Part I

Chemistry and Biological Functions
The Contribution of Fruit and Vegetable Consumption to Human Health

Elhadi M. Yahia,1∗ María Elena Maldonado Celis,2 and Mette Svendsen3

1Faculty of Natural Sciences, Autonomous University of Querétaro, Avenida de las Ciencias s/n, Juriquilla, Querétaro, Mexico
2Nutrition and Dietetic School, University of Antioquia, Medellín, Colombia
3Section for Preventive Cardiology, Centre of Preventive Medicine, Oslo University Hospital, Norway

1.1 Introduction

Increasing incidences of some chronic diseases, including cancer, cardiovascular, and neurodegenerative diseases (Parkinson’s and Alzheimer’s diseases), especially in industrial countries, have raised awareness regarding the importance of diet (Erbersdobler, 2003). It is estimated that one-third of cancer cases and up to half of cardiovascular disease rates are diet related (Goldberg, 1994).

Clinical and epidemiological studies have justified including antioxidants as dietary factors that affect brain function, promote aging, and contribute to the development of neurodegenerative diseases (Parkinson’s and Alzheimer’s) (Thomas and Beal, 2007). Numerous epidemiological studies have shown an inverse association between fruit and vegetable consumption and chronic diseases including different types of cancer, cardiovascular, and neurodegenerative diseases (Gan et al., 2015; IARC, 2008; Devalaraja et al., 2011; Thompson, 2010; Mirmiran et al., 2013; Boeing et al., 2012; Albarracin et al., 2012; Hirayama, 1990; Block et al., 1992; Howe et al., 1992; Steinmetz and Potter, 1991, 1996; World Cancer Research Fund, 1997; Joshipura et al., 2001; Bazzano et al., 2002; Kris-Etherton et al., 2002; Yahia, 2009; Yahia, 2010; Yahia et al., 2011). These studies have shown mounting evidence that people who avoid fruit and vegetables completely, or consume very little, are indeed at increased risk of these diseases. Therefore, interest in the health benefits of fruit and vegetable consumption is increasing. Moreover, 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 of 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; Dechtemmer, 2001; Abujah et al., 2015). Thus some people have conferred the status of “functional foods” on fruits and vegetables. 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 et al., 2006; Syngletary et al., 2005; Yahia et al., 2001a, 2001b; Yahia, 2009; Yahia, 2010; Yahia et al., 2011; Yahia and Ornelas-Paz, 2010). 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 et al., 2000; Wootton-Beard and Ryan, 2011; Sindhi et al., 2013).

Naturally occurring compounds such as phytochemicals, which possess anticarcinogenic and other beneficial properties, are referred to as chemopreventive agents, being classified as blocking and suppressive agents. The blocking agents are based on their antioxidant activity and the capacity to scavenge free radicals. Among the most investigated antioxidant agents against cancer are some vitamins such as C, A, and E; flavonoids and phenolic acids, which account for 60% and 30%, respectively, of dietary (poly)phenolic compounds (Ramos, 2007); and pigments such as carotenoids, chlorophylls, 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, in that the influence of at least some of them is additive.

∗Corresponding author.
Consumption of a high fruit and vegetable diet increases antioxidant concentration in blood and body tissues, and potentially protects against oxidative damage to cells and tissues. Olmedilla et al. (2001) described blood concentration of carotenoids, tocopherols, ascorbic acid, and retinol in well-defined groups of healthy nonsmokers aged 25–45 years, across a sample of 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 provitamin A to non-provitamin A carotenoid ratio was similar among countries, whereas the xanthophylls (lutein, zeaxanthin, and β-cryptoxanthin) to carotenes (α-carotene, β-carotene, and lycopene) ratio was double in southern areas (Spain) compared to northern areas (Northern Ireland and Republic of Ireland). Serum concentrations 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, while α-carotene and β-carotene were higher in the French volunteers. Due to the study design, the concentration of carotenoids and vitamins A, C, and E represent physiological ranges achievable by dietary means and may be considered as “reference values” in the serum of healthy, non-smoking middle-aged subjects from the five European countries. Results suggest that lutein (and zeaxanthin), β-cryptoxanthin, total xanthophylls, γ-tocopherol, and β-tocopherol to γ-tocopherol ratio 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 (International Agency for Research on Cancer, 2008; Cuenca-Garcia et al., 2014; Stefani and Rigacci, 2014; Ames et al., 1995; Graham and Mettlin, 1981; Giovanelli, 1999; Liu, 2004; Percival et al., 2006; Syngletary et al., 2005).

The global average for vegetables (based on availability and not including vegetable oils) and fruits consumption is 2.6% and 2.7% of total daily energy intake, respectively. Thus, it is argued that increasing intake from 400 to 800 g/day of fruits and vegetables is a public health strategy of considerable importance for individuals and communities worldwide. Vegetable consumption is highest in North Africa, the Middle East, parts of Asia, the USA, Cuba, and southern Europe. On the other hand, fruit intakes are highest in some parts of Africa, the Middle East, southern Europe, and Oceania, and lowest in other parts of Africa and Asia (WCRF/AICR, 2007).

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 (Yahia, 2009; Yahia, 2010; Yahia et al., 2011). Many of the putative chemoprotective phytochemicals in fruits and vegetables are colored (due to different pigments). The guidelines are based on selecting one serving daily 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.

Several promotional campaigns to increase fruit and vegetable consumption have been proposed by developed countries as the USA (5 a Day, now Fruits & Veggies), Australia (Go for 2&5), Canada (Canada’s Food Guide to Healthy Eating), United Kingdom (Food Dudes), Denmark (6 a Day), New Zealand (5+ a Day). Some results of these campaigns in the USA between 2004 and 2009 showed that average consumption of fruits and vegetables for adults was 1.8 cups/day, and that for children less than 6 years old and children 6 to 12 years old consumption increased 4% and 2%, respectively, for adult females 18 to 44 years old it increased by 1%, and for adult males it decreased by 7–9% (Produce for Better Health Foundation, 2010). The survey of the Australian campaign on Western adults after three years through the Health Department’s Health and Well-being Surveillance System showed a mean increase of 0.2 servings/day of fruits and 0.6 servings/day of vegetables (Pollard et al., 2008). In Denmark, in contrast to the results obtained in the USA and Australia, the Danish National Survey of Dietary Habits and Physical Activity between 1995 and 2004 showed an increase in consumption by the 4- to 10-year-old group of 29% vegetables and 58% fruits, and by the 11- to 75-year-old group of 41% fruits and 75% vegetables (Danish National Centre for Social Research, 2005). In Norway, delivery of fruits free of charge to children at school increased the daily intake of fruit from one to two portions between 2001 and 2008 (Bere et al., 2010).

A study by Johnston et al. (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 USA. The sample populations consisted of 4806 men and women (25–75 years old) who completed two non-consecutive 24 hour recalls, consuming 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 products 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 USA 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 et al., 2000; Agudo et al., 2002; USDA, 2003; Blanck et al., 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.

1.2 Effect of Consumption of Fruit and Vegetables on Some Diseases

1.2.1 Cancer

According to the study of Doll and Peto (1981) based on epidemiological studies, an average of 35% of the death rate for cancer is associated with nutritional factors. It has been proposed that absence in the diet of compounds possessing cancer preventing properties, such as fruits and vegetables, is responsible partially for this situation.

In 2007, the World Cancer Research Fund (WCRF/AICR, 2007) published its second expert report in which they found, from cohort studies since the mid 1990s, that evidence of protection by vegetables or fruits consumption is convincing. Non-starchy vegetables probably protect against cancers of the mouth, pharynx, and larynx, and those of the esophagus and stomach. There is limited evidence suggesting that they also protect against cancers of the nasopharynx, lung, colon, and rectum (WCRF/AICR, 2007). The chemopreventive properties of vegetables, fruits, and pulses against some type of cancers is attributed to some micronutrients considered markers for consumption of vegetables, fruits, and pulses (legumes). For example, foods containing carotenoids probably protect against cancers of the mouth, pharynx, larynx, and lung; whereas evidence of consumption of foods containing beta-carotene and lycopene suggests that they probably protect against esophageal and prostate cancer, respectively. On the other hand, in spite of the well-described quercetin mechanisms of action, there is limited evidence suggesting that consumption of foods containing this flavonoid, such as apples, tea, and onions, protects against lung cancer (WCRF/AICR, 2007). 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; rather, there was an association with some specific families or types of fruits and vegetables (Steinmetz and Potter, 1996; Voorips et al., 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 which 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.

Polyphenols have shown the capacity to block initiation or to suppress the stages of promotion and progression of carcinogenesis. In this context, the groups of phenolic
acids, flavonoids, stilbenes, and curcuminoids are the most important.

Several in vitro studies have shown that phenolic compo-
ounds in fruits and vegetables, such as ellagic acid from
pomegranate, have been shown to affect the metastatic potential of
tumor cells (Murakami et al., 2008). Other
azoxymethane-induced colorectal carcinogenesis in rats
than the glycosylated form (rutin), exerts inhibition of
drug transporters like quercetin. It has been shown that quercetin, other
phenotypic variations of BMT11 tumor cells induced
the results seem to provide a molecular basis for the
frequencies of the clones having undergone mutation
were 3/11 and 6/26, respectively. This suggests that
was 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 the intervention and
dietary management of human cancer risks.

Monoterpenes – natural plant products found in the
essential oils of many commonly consumed fruits and
vegetables, and widely used as flavor and fragrance addi-
tives in food and beverages – have been shown to possess
antitumorigenic activities (Kelloff et al., 1996). Limonene,
the simplest monocyclic monoterpane and found in some
citrus fruits, and perillyl alcohol, a hydroxylated limonene
analogue, have demonstrated chemopreventive and chemo-
therapeutic activity against mammary, skin, lung, pancre-
as, and colon tumors in rodent models (Crowell and
Gould, 1994; Wattenburg and Coccia, 1991; Stark et al.,
1995).

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

Numerous studies (Rungapamesty et al., 2007) have
indicated that the hydrolytic products of at least three

gluco, 4-methyl-sulfinylbutyl (glucoraphanin),
2-phenylethyl (glucoraphanin), and 3-indolylmethyl
(glucoraphanin), have anticarcinogenic activity. Indole-
3-carbinol, a metabolite of glucoraphanin, has shown
inhibitory effects in studies of human breast and ovarian
cancers. S-methyl cysteine sulfoxide and its metabolite
methyl methane thiosulfate 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 phyto-
chemicals (i.e. certain glucosinolates and S-methyl cyste-
ine sulfoxide).

Curcumin, the major curcuminoid present in turmeric,
possesses anticancer properties against a wide range of
cancers (prostate, skin, bladder, oral, breast, bone, colon,
stomach, liver, pancreas, cervical). In vitro studies have
shown that mechanisms include inhibition of NF-κB,
arrest of cell cycle, inhibition of proliferation, survival
pathways, transcription factors and other molecules
related to invasion and metastasis, and induction of apoptosis (González-Vallinas et al., 2013). Clinical studies in colorectal and pancreatic cancers have demonstrated antitumor effects. However, in damaged lung epithelium acts as a carcinogen agent, which must be taken into account for smokers and ex-smokers (Shehzad et al., 2010).

