to the observed health benefits of diets rich in fruits and vegetables, suggesting that natural phytochemicals in fresh fruits and vegetables could be more effective than a dietary supplement.

Associations between breast cancer and total and specific fruit and vegetable group intakes were examined using standardized exposure definitions (Smith-Warner and others 2001). Data sources were eight prospective studies that had at least 200 incident breast cancer cases, included assessment of usual dietary intake, and had completed a validation study of the diet assessment method or a closely related instrument.

These researchers studied 7,377 incident invasive breast cancer cases among 351,825 women whose diet was analyzed at baseline. For highest vs. lowest quartiles of intake, weak nonsignificant associations were observed for total fruits, total vegetables, and total fruits and vegetables. There was no apparent additional benefit for the highest and lowest deciles of intake. There were no associations for green leafy vegetables, eight botanical groups, or 17 specific fruits and vegetables. This study concluded that consumption of fruits and vegetables during adulthood is not significantly associated with reduced risk of breast cancer.

Some research has suggested that diets high in mushrooms may modulate aromatase activity and be useful in chemoprevention against breast cancer by reducing the *in situ* production of estrogen. The white button mushroom (*Agaricus bisporus*) suppressed aromatase activity dose dependently (Grube and others 2001). Enzyme kinetics demonstrated mixed inhibition, suggesting the presence of multiple inhibitors or more than one inhibitory mechanism. Aromatase activity and cell proliferation were then measured using MCF-7aro, an aromatase-transfected breast cancer cell line. Phytochemicals in the mushroom aqueous extract inhibited aromatase activity and proliferation of MCF-7aro cells.

Prostate

Some studies have suggested that ingestion of some fruits and vegetables may potentially reduce risk of prostate cancer (Giovannucci and others 2003; Campbell and others 2004; Stram and others 2006). Several epidemiological studies have reported associations between fruit and vegetable intake and reduced risk of prostate cancer, but the findings are inconsistent and data on clinically relevant advanced prostate cancer are limited (Kirsh and others 2007).

A study at the Harvard School of Public Health done on 48,000 men for 4 years reported that men who ate 10 or more servings of tomato products (such as tomatoes, tomato sauce, pizza sauce) per week had up to 34% less chance to develop prostate cancer (Giovannucci and others 1995). They showed that lycopene intake from tomato-based products is related to a low risk of prostate cancer, but consumption of other carotenoids (β-carotene, α-carotene, lutein, β-cryptoxanthin) or retinol was not associated with the risk of prostate cancer.

Activities of various carotenoids present in foods against human prostate cancer cell lines were investigated (Kotake-Nara and others 2001). Effects of 15 carotenoids on the viability of three lines of human prostate cancer cells, PC-3, DU 145, and LNCaP, were evaluated. When cancer cells were cultured in a carotenoid-supplemented medium for 72 hr at 20 mmol/liter, 5,6-monoepoxy carotenoids, namely, neoxanthin from spinach and fucoxanthin from brown algae, significantly reduced cell viability to 10.9 and 14.9% for PC-3, 15.0 and 5.0% for DU 145, and nearly zero and 9.8% for LNCaP, respectively. Acyclic carotenoids such as phytofluene, xi-carotene, and lycopene, all of which are present in tomato, also significantly reduced cell viability. However, phytoene, canthaxanthin, β-cryptoxanthin, and zeaxanthin did not affect the growth of the prostate cancer cells. DNA fragmentation of nuclei in neoxanthin- and fucoxanthin-treated cells was detected by *in situ* TdT-mediated dUTP nick end labeling (TUNEL) assay. Neoxanthin and fucoxanthin reduced cell viability through induction of apoptosis.

Lung

Increased fruit and vegetable consumption may protect against lung cancer, although epidemiologic findings are inconclusive. Dosil-Díaz and others (2008) analyzed the effect of fruit and vegetable intake on lung cancer risk in a population in northwest Spain, using data from a hospital-based case-control study including 295 histologically confirmed cases and 322 controls. Controls were patients attending the hospital for minor surgery. After adjustment for sex, age, tobacco use, and occupation, the researchers found no protective effect of overall consumption of fruit (odds ratio 1.49, 95% confidence interval 0.81–2.73), but green leafy vegetables conferred a protective effect (odds ratio 0.50, 95% confidence interval 0.30–0.83).