1.2.1.1 Stomach

Gastric cancer is the second most common cause of death due to cancer. Although infection with Helicobacter pylori is the strongest risk factor, epidemiological studies have suggested that specific dietary components such as chili, processed meat, smoked foods, grilled or barbecued foods, salt and salty foods, and alcohol play an important role in the etiology of gastric cancer (Ferlay et al., 2010; IARC, 2008; Kim et al., 2010; Shi kata et al., 2006; Tramacere et al., 2012).

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 et al., 1998; Larsson et al., 2006).

A meta-analysis (Wang Q. et al., 2014) showed that consumption of fruit, but not vegetables, was inversely associated with gastric cancer risk. The risk decreases when consumption of fruit is 10% in high versus low analysis, and by 5% per 100 g/day increment in fruit consumption. Above that level, a slight further reduction with higher intake is observed (an approximate 16% reduction for an intake of 500 g/day). This protective effect is attributed to selenium, β-carotene, and vitamins A, C, and E because of anti-inflammatory and antioxidant actions against H. pylori induced damage (Sezikli et al., 2012; Sjunnesson et al., 2001). Furthermore, dietary fiber plays an important role in preventing gastric cancer, acting as a nitrite scavenger like vitamin C (Moller et al., 1988); this is supported by the meta-analysis performed by Zhang et al. (2013), who concluded that a 10 g/day increment in fiber intake was associated with a reduction in the risk of gastric cancer of 44%. Results for high dietary fiber intake could indicate the value of a diet rich in whole grains, vegetables, fruit, and a variety of nutrients which have been shown to prevent gastric cancer (González et al., 2006).

Protection for all sites of digestive tract cancers (oral cavity and pharynx, esophagus, stomach, colon, rectum) has been associated with an increased intake in tomato-based foods, and an increased supply of lycopene (Franceschi et al., 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 et al., 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 et al., 1985). A significant trend in risk reduction of gastric cancers by high tomato consumption was also observed in a study which estimated dietary intake in low-risk versus high-risk areas in Italy (Buiatti et al., 1990). A similar regional impact on stomach cancer was also observed in Japan (Tsugane et al., 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 et al. (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 a reduction in gastric cancer mortality (Mei et al., 1982; You et al., 1989). Allium compounds present in garlic have been reported to inhibit the synthesis of N-nitroso compounds (Mei et al., 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 et al., 1989). In addition, two ecological studies (WCRF/AICR, 1997) showed that in areas where garlic or onion production is very high, mortality rates from stomach cancer are very low.

1.2.1.2 Colon

Colorectal cancer is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide (IARC, 2012). It is accepted that about 70% of CRC cases are linked to diet (Michels et al., 2000). Thus, food is one of the factors on which it is possible to act in order to increase primary prevention (INCa, 2009). The most consistent finding on diet as a determinant of cancer risk prevention is the consumption of vegetables and fruits. Convincing epidemiological evidence for this preventive action exists for CRC attributed to foods containing dietary fiber, and limited but suggestive evidence for fruits and non-starchy vegetables (WCRF/AICR, 2011).

In 2011 the WCRF/AICR published an updated meta-analysis concluding that consumption of 10 g/day dietary fiber reduced risk by 10% and 11% for colon and rectal cancers respectively. Specifically for whole grains (3 servings/day) there was a reduction in risk of 16–21%. In relation to non-starchy vegetables, there is a substantial amount of evidence, but it is inconsistent and did not reach conventional levels of statistical significance, in spite of findings that consumption of 100 g/day or 2
servings/day reduced risk by 1–4%. A similar conclusion was obtained for fruits in this report (WCRF/AICR, 2011). These findings were confirmed in 2015 by the European Prospective Investigation into Cancer and Nutrition (EPIC). In general they found a lower risk of colon cancer with higher self-reported consumption of fruits and vegetables combined (HR Q4 vs. Q1 0.87, 95% CI 0.75–1.01, $P_{\text{trend}}$ 0.02). However, no consistent association was observed for separate consumption of fruits and vegetables; an inverse association between colon cancer and cabbage consumption was observed (36.7 g/day reduced risk of colon cancer by 7%), attributed to glucosinolates, while an increased risk of 5% was suggested for high mushroom consumption (8.8 g/day) (Leenders et al., 2015). Explanations for the attenuation of the risk estimates include the changes over time (11.2 years) of fruits and vegetables consumption, the errors in measurement of the quantity of consumption of fruits and vegetables, which caused false negative results in the analyses regarding diet diversity, and the different dietary questionnaires used by EPIC centers; such aspects must be taken into account in these types of analysis.

Consumption of fruits and vegetables, and the associated vitamin C, carotene, and fiber, has been reported to reduce risk of colon cancer (Ziegler et al., 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 et al. (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 et al., 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 et al., 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 regular cancer registries; Cox proportional hazards models were used to estimate relative risks, and 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 fruits and vegetables; individuals who consumed less than 1.5 servings of fruit and vegetables per day had a higher relative risk of developing colorectal cancer compared with individuals who consumed greater than 2.5 servings.

Diet containing citrus fiber has 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 et al. (1981). Weanling rats were fed semi-purified 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) per kg body weight for 10 weeks; and the AOM- or vehicle-treated groups were autopsied 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 per 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.

Consumption of certain fruit juices has evidenced protective effects against colon cancer, such as pomegranate, citrus (Jaganathan et al., 2014), banana, passion fruit (Chaparro et al., 2015), and mango juice (Corrales-Bernal et al., 2014). These fruit juices contain polyphenols and other phytochemicals like carotenoids and vitamins A and C; these help in reducing the growth of colon cancer cells or the number of chemical carcinogen-induced pre-neoplastic lesions in colon mucosa in mice Balb-c or rats F344 by 91%, 65%, and 56% after consumption of pomegranate, mango, and banana and passion fruit juices (Boateng et al., 2007; Corrales-Bernal et al., 2014; Chaparro et al., 2015). These findings suggest that they can serve as a strategy to reduce the incidence of colon cancer. Pomegranate juice contains ellagic acid, ellagitannins, luteolin glycosides, quercetin, and kaempferol; punicalagin is responsible for more than 50% of the antioxidant activity in the juice (Cerdà et al., 2003), and ellagic acid acts as a blocking agent by inhibiting the CYP1 activation of procarcinogens and induces phase II enzymes like glutathione S-transferase (Barch et al., 1996). The pulp and juice of the citrus
fruit contain flavonoids such as apigenin, naringenin, hesperidin, nobiletin, and limonoids (limonin glucoside, obacunone glucoside mixture) and the carotenoid cryptoxanthin (Jaganathan et al., 2014), which may act as suppressor chemopreventive agents in colon carcinogenesis because of the arrest of cell cycle colon adenocarcinoma HT-29, and the reduction in levels of cyclins A, D1, and E, iNOS, and COX-2 enzymes (Frydoonfar et al., 2003; Pan et al., 2002; Vanamala et al., 2006).

The effect of a diet containing 10–40% lyophilized cabbage or broccoli as cruciferous vegetable or 10–40% lyophilized potato as non-cruciferous vegetable fed for 14 days on the colon mucosal glutathione (GSH) level was studied in male rats (Chen et al., 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 weight) for 20 weeks (Chen et al., 1995). DMH lowered the colon mucosal GSH level. GSH (100 mg/day per rat) dissolved in the drinking water did not affect DMH-induced colon tumorigenesis and plasma antioxidant capacity under the experimental conditions used.

Steinmetz et al. (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 et al., 2000; Voorrips et al., 2000) showed no appreciable association between fruit and vegetable intake and colon and rectal cancer.

1.2.1.3 Breast

IARC (2012) estimated that breast cancer is the second most common cancer in the world, and the most frequent cancer among women, representing 25% of all cancers in 2012.

A meta-analysis of 26 prospective and retrospective studies (Gandini et al., 2000) confirmed the reduction of the risk of breast cancer with enhanced intake of fruit and vegetables. Recently, in a meta-analysis on the risk of breast cancer and dietary factors, 13 and 11 studies evidenced that vegetables (odds ratio OR = 0.77, confidence interval 0.62–0.96, 95%) and fruits (OR = 0.66, CI 0.49–0.9, 95%) consumptions, respectively, are relevant protective factors against breast cancer. Moreover, the study found significant differences for those women who consumed soy foods (OR = 0.66, CI 0.50–0.93, 95%) rich in isoflavones that have a protective effect against this type of cancer (Varinska et al., 2015). In contrast, a pooled analysis of eight prospective studies indicated that fruit and vegetable consumption did not significantly reduce the risk of breast cancer (Smith-Warner et al., 2001). A Europe-wide prospective EPIC study with 285,526 women demonstrated that a daily intake of 370 g fruit or 246 g vegetables is not associated with a reduced breast cancer risk (van Gils et al., 2005). Shannon et al. (2003) reported a protective effect of vegetables 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 et al., 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. However, 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 per kg of body weight, reduced 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.

García-Solís et al. (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) (García-Solís et al., 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), and no differences in plasma antioxidant capacity. On the other hand, they (García-Solís et al., 2009) screened, using methylthiazolyltdiphenyl-tetrazolium bromide assay, 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 which could determine its
biological activity.

With respect to citrus fruits (oranges, tangerines, grape-
fruits, lemons, and limes), a systematic review and meta-
analysis showed an inverse association between citrus
fruits intake and the risk of breast cancer, with a 10%
reduction in risk of breast cancer associated with high
intake of citrus fruits (summary OR, 0.90; 95% CI
0.85–0.96; p < 0.001) (Song and Bae, 2013). It is consid-
ered that citrus fruits contain bioactive compounds such as
β-cryptoxanthin, β-carotene, folate, vitamin C, querce-
tin, hesperetin, and naringenin (So et al., 1996).

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 77 on
benzo[a]pyrene-induced neoplasia of the forestomach in
female ICR/Ha mice (Wattenberg and Loub, 1978). When
given by PO intubation 20 hours prior to 7,12-dimethyl-
benz[a]anthracene administration, indole-3-carbinol and
3,3′-diindolylmethane had an inhibitory effect on mam-
mary 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]anthra-
cene, inhibited mammary tumor formation, whereas
indole-3-acetonitrile did not. Dietary administration of
all three indoles inhibited benzo[a]pyrene-induced neo-
plasia of the forestomach in ICR/Ha mice.