The association of fruit and vegetable consumption and lung cancer incidence was evaluated by Linseisen and others (2007) using recent data from the European Prospective Investigation into Cancer and Nutrition (EPIC), applying a refined statistical approach (calibration) to account for measurement error potentially introduced by using food frequency questionnaire (FFQ) data. Between 1992 and 2000, detailed information on diet and lifestyle of 478,590 individuals participating in EPIC was collected, and during a median follow-up of 6.4 years, 1,126 lung cancer cases were observed. In the whole study population, fruit consumption was significantly inversely associated with lung cancer risk, whereas no association was found for vegetable consumption. In current smokers, however, lung cancer risk significantly decreased with higher vegetable consumption, and this association became more pronounced after calibration, the hazard ratio (HR) being 0.78 (95% CI 0.62–0.98) per 100 g increase in daily vegetable consumption. In comparison, the HR per 100 g fruit was 0.92 (0.85–0.99) in the entire cohort and 0.90 (0.81–0.99) in smokers. Cancer incidence decreased with higher consumption of apples and pears (entire cohort) as well as root vegetables (in smokers).

Wright and others (2008) prospectively examined associations between lung cancer risk and intakes of fruit, vegetables, and botanical subgroups in 472,081 participants aged 50–71 years in the National Institutes of Health (NIH)-AARP Diet and Health Study. Diet was assessed at baseline (1995–1996) with a 124-item dietary questionnaire. A total of 6,035 incident lung cancer cases were identified between 1995 and 2003. Total fruit and vegetable intake was unrelated to lung cancer risk in both men and women, but higher consumption of several botanical subgroups, however, was significantly inversely associated with risk only in men. Association between lung cancer risk and fruit and vegetable consumption was also investigated by Feskanich and others (2000) in 77,283 women in a Nurses' Health Study and 47,778 men in a Health Professionals' Follow-up Study. Diet was assessed using a food frequency questionnaire including 15 fruits and 23 vegetables. Relative risk (RR) of lung cancer within each cohort was estimated using logistic regression models; all statistical tests were two-sided. 519 and 274 lung cancer cases were documented among women and men, respectively. Total fruit consumption was associated with a modestly lower risk among women but not among men. RR for highest versus lowest quintile of intake was 0.79 (95% confidence interval, CI = 0.59–1.06) for women and 1.12 (95% CI = 0.74–1.69) for men after adjustment for smoking parameters. Total fruit and vegetable consumption was associated with lower risk of lung cancer among men and women who had never smoked, but the reduction was not statistically significant (RR = 0.63; 95% CI = 0.35–1.12 in the highest tertile). It is suggested that the inverse association among women was confounded by unmeasured smoking characteristics.

Goodman and others concluded in 1992 that some β-carotene rich fruits such as papaya, sweet potato, mango, and yellow orange showed little influence on survival of lung cancer patients, and the intake of β-carotene before diagnosis of lung cancer does not affect the progression of the disease. These authors also concluded that a tomato-rich diet (which contributes high lycopene content but only a little β-carotene) had a strong positive relationship with survival, particularly among women. However, other studies (Le Marchand and others 1989; Steinmetz and others 1993) concluded that lycopene intake was unrelated to lung cancer.

Cardiovascular disease (CVD)

CVD is the number one cause of death in the United States, and prevention is at the top of the public health agenda (Retelny and others 2008). Evidence shows that reducing the incidence of coronary heart disease with diet is possible (Retelny and others 2008).

Numerous epidemiological studies have demonstrated evidence that diet rich in fruits and vegetables may protect against CVD (Ness and Powles 1997; Law and Morris 1998; Ness and others 1999; Joshipura and others 2001; Bazzano and others 2002). The positive effect has been accomplished by three servings of vegetables and fruits, and the relative risk could be minimized to a great extent by enhancing the vegetable and fruit consumption by up to 10.2 servings per day. A study on 2,682 men in Finland has also indicated that high intake of fruits and vegetables correlates with reduced risk of cardiovascular disease (Rissanen and others 2003). The inverse relationship between vegetable intake and cardiovascular disease was more evident with smokers consuming at least 2.5 servings per day in comparison with less than one serving per day (Liu and others 2001). Legume consumption was significantly and inversely associated with cardiovascular disease, lowering the risk by about 11% (Bazzano and others 2001).

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Nagura and others 2009), with 25,206 men and 34,279 women aged 40–79 years, whose fruit, vegetable, and bean intakes were assessed by questionnaire at baseline in 1988–1990 and followed for 13 years, concluded that intakes of plant-based foods, particularly fruit intake, were associated with reduced mortality from CVD and all causes among Japanese men and women. However, Nakamura and others (2008) assessed the intake of fruits and vegetables in 13,355 men and 15,724 women in Takayama, Gifu, Japan, using a validated FFQ and found that for women, the highest quartile of vegetable intake compared with the lowest was marginally significant and inversely associated with CVD mortality after adjusting for total energy, age, and nondietary and dietary covariates, but in men, CVD death was not associated with fruit or with vegetable intake.

Radhika and others (2008) examined the relationship between fruit and vegetable intake (g/day) and CVD risk factors in urban south Indians. The study population composed of 983 individuals aged at least 20 years selected from the Chennai Urban Rural Epidemiological Study (CURES), a population-based cross-sectional study on a representative population of Chennai in southern India, and fruit and vegetable intake (g/day) was measured using a validated semiquantitative FFQ. Linear regression analysis revealed that after adjusting for potential confounders such as age, sex, smoking, alcohol, body mass index (BMI), and total energy intake, the highest quartile of fruit and vegetable intake (g/day) showed a significant inverse association with systolic blood pressure, total cholesterol, and low-density lipoprotein (LDL)-cholesterol concentration when compared with the lowest quartile. A higher intake of fruit and vegetables explained 48% of the protective effect against CVD risk factors.

It has been reported that death attributed to cardiovascular and coronary heart diseases showed strong and consistent reductions with increasing nut/peanut butter consumption (Blomhoff and others 2006). Nuts, including peanuts, have been recognized as having the potential to improve the blood lipid profile, and, in cohort studies, nut consumption has been associated with a reduced risk of coronary heart disease (CHD) (Jenkins and others 2008). Data from the Nurses Health Study indicate that frequent nut consumption is associated with a reduced risk of developing cardiovascular disease. Epidemiologic and clinical trial evidence has demonstrated consistent benefits of nut and peanut consumption on coronary heart disease (CHD) risk and associated risk factors (Kris-Etherton and others 2008). A pooled analysis of four US epidemiologic studies showed that subjects in the highest intake group for nut consumption had an approximately 35% reduced risk of CHD incidence, and the reduction in total CHD death was due primarily to a decrease in sudden cardiac death. Clinical studies have evaluated the effects of many different nuts and peanuts on lipids, lipoproteins, and various CHD risk factors, including oxidation, inflammation, and vascular reactivity (Kris-Etherton and others 2008). Evidence from these studies consistently shows a beneficial effect on these CHD risk factors. The LDL cholesterol-lowering response of nut and peanut studies is greater than expected on the basis of blood cholesterol-lowering equations that are derived from changes in the fatty acid profile of the diet. Thus, in addition to a favorable fatty acid profile, nuts and peanuts contain other bioactive compounds that explain their multiple cardiovascular benefits. Other macronutrients include plant protein and fiber; micronutrients including potassium, calcium, magnesium, and tocopherols; and phytochemicals such as phytosterols, phenolic compounds, resveratrol, and arginine. Kris-Etherton and others (2008) have indicated that nuts and peanuts are food sources that are a composite of numerous cardioprotective nutrients and if routinely incorporated in a healthy diet, population risk of CHD would therefore be expected to decrease markedly.

Hung and others (2003) evaluated the association of consumption of fruits and vegetables with peripheral arterial disease in a cohort study of 44,059 men initially free of cardiovascular disease and diabetes, reporting no evidence that fruit and vegetable consumption protects against peripheral arterial disease, although a modest benefit cannot be excluded. In the age-adjusted model, men in the highest quintile had a relative risk of 0.55 (95% confidence interval = 0.38–0.80) for overall fruit and vegetable intake, 0.52 (0.36–0.77) for fruit intake, and 0.54 (0.36–0.81) for vegetable intake, compared with those in the lowest quintile of intake. However, the associations were greatly weakened after adjustment for smoking and other traditional cardiovascular disease risk factors.

Pure β-carotene supplementation (30–50 mg per day) had no depressive effects on cardiovascular disease risk (Hennekens and others 1996; Omenn and others 1996; Lee and others 1999).

Monounsaturated fats in avocados have been shown to reduce blood cholesterol while preserving the level of high-density lipoproteins (Yahia 2009b). An avocado-enriched diet produced a significant reduction in LDL and total cholesterol in patients with high cholesterol levels, whereas diets enriched with soy and sunflower did not change the total cholesterol concentrations (Carranza and others 1997).

Lycopene from tomato fruit was found to prevent the oxidation of LDL cholesterol and to reduce the risk of developing atherosclerosis and coronary heart disease (Agarwal and Rao 1998), and a daily consumption of tomato products providing at least 40 mg of lycopene was reported to be enough to substantially reduce LDL oxidation. Lycopene is recognized as the most efficient singlet oxygen quencher among biological carotenoids (Di Mascio and others 1991, 1989). Lycopene has also been reported to increase gap-junctional communication between cells and to induce the synthesis of connexin-43 (Zhang and others 1992).