The consumption of a mixture of phenolic compounds
presented in apple or purple grape juice inhibited mam-
mary carcinogenesis in DMBA-treated rats (Liu et al.,
2005; Jung et al., 2006). Similar effects were observed
using polyphenolic extracts from peach and plum, which
showed selective cytotoxic action against the estrogen-
-independent MDA-MB-435 breast cancer cells compared
to the estrogen-dependent MCF-7 cells, and small or no
effects on the MCF-10A non-cancerous breast cell line;
chlorogenic acid and caffeic acid were the most active
phenolic compounds (Vizzotto et al., 2014). 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 preventative effects compa-
rable 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 spe-
cific fruit and vegetable group intakes were examined
using standardized exposure definitions (Smith-Warner
et al., 2001). Data sources were eight prospective studies
that had greater than or equal to 200 incident breast
cancer cases, included assessment of usual dietary intake,
and had completed a validation study of the diet assess-
ment method or a closely related instrument. They studi-
ed 7377 incident invasive breast cancer cases among
351,825 women whose diet was analyzed at baseline.
For highest versus lowest quartiles of intake, weak non-
significant 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. The study concluded that consump-
tion of fruits and vegetables during adulthood is not
significantly associated with reduced risk of breast cancer.

Some research has suggested that diets high in mush-
rooms may modulate aromatase activity and be useful in
chemoprevention against breast cancer by reducing the
in situ production of estrogen. The white button mush-
room (Agaricus bisporus) suppressed aromatase activity
dose dependently (Grube et al., 2001). Enzyme kinetics
demonstrated mixed inhibition, suggesting the presence
of multiple inhibitors or more than one inhibitory mech-
anism. 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 prolif-
eration of MCF-7aro cells.

The role of intake of dietary fiber and sources of fiber for
protection in an earlier stage of breast cancer has been
considered in adolescents with breast benign disease,
because of significant inverse associations between con-
sumption of fiber and risk of proliferative initiated cells
(Su et al., 2010). This result was attributed partly to the
anti-estrogenic effects of lignans and isoflavonoid com-
ounds, which occur naturally in fiber-rich foods (Var-
inska et al., 2015; Adlercreutz et al., 2007). Green tea
components, especially catechins, have been considered
for prevention and treatment of breast cancer based on
numerous in vitro and preclinical studies, with promis-
sory results including reducing tumor volume, interfering
with estrogen receptor function, inhibiting estrogen-
induced breast cancer cells proliferation, and potentiating
effect of curcumin, paclitaxel, and tamoxifen (Li et al.,
2014; Yiannakopoulou, 2014).

1.2.1.4 Prostate
Prostate cancer is the second most common cancer in
men. An estimated 1.1 million new cases worldwide were
diagnosed in 2012, accounting for 15% of the cancers diagnosed in men IARC 2015.

Some studies have suggested that ingestion of some fruits and vegetables may potentially reduce the risk of prostate cancer (Giovannucci et al., 2003; Campbell et al., 2004; Stram et al., 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 et al., 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 of developing prostate cancer (Giovannucci et al., 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. Etminan et al. published a meta-analysis in 2004 which confirmed the protective effect of lycopene and/or tomato intake. They found that serum lycopene intake (relative risk RR = 0.71, 95% CI 0.59–0.92), lycopene intake (RR = 0.89, 95% CI 0.81–0.98), and cooked tomato intake (RR = 0.81, 95% CI 0.71–0.92) (six studies), but not raw tomato intake (RR = 0.89, 95% CI 0.80–1.00) (nine studies), were associated with a significant decrease in prostate cancer risk. In preclinical studies in animals where prostate cancer was induced by chemical agents or xenograft cancer cells, it has been observed that tomato powder (250 mg/kg diet) was more effective than lycopene alone (100, 200, or 300 mg/kg diet) (Boileau et al., 2003, Tang et al., 2005). Although in general this carotenoid alters prostate cancer development and/or tumor growth, this suggests that the cancer chemopreventive action of lycopene is effective together with that of other compounds of tomato.

Activities of various carotenoids present in foods against human prostate cancer cell lines have been investigated (Kotake-Nara et al., 2001). The 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 hours at 20 mmol/L, 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, ξ-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.

Epigallocatechin-3-gallate (EGCG), resveratrol, curcumin, and the isoflavones (genistein and daidzein) from soy have shown chemopreventive effects against prostate cancer. Epidemiological studies have suggested that increasing intake of green tea is correlated with significant decrease in the development of prostate cancer (Johnson et al., 2010). However, recent epidemiological studies have revealed inconclusive results (Zheng et al., 2011; Montague et al., 2012; Lin et al., 2014), contrary to those observed in laboratory studies where EGCG, green tea extract, or black tea extract induce apoptosis, cell cycle arrest, inhibition of COX-2 and metalloproteinase-9 and -2 enzymes, and reduction of vascular endothelial growth factor (VEGF) levels in prostate cancer cell lines (Cimino et al., 2012). The contradiction may be attributed to the blood–prostate barrier which reduces penetration of active compounds from tea. An additional factor is the lower quantities of human tea consumption compared to the doses used in experimental studies (Fulmer and Turner, 2000). Resveratrol and curcumin are considered promising molecules because of findings (overcome resistance, enhance radiosensitivity, antioxidant in premalignant cells, antiproliferative, and pro-apoptotic) in many in vitro and preclinical experimental studies. Furthermore, curcumin (2–5 μM) in combination with radiation showed significant enhancement of radiation-induced clonogenic inhibition and apoptosis in PC-3 (Cimino et al., 2012; Chendil et al., 2004). However, there are no results from human clinical trials that justify a recommendation for the administration of resveratrol or curcumin in healthy or prostate cancer patients (Cimino et al., 2012; Jasiński et al., 2013).

It has been suggested that soy isoflavones and their metabolites may be beneficial for the prevention or treatment of prostate cancer, and some epidemiologic studies have shown that total soy isoflavone levels in serum are associated with a reduced risk of this cancer (Hwang et al., 2009). In prostate tissue, levels of total soy isoflavones (2.3 μmol/L) exceed serum levels (0.7 μmol/L) by sixfold in people daily consuming soy after dietary supplementation (82 mg/day aglycone equivalents) for two weeks (Gardner et al., 2009). The inhibition of prostate cancer cells by soy isoflavones involves inhibition of cell growth by modifying the expression of some central genes for cell survival, cell cycle, apoptosis, androgen receptor, and reduction of prostate-specific antigen levels, inducing the expression of several enzymes involved in the antioxidant defense system and capable of reversing promoter hypermethylation in some tumor suppressor genes (including Ras association domain family 1 (RASSF1A),
Increased fruit and vegetable consumption may protect against lung cancer, although epidemiologic findings are inconclusive. Dosil-Díaz et al. (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, they found no protective effect of overall consumption of fruit (OR 1.49, 95% CI 0.81–2.73), but green leafy vegetables conferred a protective effect (OR 0.50, 95% CI 0.30–0.83).

The association of fruit and vegetable consumption and lung cancer incidence was evaluated by Linseisen et al. (2007) using data from the EPIC study, applying a refined statistical approach (calibration) to account for measurement error potentially introduced by using food frequency questionnaire data. Between 1992 and 2000, detailed information on the diet and lifestyle of 478,590 individuals participating in EPIC was collected, and during a median follow-up of 6.4 years, 1126 lung cancer cases were observed. In the whole study population, fruit consumption was significantly inversely associated with lung cancer risk while 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 et al. (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–American Association of Retired Persons (NIH–AARP) Diet and Health Study. Diet was assessed at baseline (1995–6) with a 124-item dietary questionnaire. A total of 6035 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 was significantly inversely associated with risk only in men. Association between lung cancer risk and fruit and vegetable consumption was also investigated by Feskanich et al. (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 of lung cancer within each cohort was estimated using logistic regression models; all statistical tests were two-sided. Totals of 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% 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 et al. concluded in 1992 that some β-carotene-rich fruits such as papaya, sweet potato, mango, and yellow orange show 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 have also concluded that a tomato-rich diet (which contributes high lycopene content but little β-carotene) had a strong positive relationship with survival, particularly among women. However, other studies (Le Marchand et al., 1989; Steinmetz et al., 1993) concluded that lycopene intake was unrelated to lung cancer.

**1.2.2 Cardiovascular Disease (CVD)**

CVD is the number one cause of death in developed and developing nations (Go et al., 2014), and prevention is at the top of the public health agenda (Retelny et al., 2008). In 2008, 17 million deaths worldwide were due to cardiovascular diseases; this represents 48% of non-communicable disease deaths (WHO, 2011). Evidence shows that reducing the incidence of coronary heart disease (CHD) with diet is possible (Retelny et al., 2008). This was recently shown in the Prevención con Dieta Mediterránea (PREDIMED) study, a randomized controlled trial including 7447 obese men and women with a mean age of 67 years at high risk for cardiovascular disease (50% of the participants had diabetes type 2, more than 70% had dyslipidemia, and more than 80% had hypertension). After a median follow-up of 4.8 years, the study showed that a Mediterranean diet supplemented with extra virgin olive oil or a mix of nuts (almonds, walnuts, and hazelnuts) reduced incidence of CVD (myocardial infarction,
stroke, or cardiovascular death) by 30% in the olive oil group (HRadj = 0.70, 95% CI 0.54, 0.92) and 28% in the nut group (HRadj = 0.72, 95% CI 0.54, 0.96) compared to the control group, which was instructed to eat a more fat-reduced diet (Estruch et al., 2013). Moreover, in the prospective part of the PREDIMED study, the baseline intake of fruit was inversely associated with all-cause mortality (HR for the fifth compared with the first quintile = 0.59, 95% CI 0.44, 0.78) and the associations were stronger for CVD mortality than for other causes of death (Buil-Cosiales et al., 2014).

Two important meta-analyses by Dauchet in 2006 and by He in 2007, which included nine and 13 cohort studies, concluded that a higher fruit and vegetable consumption was inversely associated with the risk of CHD. These findings were coherent with following meta-analyses such as the EPIC Heart Study (Crowe et al., 2011) and the Morgan Study (Oude Griep et al., 2010); the exception is the Italian study within EPIC where no association was found for fruit and vegetable intake in total, but only for leafy vegetables (Bendinelli et al., 2011). A recent meta-analysis, which included 23 studies involving 937,665 participants and 18,047 patients with CHD, confirmed that fruit and vegetable intake >5 servings/day was significantly associated with a lower risk of CHD in Western populations, but not in Asian populations. This meta-analysis found that in dose–response studies the relative risk of CHD decreased by 12%, 16%, and 18% for daily 477 g of total fruit and vegetables, 300 g of fruit, and 400 g of vegetables, respectively (Yu et al., 2014).

Some biological mechanisms have been proposed to explain these protective effects by using in vivo models, such as inhibition of lipid oxidation, an increase in the antioxidant capacity of serum or plasma (Harasym and Oledzki, 2014), protection against the oxidation of cholesterol and other lipids in cell membranes (da Silva Pereira et al., 2014), reduction in oxidative stress (Thompson, 2010), an anti-inflammatory effect (Loke et al., 2008), prevention of platelet aggregation, reduction in vascular tone (Wang X. et al., 2014), and induction of glutathione, endothelial NO synthase (eNOS), and inducible NOS (iNOS) (Mukai and Sato, 2009). Using rat cardiomyoblast H9c2 cells (Park et al., 2009; Angeloni et al., 2007), human umbilical vein endothelial cells (HUVECs) (Gong et al., 2010), J774A.1 macrophages (Hwang et al., 2003), and monocyte-derived macrophages (La et al., 2009), cell lines treated with methanolic onion extract (0.05 and 0.1 g/mL), quercetin (30 μM), rutin (200 μM), resveratrol (20 μM), and cranberry proanthocyanidins (25 and 50 μg/mL) induced anti-apoptotic effects, evidenced by inhibition of cytochrome C release to cytoplasm and inactivation of H2O2-induced caspases-3, increase in bioavailability of nitric oxide (NO), and reduction in matrix metalloproteinases 9, 7, 8, and 13 production.

Numerous epidemiological studies have provided evidence that a diet rich in fruits and vegetables may protect against CVD (Ness and Powles, 1997; Law and Morris, 1998; Ness et al., 1999; Liu et al., 2000, 2001; Joshipura et al., 2001; Bazzano et al., 2002). The positive effect has been accomplished by 3 servings/day 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/day. A study on 2682 men in Finland has also indicated that high intake of fruits and vegetables correlates with reduced risk of cardiovascular disease (Rissanen et al., 2003). The inverse relationship between vegetable intake and cardiovascular disease was more evident with smokers consuming at least 2.5 servings/day in comparison with less than 1 serving/day (Liu et al., 2001). Legume consumption was significantly and inversely associated with cardiovascular disease, lowering the risk by about 11% (Bazzano et al., 2001).

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Nagura et al., 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 1988–90 and followed for 13 years, concluded that intakes of plant-based foods, particularly fruit intake, are associated with reduced mortality from CVD and all causes among Japanese men and women. However, Nakamura et al. (2008) assessed the intake of fruit and vegetables in 13,355 men and 15,724 women in Takayama, Gifu, Japan using a validated food frequency questionnaire (FFQ), and found that for women, the highest quartile of vegetable intake compared with the lowest was marginally significant and was inversely associated with CVD mortality after adjusting for total energy, age, and non-dietary and dietary covariates, whereas for men, CVD death was not associated with fruit or with vegetable intake.

Radhika et al. (2008) examined the relationship between fruit and vegetable intake (g/day) and CVD risk factors in urban south Indians. The study population comprised 983 individuals aged >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 semi-quantitative FFQ. Linear regression analysis revealed that after adjusting for potential confounders such as age, sex, smoking, alcohol, BMI, and total energy intake, the highest quartile of fruit and vegetable intake (g/day) showed a significant inverse association with systolic blood pressure (BP), 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 or peanut butter consumption (Blomhoff et al., 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 CHD (Jenkins et al., 2008; Kris-Etherton et al., 2008). These findings have recently been confirmed in systematic reviews and meta-analyses (Afshin et al., 2014; Grosso et al., 2015). Afshin et al. (2014) found that fatal ischemic heart disease (IHD) was inversely associated with nut consumption (per 4 weekly servings of 28 g nuts, RR = 0.76, 95% CI 0.69, 0.84), as was non-fatal IHD (RR = 0.78, 95% CI 0.67, 0.92). Likewise, Grosso et al. (2015) reported a 27% reduced risk of all-cause mortality (RR = 0.73, 95% CI 0.60, 0.88) for 1 serving of nuts per day and a 39% risk for CVD mortality (RR = 0.61, 95% CI 0.42, 0.91) per daily serving of nuts. However, as the authors pointed out, confounding factors such as body mass index, smoking status, increased intake of fruit and vegetables, as well as intake of alcohol have to be taken into account when considering the findings (Grosso et al., 2015).

Both in meta-analysis and in clinical studies, the beneficial effects of different nuts and peanuts on lipids, lipoproteins, and various CHD risk factors, including oxidation, inflammation, endothelial function, and arterial stiffness, have been shown (Kris-Etherton et al., 2008; Sabaté et al., 2010; Kasliwal et al., 2015). In the meta-analysis by Sabaté et al. (2010) it was shown that a mean daily consumption of 67 g nuts reduced total cholesterol concentrations by 5%, reduced LDL cholesterol by 7%, and improved the LDL cholesterol to high-density lipoprotein (HDL) cholesterol ratio. Moreover, a reduction in small dense LDL particles after consumption of 57 g pistachios has been shown among subjects with prediabetes (Hernández-Alonso et al., 2015).

The LDL cholesterol lowering response of nut and peanut studies is generally 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 the 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 such as potassium, calcium, magnesium, and tocopherols; and phytochemicals such as phytosterols, phenolic compounds, resveratrol, and arginine. Kris-Etherton et al. (2008) have indicated that nuts and peanuts are food sources that are a composite of numerous cardioprotective nutrients and, if they are routinely incorporated in a healthy diet, the population risk of CHD would be expected to decrease markedly.

Hung et al. (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% CI 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/day) had no depressive effects on cardiovascular disease risk (Hennekens et al., 1996; Omenn et al., 1996; Lee et al., 1999).

Mono-unsaturated fats in avocados have been shown to reduce blood cholesterol while preserving the level of high-density lipoproteins (Yahia, 2012b). Avocado enriched diet produced a significant reduction in LDL and total cholesterol in patients with high cholesterol levels, while diets enriched with soy and sunflower did not change the total cholesterol concentrations (Carranza et al., 1997). These findings were confirmed in a randomized, crossover controlled feeding study among 45 overweight or obese hyperlipidemic men and women. In this study the inclusion of one avocado per day reduced LDL cholesterol, non-HDL cholesterol, and the overall LDL particle number (Wang et al., 2015).

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 et al., 1989, 1991). Lycopene has also been reported to increase gap-junctional communication between cells and to induce the synthesis of connexin-43 (Zhang et al., 1992).

1.2.2.1 Hypertension
Blood pressure (BP) is a continuous, consistent, and independent risk factor for CVD that is modifiable through lifestyle. Indeed, a recent meta-analysis reported a moderate average BP reduction of 3.5 and 2.0 mmHg for systolic and diastolic BP, respectively, which was associated with a 24% reduction in stroke (Aburto et al., 2013). In the PREMIDE study the reduced incidence of CVD was mainly driven by reduced incidence of stroke (Estruch et al., 2013) and favorable effects of both Mediterranean
diets were seen on BP (Martinez-Gonzales, 2015). A meta-analysis including 21 randomized clinical trials showed that nut consumption was associated with a reduction in systolic BP among participants without diabetes type 2 (−1.3 mmHg, 95% CI −2.3, −0.22) and that pistachios had the strongest effect on systolic (−1.8 mmHg, 95% CI −3.0, −0.7) and diastolic BP (−0.8 mmHg, 95% CI −1.4, −0.2) (MohammadiFard et al., 2015).

Diet plays a major role in BP control, and the Dietary Approaches to Stop Hypertension (DASH) studies clearly showed that eating vegetables, fruit, and low-fat dairy products lowered BP (Zhao et al., 2011). In particular, the evidence for recommending vegetables and fruit to reduce BP is convincing (Boeing et al., 2012; Bupathiraju and Tucker, 2011). Indeed, a recent meta-analysis, including clinical trials and a total of 311 participants, showed that a vegetarian diet was associated with a reduction in mean systolic BP (−4.8 mmHg, 95% CI −6.6, −3.1) and diastolic BP (−2.2 mmHg, 95% CI −3.5, −1.1) (Yokoyama et al., 2014).

The BP lowering effects of fruits and vegetables may involve several mechanisms, but fruits and vegetables are generally high in antioxidants (Halvorsen et al., 2006). Oxidative stress has been postulated to have a possible role in the pathogenesis of hypertension (Ceriello, 2008), and higher intake of antioxidants may increase the bioavailability of NO by decreasing endogenous oxidant formation (McCarty, 2008). Another possibility may be increased intake of potassium. Potassium has been shown to promote vasodilation and to reduce renin, renal sodium reabsorption, reactive oxygen production, and platelet aggregation (McDonough and Nguyen, 2012). Also, inhibition of the angiotensin-converting enzyme (ACE) activity by fruit and vegetables has been postulated, and dietary involvement of the renin–angiotensin system by the DASH diet has been shown (Conlin et al., 2003).

1.2.2 Chronic Heart Failure

Chronic heart failure (CHF) has a prevalence of about 80% among individuals aged more than 80 years worldwide, and is seen as the end-stage of CVD and the final pathway of diseases such as hypertension and CVD (Rich, 2001; Lloyd-Jones et al., 2010). CHF has many causes, but oxidative stress has also been proposed as a risk factor (Ingelsson et al., 2005). In a population-based prospective cohort study, more than 30,000 women aged 49–83 years were followed for 11.3 years, and total antioxidant capacity of the diet measured by oxygen radical absorbance capacity was inversely associated with heart failure (the multivariable adjusted relative risk in the highest quintile compared to the lowest was 0.58, 95% CI 0.47, 0.72) (Rautiainen et al., 2013). Among Swedish men a dietary pattern in accordance with the DASH diet rich in fruit and vegetables has been associated with reduced incidence of CHF (22%, 95% CI 5%, 35%) (Levitan et al., 2009).

1.2.3 Diabetes Mellitus

The prevalence of type 2 diabetes mellitus is increasing worldwide. In 2013 it was reported to be 382 million, and it is expected to rise to 592 million by 2035 (Guariguata et al., 2014). Because diabetes is characterized by either resistance to the blood glucose regulating hormone insulin or its relative deficiency (WHO, 2006), it has been proposed that antioxidants may play a role in increasing or reducing insulin sensitivity (Bryans et al., 2007). Thus, fruit and vegetable consumption has been considered as a strategy to lower markers of oxidative stress and inflammation present in 54 type 2 diabetes (T2D) patients as observed by Asgard et al. (2007) in a cross-sectional study, where fruit and vegetable intake was negatively correlated with DNA oxidation and lipid peroxidation. These effects were negatively correlated with dietary vitamin C, and plasma carotenoids were negatively correlated with inflammation, measured as IL-6 (Asgard et al., 2007). Similar results were obtained in the study of Hegde et al. (2013), where 60 patients were assigned to receive additional dietary therapy and 63 received standard diet (control). The dietary intervention resulted in significant reduction in malondialdehyde, plasma glucose, and glycated hemoglobin, and improvement in antioxidants like vitamin C and reduced glutathione when compared with the control group. Mean plasma levels of vitamin C increased by 64% (p < 0.001) (Hegde et al., 2013).

On the other hand, Hamer and Chida (2007) have suggested that the consumption of 3 or more daily servings of fruit or vegetables was not associated with a substantial reduction in the risk of T2D, 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 4858 incident cases of T2D, with a mean follow-up of 13 years, were reviewed by Hamer and Chida (2007). The relative risk of T2D was 0.96 (95% CI 0.79–1.17, P = 0.96) for consuming 5 or more servings of fruit and vegetables daily, 1.01 (0.88–1.15, P = 0.88) for 3 or more servings of fruit, and 0.97 (0.86–1.10, P = 0.59) for 3 or more servings of vegetables. Nine cohort studies of antioxidant intake and the risk of diabetes were also identified, incorporating 139,793 participants and 8813 incident cases of T2D, with a mean follow-up of 13 years (Hamer and Chida, 2007); these 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 et al. (2008) examined the associations between fruit and vegetable intake and the incidence of 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.