Diabetes Mellitus

The association between the intake of fruit and vegetables and the risk of type 2 diabetes is unclear. Hamer and Chida (2007) have suggested that the consumption of three or more daily servings of fruit or vegetables was not associated with a substantial reduction in the risk of type 2 diabetes, but the intake of antioxidants was associated with a 13% reduction in risk, mainly attributed to vitamin E. Five cohort studies of fruit and vegetables intake and the risk of diabetes using 167,128 participants and 4,858 incident cases of type 2 diabetes, with a mean follow-up of 13 years, were reviewed by Hamer and Chida (2007). The relative risk of type 2 diabetes for consuming five or more servings of fruit and vegetables daily was 0.96 (95% CI, 0.79–1.17, $P = 0.96$), 1.01 (0.88–1.15, $P = 0.88$) for three or more servings of fruit, and 0.97 (0.86–1.10, $P = 0.59$) for three or more servings of vegetables. Nine cohort studies of antioxidant intake and the risk of diabetes were also identified, incorporating 139,793 participants and 8,813 incident cases of type 2 diabetes, with a mean follow-up of 13 years (Hamer and Chida 2007) indicated that the pooled relative risk was 0.87 (0.79–0.98, $P = 0.02$) for the highest compared with the lowest antioxidant intake. Villegas and others (2008) examined the associations between fruit and vegetable intake and the incidence of type 2 diabetes (T2D) in a population-based prospective study of 64,191 Chinese women with no history of T2D or other chronic diseases at study recruitment and with valid dietary information. Individual vegetable groups were all inversely and significantly associated with the risk of T2D, but there was no association with fruit intake.

Randomized controlled trials of patients with type 2 diabetes have confirmed the beneficial effects of nuts on blood lipids, also seen in nondiabetic subjects, but the trials have not reported improvement in A1c or other glycated proteins (Jenkins and others 2008). Therefore, Jenkins and others (2008) concluded that there is justification to consider the inclusion of nuts in the diets of individuals with diabetes in view of their potential to reduce CHD risk, even though their ability to influence overall glycemic control remains to be established.

Nettleton and others (2008) characterized dietary patterns and their relation to incident type 2 diabetes in 5,011 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) and found that high intake of whole grains, fruit, nuts/seeds, green leafy vegetables, and low-fat dairy was associated with a 15% lower diabetes risk.

Bazzano and others (2008) concluded that consumption of green leafy vegetables and fruit was associated with a lower hazard of diabetes, whereas consumption of fruit juices may be associated with an increased hazard among women. A total of 71,346 female nurses aged 38–63 years who were free of cardiovascular disease, cancer, and diabetes in 1984 were followed for 18 years, and dietary information was collected using a semiquantitative FFQ every 4 years (Bazzano and others 2008). During follow-up, 4,529 cases of diabetes were documented; the cumulative incidence of diabetes was 7.4%, and an increase of three servings/day in total fruit and vegetable consumption was not associated with development of diabetes, whereas the same increase in whole fruit consumption was associated with a lower hazard of diabetes. An increase of 1 serving/day in green leafy vegetable consumption was associated with a modestly lower hazard of diabetes, whereas the same change in fruit juice intake was associated with an increased hazard of diabetes.

Experimental evidence showed that consumption of prickly pear cladodes (nopal) could decrease blood glucose levels (Frati and others 1990a). The intake of broiled *Opuntia* stems for 10 days improved glucose control in a small group of adults with non-insulin-dependent diabetes mellitus (NIDDM) (Frati and others 1990b, 1983). The rise in serum glucose levels that follows the intake of a sugar load (oral glucose tolerance test) was lower with previous ingestion of *Opuntia* stems compared to the ingestion of sugar alone (Frati and others 1990a). In patients with NIDDM, the ingestion of some species of nopal (*Opuntia streptacantha, O. ficus-indica)* in fasting condition is generally followed by a decrease of serum glucose and serum insulin levels (Frati 1992). These positive health effects of *Opuntia* stems might be associated with dietary fiber, since similar results can be achieved by *Plantago psyllium* or other sources of dietary fiber (Frati 1992). Ingestion of raw and cooked *Opuntia ficus-indica* extracts resulted in beneficial effects on total cholesterol, without any secondary effect on glucose and lipoproteins amounts in blood (Medellin and others 1998).

Some flavonoids, such as procyanidins, have antidiabetic properties because they improve altered glucose and oxidative metabolisms of diabetic states (Pinent and others 2004). Extract of grape seed procyanidins (PE) administered orally to streptozotocin-induced diabetic rats resulted in an antihyperglycemic effect, which was significantly increased if PE administration was accompanied by a low insulin dose (Pinent and others 2004). The antihyperglycemic effect of PE may be partially due to the insulinomimetic activity of procyanidins on insulin-sensitive cell lines.

Obesity

Nowadays, obesity is considered a major public health issue, especially in most developed countries, because it is widely spread across population groups and because it contributes to the development of chronic diseases, particularly cardiovascular diseases and diabetes.

Despite the alarming increase in the prevalence of obesity in the world, epidemiologic studies on the relation between fruit and vegetable consumption and weight gain