This suggests that the association between the intake of fruit and vegetables and the risk of T2D is unclear. However, it has been proposed that this inconsistency between studies examining the association between fruits and vegetables intake and risk of diabetes could be due to the extent of measurement error associated with the FFQ because people overestimate their fruit and vegetable consumption. In addition, these studies include consumption of fruit juices, which contain both an important sugar load and fructose which contribute to the development of diabetes and insulin resistance (Bazzano et al., 2008). Recently, Wu et al. (2015) carried out a dose–response meta-analysis to quantitatively assess the association of T2D risk with consumption of vegetables (seven studies), fruits (nine studies), and total fruits and vegetables (seven studies). They found that there was a threshold around 2–3 servings/day of vegetable and 2 servings/day of fruit, after which the T2D risk did not reduce further; these findings are consistent with the general recommendation to consume 5 servings of fruit and vegetables a day (3 of vegetable and 2 of fruit), but the effect of specific types of fruit and vegetable on T2D risk is unknown (Wu et al., 2015).

Randomized controlled trials of patients with T2D have confirmed the beneficial effects of nuts on blood lipids, also seen in non-diabetic subjects, but the trials have not reported improvement in A1c or other glycated proteins (Jenkins et al., 2008). Therefore, Jenkins et al. (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 et al. (2008) characterized dietary patterns and their relation to incident T2D in 5011 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 et al. (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 semi-quantitative FFQ every 4 years (Bazzano et al., 2008). During follow-up, 4529 cases of diabetes were documented, and the cumulative incidence of diabetes was 7.4%; an increase of 3 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 reduce blood glucose levels (Frati et al., 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 et al., 1983, 1990b). The rise in serum glucose levels which follows the intake of a sugar load (oral glucose tolerance test) was lower with previous ingestion of Opuntia stems compared to when the sugar is ingested alone (Frati et al., 1990a). In patients with NIDDM, the ingestion of some species of nopal (O. streptacantha, O. ficus-indica) in fasting condition is generally followed by a decrease in serum glucose and serum insulin levels (Frati, 1992). These positive health effects of Opuntia stems might be associated with dietary fibers, since similar results can be achieved with Plantago psyllium or other sources of dietary fiber (Frati, 1992). Ingestion of raw and cooked O. ficus-indica extracts resulted in beneficial effects on total cholesterol, without any secondary effect on glucose and lipoprotein amounts in blood (Medellin et al., 1998).

Some flavonoids, such as procyanidins, have antidiabetic properties because they improve altered glucose and oxidative metabolisms of diabetic states (Pinent et al., 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 et al., 2004). The antihyperglycemic effect of PE may be partially due to the insulinomimetic activity of procyanidins on insulin-sensitive cell lines.

### 1.2.4 Obesity

Obesity is characterized by the accumulation of excess fat in adipose tissues. It is considered a major public health issue, especially in most developed countries nowadays because of its wide spread across population groups, as well as its contribution to the development of chronic diseases, particularly cardiovascular diseases, type 2 diabetes, and some types of cancer (i.e. colorectal, breast) (IARC, 2008). These result from a sedentary lifestyle and
unhealthy dietary practices, which mean high energy intake and low energy expenditure.

Despite the alarming increase in the prevalence of obesity across the world, epidemiologic studies on the relation between fruit and vegetable consumption and weight gain (WG) are still insufficient. In a systematic review, Fogelholm et al. (2012) showed that a high intake of fiber-rich foods and nuts predicted less WG and reduced waist circumference. Indeed, a recent analysis from the National Health and Nutrition Examination Survey 2004–2010 showed that nut consumers who ate a mean of 44 g nuts per day had lower BMI and waist circumference than non-nut consumers ($p < 0.01$ for both) (O’Neil et al., 2015). The mechanism for the beneficial effect of nuts on body weight may be due to their satiating effect and subsequent food compensation (Mattes et al., 2008).

The evidence accumulated indicates that the combination of an increased fruits and vegetables intake, together with other dietary recommendations, might promote satiety and weight loss in overweight and obese individuals. Fruits and vegetables are low in fat but high in water content, indigestible fiber, and soluble dietary fiber which contribute to reduce the energy intake of meals, or the calorie intake, and consequently the body weight. It has been proposed that soluble dietary fiber delays gastric emptying of ingested food and forms a gel-like environment in the small intestine that partly diminishes the activity of enzymes involved in the digestion of macronutrients and absorption. This prolongs the contact of the nutrients with receptors in the small intestine such as fructose, causing the release of putative satiety peptides and creating a hyperosmolar environment in the colon – leading, for example, to a decrease in insulin secretion and an improvement in glucose control, an attraction of fluids into the gut lumen, and a loss of interest in further food consumption (Mirmiran et al., 2013).

Vioque et al. (2008) explored the associations between fruit and vegetable intake and WG over a 10 year period in an adult Mediterranean population of 206 aged 15–80 years at baseline in 1994, who participated in a nutrition survey in Valencia, Spain. They concluded that dietary patterns associated with a high intake of fruits and vegetables in Mediterranean populations may reduce the long-term risk of subsequent WG and obesity among adults.

Svendsen et al. (2007) assessed the effect of increased consumption of vegetables and fruit on body weight, risk factors for CVD, and antioxidant defense in obese patients with sleep-related breathing disorders (SRBD). They concluded that targeted dietary advice to increase the intake of vegetables and fruit among subjects with SRBD contributed to weight reduction and reduced systolic and diastolic BP, but had no effect on antioxidant defense measured by ferric-reducing/antioxidant power (FRAP) assay.

He et al. (2004) examined the changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women through a prospective cohort study with 12 years of follow-up, conducted in the Nurses’ Health Study with a total of 74,063 female nurses aged 38–63 years, who were free of cardiovascular disease, cancer, and diabetes at baseline in 1984. During the 12 year follow-up, participants tended to gain weight with aging, but those with the largest increase in fruit and vegetable intake had a 24% lower risk of becoming obese compared with those who had the largest decrease in intake after adjustment for age, physical activity, smoking, total energy intake, and other lifestyle variables. For major weight gain (>25 kg), women with the largest increase in intake of fruits and vegetables had a 28% lower risk compared to those in the other extreme group.

Bes-Rastrollo et al. (2006) assessed the association between fiber intake and fruit and vegetable consumption with the likelihood of weight gain in a Mediterranean (Spain) population with a cross-sectional analysis of 5094 men and 6613 women in a multipurpose prospective cohort (Seguimiento Universidad de Navarra Study). There was a significant inverse association between total fruit and vegetable consumption and weight gain, but only among men; it was more evident among those with a high intake of total fiber, and the benefit of total fiber was more evident among those with a high consumption of fruits and vegetables.

De Carvalho et al. (2006) evaluated the dietary fiber intake of adolescents in the metropolitan area of São Paulo city and the association between low dietary fiber intake and constipation and overweight. The study included 716 adolescents, and evaluation of fiber intake was based on a 24 hour daily intake record and a frequency questionnaire. Adolescents who did not eat beans on more than 4 days per week presented a higher risk of fiber intake below that recommended, and dietary fiber intake below that recommended was associated with a greater risk toward overweight in students attending public schooling.

1.2.5 Pulmonary Health

Several studies have suggested a positive association between fruit and vegetable intake (particularly fruit) and pulmonary function (Walda et al., 2002; Watson et al., 2002; Celik and Topcu, 2006). Fruit and vegetable consumption has been suggested to maintain a healthy pulmonary function in well-adult populations, and to improve lung function in those with established pulmonary disorders. Phytochemicals, especially of antioxidant
potential, have been suggested to be important in protecting lungs from oxidative stress. In a study of 2917 men in seven European countries, higher fruit intake was found to be consistently associated with lowered mortality from chronic obstructive pulmonary disease (COPD) related causes, and the trend was statistically significant when age, country of residence, and smoking were considered (Wald et al., 2002). This study has shown that vegetables and the antioxidant nutrients vitamins C and β-carotene did not correlate with COPD mortality, but vitamin E intake did appear to be protective when data were adjusted for age, country, and smoking. Fruit intakes of over 121 g/day and increased vegetable consumption were reported to be associated with significantly reduced COPD (Watson et al., 2002; Celik and Topcu, 2006).

It has been suggested that reduced antioxidant intake is one critical factor associated with increased susceptibility to asthma (Devereux and Seaton, 2005), and therefore fruit and vegetable intake has been suggested to reduce it ( Patel et al., 2006) by improving ventilatory function and respiratory symptoms (Romieu et al., 2006). Fruits and vegetables that were found to be associated with reduced incidence of asthma included green leafy vegetables (intake of >90 g/day; 22% risk reduction), tomato (intake of >28.2 g/day; 15% risk reduction), carrots (intake of >24.9 g/day; 19% risk reduction), and apples (intake of >31.2 g/day; 10% risk reduction). These studies have suggested that high carotenoid content in the food could account for the effect, although results of studies focused on β-carotene have not been consistent. The consumption of fruit and vegetables was reported to be significantly associated with reduced occurrence of wheezing and shortness of breath in 2103 boys and 2001 girls aged 6–7 years from Italy (Farchi et al., 2003), and in more than 20,000 children aged 7–11 from 25 areas in Central and Eastern Europe (Antova et al., 2003). Kelly et al. (2003) suggested an association between fruit and vegetable intake and improved respiratory function in more than 6000 healthy adults in Scotland. However, contradicting data have also been reported, such as in the study of Lewis et al. (2005) which reported no association between asthma prevalence and fruit intake in 11,562 children aged 4–6 years living in the United Kingdom, based on data provided by parents of the study subjects; and in 598 Dutch children aged 8–13 years (Tabak et al., 2006).

1.2.6 Bone Health

The loss of bone mass is a global epidemic associated with osteoporosis (Lanham-New, 2006). Fruit and vegetable consumption has been suggested to improve bone (Lanham-New, 2006; Bueline et al., 2001; Pryne et al., 2006; Li et al., 2013; Liu et al., 2015). Higher fruit and vegetable intake was associated with improved markers of bone status in males and females between 16 and 83 years old (Pryne et al., 2006). Tylavsky et al. (2004) showed that fruit and vegetable intake might be important in bone health in white girls aged 8–13 years. The effect was high with 3 servings/day or more and low with less than 3 servings/day, with 4.0 servings (1.6 fruit, 2.4 vegetables) in the high group and 1.7 servings (0.6 fruit, 1.1 vegetables) in the low group. Girls in the high fruit and vegetable intake group had significantly larger bone area across the whole body and the wrist, and higher mineral content for whole body and at the wrist. A study of 1407 premenopausal farm women from five rural districts in Japan has concluded that fruit and vegetable intake is positively correlated with bone health (Okubo et al., 2006). In a study conducted with 85 boys and 67 girls aged 8–20 years in Saskatchewan, Canada (Vatanparast et al., 2005), fruit and vegetable intake was reported to be an important independent predictor of accrued total body mineral content in boys but not in girls. In a study with adolescents aged 12 and 15 years in Northern Ireland (n = 1345), 12-year-olds consumed the highest quantity of fruit and a positive association has been demonstrated between bone density and fruit intake (Gartland et al., 2004). Antioxidants in fruits and vegetables, including vitamin C and β-carotene, reduce oxidative stress on bone mineral density, in addition to the potential role of some nutrients such as vitamin C and vitamin K that can promote bone cell and structural formation (Lanham-New, 2006). Many fruits and vegetables are rich in potassium citrate and generate basic metabolites to help buffer acids and thereby may offset the need for bone dissolution and potentially preserve bone. Potassium intake was significantly and linearly associated with markers of bone turnover and femoral bone mineral density (Macdonald et al., 2005).

Lin et al. (2003) indicated that high potassium, magnesium, and calcium content in addition to antioxidants, phytochemicals, and lower acidity of fruits and vegetables could be important factors for bone health. In a study with 40 healthy men and women, average age 63.7 years, who were randomized to either an “alkali” diet (meat plus fruits and vegetables) or an “acid” diet (meat plus cereal grains) (Jajoo et al., 2006), altering the renal net acid excretion over a period of 60 days impacted several biochemical markers of bones turnover and calcium excretion. The acidity of the diet had a significant effect on increasing NTX, a urinary marker of bone breakdown, and increasing the amount of calcium excreted in the urine.

Li et al. (2013) reported a significantly positive association between fruit intakes and bone mineral density (BMD) and bone mineral content (BMC) in all participants, including boys and girls (11–14 years), young
women (20–34 years including postpartum within 2 weeks), and postmenopausal women (50–70 years), in a cross-sectional study where the mean fruit intake was 185, 206, 380, and 174 g/day in boys, girls, young women, and postmenopausal women, respectively. About 40% of the fruit intake was from the group of apple, pear, peach, pineapple, and plum, and 20% from the group of orange, grapefruit, and lemon. In addition, Liu et al. (2015) recently found that a daily increase of 100 g/kcal total fruit intake was associated with 4.5% and 6.4% increase of BMD across the whole body, and 3.9% and 4.8% increase at the femoral neck, in Hong Kong Chinese men and women aged 65 years and older, respectively. Similar to the study of Li et al. (2013), these authors did not find significant association between vegetable intake and bone mass.

1.2.7 Cataracts and Eye Health

Oxidative mechanisms have been implicated in the etiology of cataracts in humans, and fruit and vegetables intake has been associated with this problem. A study involving 35,724 healthy professional women over the age of 45 years in the USA was conducted to determine the potential association between fruit and vegetable intake and subsequent risk of cataract development over a 10 year follow-up period (Christen et al., 2005). Relative risk of developing cataracts during the 10 year study was only slightly reduced in women with the highest intake of fruits and vegetables (10 servings/day) compared to those with the lowest intake (2.6 servings/day). A study of 479 women with an average fruit intake of 2.5 servings/day and average vegetable intake of approximately 4 servings/day also indicated that fruit and vegetable intake did not differ between women with and without nuclear opacities (Moeller et al., 2004). The authors concluded that multiple aspects of the diet are more important in reducing the risk of cataracts than emphasizing one particular food group or component over another. A study with 98 participants, 68% women, ranging in age between 45 and 73 years, using macular pigment optical density (MPOD) as a marker to correlate diet and serum carotenoid levels with the amount of molecular pigment in the retina, showed that high (≥5 servings/day) intake of fruit and vegetables was associated with significantly higher MPOD compared with measurement in subjects with lower (<3 servings/day) intake (Burke et al., 2005).

1.2.8 Arthritis

Dietary antioxidants and anti-inflammatory components in food are thought to be important in reducing the risk or improving the course of rheumatoid arthritis (RA), and therefore fruit and vegetable consumption has been associated with reduced risk of RA (Pattison et al., 2004b). A study with 29,368 married women from the USA, predominately white, average age 61.4 years, over 11 years, indicated that total fruit consumption (>83 servings/month) was associated with reduced risk of RA (Cerhan et al., 2003). Oranges were the only individual fruit linked to reduced incidence of RA, and β-cryptoxanthin, a carotenoid found in this fruit, was consistently highly protective. Total vegetable intake was not associated with reduced incidence of RA, but intake of cruciferous vegetables (>11 servings/month), particularly broccoli (>3 servings/month), was associated with a moderate effect on RA. In a study where dietary intake for 73 cases was compared to intake of 146 controls (mean age 60–61 years; 70% women), results indicated that lower but not statistically significant intake of fruits and vegetables was weakly associated with higher incidence of inflammatory polyarthritis (IP) (Pattison et al., 2004a). Subjects with the lowest intake (<55.7 mg/day) of vitamin C were three times more likely to develop IP than those with the highest intake (>94.9 mg/day). A related study to determine the relationship with carotenoid intake, in which the diets of 88 cases were compared to those of 176 controls (mean age 61 years; 69% women), found that intake of vitamin C and dietary carotenoids, particularly β-cryptoxanthin and to a lesser extent zeaxanthin, were significantly correlated with reduced risk of IP (Pattison et al., 2005).

1.2.9 Birth Defects

The effect of folic acid supplementation on reducing the risk of neural tube defects of the brain and spine, including spina bifida and anencephaly, is well documented (Eichholzer et al., 2006). Fruits and vegetables are an important source of dietary folate and their consumption has been associated with increased plasma levels of folate. Plasma folate concentration increased by 13% to 27% after short-term feeding experiments with fruits and vegetables (Brevick et al., 2005), and red blood cell folate also increases with increasing fruit and vegetable intake (from 1 to 7 servings/day) (Silaste et al., 2003).

1.2.10 Diverticulosis

Diverticulosis, or the presence of several diverticula, affects 50% or more of the population over the age of 60 years in several countries (Ye et al., 2005). Studies have established an association between low-fiber diets and the presence of diverticulosis (Aldoori and Ryan-Harshman, 2002). The intake of fruit and vegetable fiber was inversely
associated with risk of diverticulosis in a large prospective study of male health professionals, and therefore a high-fiber diet including fruits and vegetables remains an important aspect of therapy for diverticulosis (American Dietetic Association, 2002).

1.2.11 Skin Diseases

Skin is the largest organ that is exposed constantly to environmental factors able to induce oxidative stress, such as ultraviolet radiation (UVR), air pollutants, and chemical oxidants favoring skin aging, an inevitable normal process. However, premature skin aging may occur due to non-healthy lifestyle (smoking, unbalanced nutrition, excessive caloric restrictions, and mental stress) (Biesalski et al., 2003). In vitro and in vivo studies suggest that antioxidants regulate the biomarkers associated with premature aging by reducing oxidative stress in skin.

Lycopene had a protective effect on the oxidative stress-mediated damage of the human skin after irradiation with UV light (Ribaya-Mercado et al., 1995).

A formulation of a synergistic blend named OptiBerry that contains wild blueberry, bilberry, cranberry, elderberry, strawberry, and raspberry seed extracts developed by Bagchi et al. (2006) showed whole-body antioxidant protection in vitamin E deficient rats after exposure to pressure of 2 atmospheres (atm) for 2 hours with hyperbaric oxygen (HBO). The animals were supplemented for 8 weeks, significantly reducing GSH levels compared to placebo-fed rats (Bagchi et al., 2006). In addition, VEGF expression induced in keratinocytes by treatment with H2O2 and tumor necrosis factor alpha (TNF-α, an inflammatory cytokine) was inhibited after 12 hours of treatment with OptiBerry; and pretreatment of cells with OptiBerry inhibited ROS- and inflammation-induced VEGF protein expression (Roy et al., 2002; Bagchi et al., 2004).

Promising results have been obtained for the prevention of UV-induced skin alterations and premature skin aging by using extracts of pomace from Riesling grapes, which showed a dose-dependent inhibitory activity against both enzymes with IC50 values of 20.3 μg/mL and 14.7 μg/mL for collagenase and elastase activity, respectively, these being the most active in the free phenolic acids fraction (Wittenauer et al., 2015). Human dermal fibroblasts incubated with strawberry extract at 0.5 mg/mL and stressed with H2O2 showed an increase in cell viability, a smaller intracellular amount of ROS, and a reduction of membrane lipid peroxidation and DNA damage; they were also able to improve mitochondrial functionality, increasing the basal respiration of mitochondria, and to promote a regenerative capacity of cells after exposure to pro-oxidant stimuli (Giampieri et al., 2014). These findings promote the use of natural sources of antioxidants like fruits and plant extracts (green and black tea, carotenoids, coffee) for protecting skin against premature aging. Moreover, vitamins A, B, C, and E, CoQ10 and its analogs, and flavonoids are currently incorporated into a variety of anti-aging skin care systems by oral administration and topical application. However, many controlled clinical studies are needed to determine the efficacy and risks of plant-derived products in dermatology. Safety aspects, especially related to sensitization and photodermatitis, have to be taken into account for dermatologic disorders and cosmetic purposes (Bruce, 2008; Reuter et al., 2010).

1.2.12 Aging and Cognition

Oxidative stress and inflammation are considered significant mediators in healthy aging of the brain and in age-related neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases (Shukitt-Hale et al., 2006). Animal and human studies have suggested that fruits and vegetables have the potential to reduce some age-related processes, primarily due to the antioxidant and anti-inflammatory properties of several phytochemicals. An in vitro study has suggested that some classes of phytochemicals also act in cell signaling and thus may protect against aging by mechanisms other than oxidative and inflammatory processes (William et al., 2004). Fruit and vegetable extracts have been demonstrated to reverse or retard various age-related cognitive and motor deficits in rats (Lau et al., 2005).

Strawberry and spinach extracts attenuated age-related cognitive and neuronal decline in rats over 6–15 months, and blueberry extracts were effective in reversing existing cognitive deficits and improving motor function in aged rats (Joseph et al., 2005a, 2005b). Examination of the brain tissue from these animals showed evidence of reduced inflammatory and oxidative processes in the supplemented groups. Transgenic mice models of Alzheimer’s disease fed blueberry extract exhibited cognitive performance equivalent to that of normal non-supplemented mice and were significantly improved compared to non-supplemented transgenic mice (Joseph et al., 2003). Blueberry supplementation in the transgenic mice increased concentration of cell signaling kinases thought to be involved in converting short-term memory to long-term memory, and increased other aspects of cell signaling including increased muscarinic receptor activity, which is also known to be important in cognitive function (Casadesus et al., 2004). Aging rats provided with Concord grape juice at low concentration (10%) for 9 weeks improved cognitive performance, while high (50%) concentration improved motor performance (Shukitt-
Hale et al., 2006). Concord grape and juice contain a variety of flavonoids, and 10% grape juice supplementation was reported to be associated with the most effective increase in muscarinic receptor sensitivity in aging rats.

A study that interviewed 13,388 women living in 11 states in the USA over a period of 10–16 years (Kang et al., 2005) showed that baseline cognitive performance was stronger in women who reported the highest intake of cruciferous vegetables compared to those with lower intake.

It is believed that oxidative stress plays a key role in the development of Alzheimer’s disease because of the characteristic lesions associated with free radical damage and the attenuation of these processes with supplementation of some antioxidants. To date, there are no clinical trials that specifically address the role of dietary fruits and vegetables, although there are trials to investigate the association between dietary antioxidants in food and the risk of Alzheimer’s disease. A study involving 5395 men with an average age of 67.7 years, living in the Netherlands and followed for 6 years (Engelhart et al., 2002), reported that baseline dietary intake of vitamins C and E as well as the use of antioxidant supplements was associated with reduced risk of developing Alzheimer’s during the follow-up period, with a stronger protective effect in subjects who were smokers, and that flavonoids and β-carotene intake was protective in smokers but not in non-smokers.

The mechanisms proposed are based on the antioxidant action of curcumin by increasing glutathione levels, reducing lipid peroxidation in 3-nitropropionic acid (3-NP) induced neurotoxicity in rats and improving learning and memory (Mythri et al., 2011; Harish et al., 2010; Kumar et al., 2007). Epigallocatechin gallate is able to protect neuronal cell lines submitted to glucose or glutamate toxicity (Romeo et al., 2009; Kang et al., 2010) and age-associated oxidative damage in rat brain by increasing activities of superoxide dismutase, catalase, glutathione peroxidase, and glucose-6-phosphate dehydrogenase (Srividhya et al., 2008). Another mechanism observed with epigallocatechin gallate, genistein, kaempferol, and quercetin is the inhibition of cholinesterase activity, which improves cognitive functions like learning and memory (Zhang et al., 2009; Huang and Zhang, 2010; Liu et al., 2010; Tota et al., 2010; Kim et al., 2011). It has also been observed that curcumin (Wang et al., 2009), grape extracts and resveratrol (Vislocky and Fernandez, 2010; Vingtdeux et al., 2010; Karuppaganounder et al., 2009), and epigallocatechin gallate (Avramovich-Tirosh et al., 2007) have the capacity to reduce amyloid-beta (Aβ) deposition and Aβ protein in preclinical animal models and in hippocampus neuronal cells and neuroblastoma cells.

Thus, there is a growing body of evidence on the potential of natural polyphenols to combat neurodegenerative diseases. Nevertheless, application to clinical routine has been limited because it is necessary to understand systemic metabolism, pharmacokinetics, brain bioavailability, local metabolism, and modification within the central nervous system.

1.3 Nutritional and Health Importance of Some Fruits and Vegetables

Fruits and vegetables are rich sources of phytochemicals, as well as of other components that may act synergistically with phytochemicals to contribute to the nutritional and health benefits of these food commodities.

1.3.1 Apples and Pears

Apples are a widely consumed, rich source of phytochemicals, including phenolic compounds, pigments, and vitamin C among others. There are six classes of polyphenols in apple fruit (Thompson et al., 1972; Lea and Timberlake, 1974; Whiting and Coggins, 1975a, 1975b; Lea, 1978; Oleszek et al., 1988; Spanos et al., 1990). The anthocyanins and flavonol glycosides are mainly found in the skin. The phenolic acids are mainly chlorogenic and p-coumaroylquinic acid. The dihydrochalcones are phloretin glucoside (phloridzin) and xylo-glucoside. The main catechin is (−)-epicatechin, and the procyanidins are the (4→8)-linked epicatechin series with some mixed (+)-catechin/(−)-epicatechin. There is no significant amount of glutathione in apple fruit, and none in apple juice (Jones et al., 1992). Fresh apple fruit may contain up to 100 ppm of vitamin C, but during processing into juice this is rapidly lost (Lea, 1992). The phytochemical composition of apples varies greatly between different varieties, and changes during maturation, ripening, storage, and processing (Curry, 1997). The accumulations of antioxidants in apple peels before harvest were found to be affected more by ripening and light intensity than by low temperature (Barden and Bramlage, 1994). Total antioxidant activity in four apple cultivars were in the order ‘Golden Delicious’ > ‘Empire’ > ‘Delicious’ > ‘Cortland’ (Ju and Bramlage, 1999). Ascorbate and non-protein thiols (glutathione) content significantly decreased with increasing pear (Pyrus communis L. ‘Conference’) maturity (Lentheric et al., 1999). Concomitantly, the activity of superoxide dismutase and catalase decreased about fivefold and twofold, respectively, when the fruit was picked more mature. Pears were reported to have lower antioxidant activity compared to pigmented fruits (Prior and Cao, 2000). The antioxidant potentials measured...
by 1,1-diphenyl-2-picrylhydrazyl (DPPH), β-carotene bleaching, and nitric oxide inhibition radical scavenging tests in apple peel and pulp were significantly higher than in pear peel and pulp (Leontowicz et al., 2003). The ethanol extract of apple peels showed the strongest inhibition of lipid peroxidation as a function of its concentration, pear pulp had the weakest antioxidant ability, whereas apple pulp and pear peel were equal (Leontowicz et al., 2003). Diets supplemented with peels of both fruits exercised a significant higher positive influence on plasma lipid levels and on plasma antioxidant capacity of rats than diets with fruit pulps (Leontowicz et al., 2003).

Apple extracts with 70% acetone tested on the basis of their dry weight showed strong antioxidant activities towards oxidation of methyl linoleate, although apples were reported to be low in total phenolics (Kähkönen et al., 1999). In apple juice, vitamin C activity represented a minor fraction of the total antioxidant activity, with chlorogenic acid and phloretin glycosides as the major identifiable antioxidants (Miller and Rice-Evans, 1997). Chlorogenic acid was found to contribute 27% of the total activity of apple extract to scavenge hydroxyl radicals (Plumb et al., 1996b). It has been reported (Eberhardt et al., 2000; Lee et al., 2003) that the antioxidant and antiproliferative activities of apples are the consequences of synergistic activities of phenolics rather than vitamin C. In pear fruit, the contribution of phenolic compounds to antioxidant activity has also been reported to be much greater than that of vitamin C (Galvís-Sanchez et al., 2003). Phenolics in apple skin showed a much higher degree of contribution to the total antioxidant and antiproliferative activities of whole apple than those in apple flesh (Eberhardt et al., 2000; Wolfe et al., 2003). Some of the important antioxidant phenolics found in apples include chlorogenic acid, epicatechin, procyanidin B2, phloretin, and quercetin (Burda et al., 1990; Mayr et al., 1995). The relative antioxidant activities of some of these phenolic compounds in apples were in the order of quercetin > epicatechin > procyanidin > phloretin > vitamin C > chlorogenic acid (Lee et al., 2003).

Epidemiological studies have linked the consumption of apples with reduced risk of cardiovascular disease, asthma, and diabetes (Liu et al., 2005) and some types of cancer. A meta-analysis of multicenter case-control studies conducted in Italy revealed that consumption of ≥1 apple/day in comparison with ≤1 apple/day significantly reduced the odds ratio for colorectal cancer (OR 0.80, 95% CI 0.71–0.90) as well as for cancers of the oral cavity (OR 0.79, 95% CI 0.62–1.00), larynx (OR 0.58, 95% CI 0.44–0.76), breast (OR 0.82, 95% CI 0.73–0.92), and ovary (OR 0.85, 95% CI 0.72–1.00) (Gallus et al., 2005). In the Nurses’ Health Study, a large prospective cohort study conducted in the USA reported that the 20% of women who consumed almost 2 apples/day had a significantly reduced risk of developing colorectal adenomas (OR 0.83, 95% CI 0.70–0.98) in comparison to the 20% with the lowest intake (OR 1.00, P_trend 0.05) (Michels et al., 2006). In a South Korean case-control study, fruit consumption (apples combined with banana, pear, and watermelon) lowered the risk for colon cancer in men (adjusted OR 0.36, 95% CI 0.16–0.84) but not in women (adjusted OR 1.14, 95% CI 0.54–2.40) (Lee et al., 2005).

In the laboratory, apples have been found to reduce lipid oxidation, to lower cholesterol, and to have very strong antioxidant activity (Boyer and Liu, 2004). Apple constituents such as procyanidins (PCy) have been shown to inhibit proliferation of HT29 (Veeriah et al., 2006), SW480, and SW620 colon cancer cells (Gossé et al., 2005; Maldonado-Celis et al., 2009) at subcytotoxic concentrations.

One study has addressed the toxicology and safety of a polyphenol-rich extract from unripe apples (Applephen®), which is sold in Japan as a food additive and nutritional supplement and contains high levels of PCy (64%, dimers to 15-mers), 12% flavan-3-ol monomers, 7% flavonoids, and 18% non-flavonoids (Ohnishi-Kameyama, 1997). One gram of extract was reported to contain polyphenols equivalent to approximately four apples (Akaizome, 2004). In the Ames mutagenicity test, only one out of five bacterial strains showed a slight increase in revertants indicative of mutagenic potential. No signs of mutagenicity were detected in the chromosomal aberration test in Chinese hamster lung cell culture and the micronucleus test in Sprague-Dawley rats. Also, no signs of toxicity at a dose of 2000 mg/kg body weight were observed in an acute and subchronic toxicity test. The extract was therefore regarded as safe (Shoji et al., 2004).

As a first indication of cancer chemopreventive efficacy in vivo, apple products have been tested in experimental animal models for chemically or genetically induced tumors of colon (Gossé et al., 2005), as well as in xenograft models for solid tumors and melanoma (Miura et al., 2008). Apple PCy applied at 1% in drinking water inhibited the growth of transplanted B16 mouse melanoma cells in vivo, and increased the survival rate of the host mice transplanted with B16 cells (Miura et al., 2008).

1.3.2 Citrus

Citrus fruit and their juices are rich sources of vitamin C; an 8 fl oz serving was reported to supply the entire reference daily intake (RDT) amount for vitamin C (Rousseff and Nagy, 1994). There is considerable variation in the vitamin C content of juices of different citrus fruits. Grapefruit, tangerine, and lemon generally contain between 20 and 50 mg per 100 mL juice. However, it is important to take into account that vitamin C content in
oranges, tangerines, and grapefruits decreases with maturity. Conversely, thiamin, niacin, B₆, and folic acid vitamins increase with ripening; folic acid is susceptible to oxidation but is protected by vitamin C in fresh fruit. Orange juice contains more niacin, thiamin, riboflavin, and B₆ than tangerine and grapefruit; of these vitamins, niacin is the highest at 200–600 μg, followed by thiamin at 30–80 μg, B₆ at 18–66 μg, and riboflavin at 20–40 μg. In a glass (177 mL) of each of orange, tangerine, and grapefruit juice, the content of folic acid is 34 μg, 21 μg, and 8 μg.

With respect to minerals content, citrus fruit is high in potassium and low in sodium. For example, 178 mL of each of orange and grapefruit juice contains 300 mg and 200 mg of potassium, whereas sodium content is 3–4 mg and 5.5 mg respectively in the same volume (Ladaniya, 2008).

Citrus limonoids (such as limonin and nomilin), one of the two main classes of compounds responsible for the bitter taste in citrus fruits, have certain biological activities that may be used as chemopreventive agents (Lam et al., 1994). The main flavonoids in oranges and grapefruits are hesperidin and naringin, respectively, and hesperidin is also found in mandarins, lemons, and limes. The polymethoxyflavones and the glycosylated flavones – only found in citrus fruits, and their pattern is specific to each species – have been shown to have a broad spectrum of biological activities such as anti-inflammatory, anticancer, and anti-atherogenic properties (Li et al., 2009). Citrus flavonoids have been reported to possess anticancer activity both in vitro and in vivo (Middleton and Kandaswami, 1994), in addition to antiviral and anti-inflammatory activities, and the ability to inhibit human platelet aggregation (Huet, 1982; Benavente-García et al., 1997) and to reduce cholesterol levels and increase HDL in serum (Aptekmann and Cesar, 2013; Cesar et al., 2010). Citrus fruits are particularly rich sources of pectin, which occurs both in the edible portion and in the inedible residues such as peel, rag, and core (Baker, 1994). Dietary incorporation of citrus pectins appears to affect several metabolic and digestive processes, such as the effect on glucose absorption, and cholesterol levels (Baker, 1994). It has been found that pectin of lemons is able to inhibit the binding of fibroblast growth factor 1 to the receptor in the presence of 0.1 μg/mL heparin (Liu et al., 2000); thus pectin may be used as an anti-growth factor agent in fibroblasts.

Orange (Citrus sinensis) was found to be more active than pink grapefruit (C. paradisi) in scavenging peroxyl radicals. While grapefruit juice was more active than orange juice, when the oxygen radical absorbance capacity (ORAC) assay was used (Wang et al., 1996). Grapefruit extracts inhibited ascorbate-iron-induced lipid peroxidation of liver microsomes in a dose-dependent way, but were less effective antioxidants towards an NADH-iron-induced system (Plumb et al., 1996b). The total antioxidant activity in orange juice was thought to be accounted for by hesperidin and narirutin (Miller and Rice-Evans, 1997). Seeds of lemons, sour oranges, sweet oranges, mandarins, and limes had greater antioxidant activity than the peels (Bacco et al., 1998). Antioxidant activity is generally higher in the seeds than in the peels (Bacco et al., 1998).

1.3.3 Grapes and Berries

Grapes and berries are rich sources of phytochemicals including phenolic compounds, pigments, and ascorbic acid. Fresh grapes and grape juices are excellent sources of phenolic antioxidants (Frankel and Meyer, 1998). Grapes and other dietary constituents derived from them, like grape juice and wine, have attracted a great deal of attention in recent years, and therefore the composition and properties of grapes have been extensively investigated. Grapes are considered one of the major sources of phenolic compounds among fruits (Macheix et al., 1990). The phenolic compounds found in Vitis vinifera include phenolic acids, stilbenes, and flavonoids, which include flavonols, flavonans, and anthocyanins, and play an important role in the quality of grapes and wines (Downey et al., 2006). Anthocyanins are directly responsible for the color of grape fruit and young wines; astrigency and structure of wines are related to catechins and proanthocyanidins, and flavonols contribute to bitterness (Hufnagel and Hoffman, 2008). The diverse classes and large amounts of phenolic compounds found in grapes (Somers and Ziemelis, 1985; Macheix et al., 1990; Ricardo-da-Silva et al., 1990) were reported to play an important role in human health, such as lowering of low-density lipoprotein (LDL) (Frankel et al., 1993; Tussedre et al., 1996). It has been demonstrated that products derived from grapes have high antioxidant capabilities (Alonso et al., 2002). In addition, viniferin, a potent antifungal agent, and anthocyanins, which are strong antioxidants that inhibit platelet aggregation, are also present in grapes (Escarpa and Gonzalez, 2001). Extracts of fresh grapes inhibited human LDL oxidation from 22% to 60% and commercial grape juice from 68% to 75% when standardized at 10 μM gallic acid equivalents (GAE) (Frankel et al., 1998). The LDL antioxidant activity correlated highly with the concentration of total phenolics for both grape extracts and commercial grape juices, with the level of anthocyanins and flavonols for grape extracts, with the levels of anthocyanins for Concord grape juices, and with the levels of hydroxycinnamates and flavan-3-ols for the white grape juice samples (Frankel et al., 1998). Berries contribute significant numbers and amounts of phytochemicals such as ascorbic acids, carotenoids,
flavonoids, phenolic acids, and tocopherols. Some wild berries with very high antioxidant activities include crowberries (*Empetrum nigrum*), cloudberry (*Rubus chamaemorus*), whortleberry (*Vaccinium uliginosum*), lingonberry (*V. vitis-idaea*), aronia (*Aronia melanocarpa*), cranberry (*V. oxyccocus*), and rowanberry (*Sorbus aucuparia*), but some of the cultivated berries such as straw-berries (*Fragaria ananassa*), redcurrant (*Ribes rubrum*), blackcurrant (*R. nigrum*), and raspberry (*Rubus idaeus*) exerted lower antioxidant activity (Kakhonen et al., 1999). Different blueberries (*V. corymbosum*) and bilberries (*V. myrtillus*) were reported to exhibit good antioxidant activity in the ORAC assay (Prior et al., 1998; Kalt et al., 1999). The antioxidant capacity of blueberries was about threefold higher than either strawberries or raspberries, with only a small contribution of ascorbic acid to the total antioxidant capacity compared to total phenolics and anthocyanins (Kalt et al., 1999). Berry (poly)phenols may exert potential inside the initiated cell anticancer effects by chelating redox active metals (such as iron) or by directly scavenging intracellular ROS, although this mechanism may be an oversimplification of the processes involved. It may be that berry (poly)phenols interact with cell receptors or enzymes resulting in altered cell redox status, which activates redox-dependent reactions (Forman et al., 2002).

On the other hand, it is important to consider the effect of intestinal digestion and bacterial fermentation on the antioxidant properties of berries, because ileostomy feeding studies have demonstrated that substantial amounts of (poly)phenolic compounds in berries are not absorbed into circulation from the small intestine but rather pass into the large intestine, where they come into direct contact with the colonic epithelium and exert beneficial effects (antioxidant, antigenotoxic, anti-inflammatory, anticarcinogenic) (Johnson, 2004; Del Rio et al., 2010) in healthy populations and in colorectal cancer patients who consumed whole fruit or juice (blueberry, bilberry, blackberry, blackcurrant, chokeberry) (Wang et al., 2011; Mentor-Marcel et al., 2012; Thomasset et al., 2009; Del Bo et al., 2013; Riso et al., 2013). Strawberries are good sources of natural antioxidants (Heinonen et al., 1998; Wang et al., 1996). The extract of strawberries (*F. ananassa*) had the highest total antioxidant activity compared with extracts of plums, orange, red grapes, kiwifruit, pink grapefruit, white grapes, banana, apple, tomato, pears, and honeydew melons when the ORAC assay was used (Wang et al., 1996), but ranked among the least compared to some other berries when lipid oxidation model (methyl linoleate, LDL) assays were used (Heinonen et al., 1998; Kakhonen et al., 1999). Strawberry extracts exhibited high enzymatic activity for oxygen detoxification (Wang et al., 2005) and a high level of antioxidant capacity against free radical species including peroxy radicals, superoxide radicals, hydrogen peroxide, hydroxyl radicals and singlet oxygen (Wang and Lin, 2000; Wang and Jiao, 2000). The major pigments of wild strawberries (*F. vesca*) were pelargonidin-3-monoglucoside and cyanidin-3-monoglucoside, while in cultivated strawberries the main pigment was only pelargonidin-3-monoglucoside (Sondheimer and Karash, 1956). Strawberry extracts exhibited chemopreventive and chemotherapeutic activities in vitro and in vivo (Carlton et al., 2001; Meyers et al., 2003; Wang et al., 2005). They also inhibited proliferation of the human lung epithelial cancer cell line A549 and reduced tetradecanoylphorbol-13-acetate (TPA) induced neoplastic transformation of JB6 P+ mouse epidermal cells (Wang et al., 2005).

### 1.3.4 Avocados

Avocado fruit is a high-fat fruit, contains rare sugars of high carbon number, and is relatively rich in certain vitamins, dietary fiber, minerals, and nitrogenous substances (Yahia, 2012b). It has a high oil content with a wide range (3–30%) and low sugar (about 1%); hence it is recommended as a high-energy food for diabetics (Yahia, 2012b). It is a rich source of potassium, containing 1.6 times as much as bananas. A 100 g serving has about 177 calories, contains no cholesterol, and has about 17 g of fat, which is primarily of the mono-unsaturated type. Oil content is a key part of the sensory quality of the fruit. Oil quality is very similar to that of olive oil, with a high proportion of the oil being approximately 75% mono-unsaturated, 15% saturated, and 10% polyunsaturated fatty acids. The high mono- and poly-unsaturation and low saturated content makes it a “healthy” oil in terms of effect on heart disease. In addition, avocado oil contains a range of other health-promoting compounds such as chlorophyll, carotenoids, α-tocopherol, and β-sitosterol. The edible portion of the fruit is rich in oleic, palmitic, linoleic, and palmitoleic acids, while stearic acid is present only in trace amounts. The fatty acid composition of the lipids of avocado fruit and avocado oil differs greatly with cultivar, stage of ripening, anatomical region of the fruit, and geographic location (Itoh et al., 1975). However, the major fatty acid is always oleic followed by palmitic and linoleic acids, while the fatty acids present in trace amounts are myristic, stearic, linolenic, and arachidonic (Itoh et al., 1975; Gutfinger and Letan, 1974; Tango et al., 1972; Mazliak, 1971; Swisher, 1984). The cuticular wax contains C20 to C27 long-chain fatty acids (Mazliak, 1971). Avocados are rich in vitamin B6 (3.9–6.1 µg/g pyridoxine) and contain lesser amounts of biotin, folic acid, thiamine, and riboflavin (Hall et al., 1955), calciiferol (vitamin D), α-tocopherol (vitamin E),...
and 2-methyl-1,4-naphthoquinone (vitamin K) (Yahia, 2012b). Therefore, besides being a source of energy and vitamins, avocados also contain several phytochemicals that are thought to be beneficial for health, and are considered by some as “functional food” (Mazza, 1998). Some nutraceutical ingredients that have been found in avocado pulp are antioxidants such as tocopherols (about 4.3 IU/100 g) and glutathion (18 mg/100 g). It has also been reported that avocado is a source of lutein (up to 248 mg/100 g). Lutein is included in the subclass of carotenoids known as xanthophylls, which are oxygen-containing fat-soluble antioxidants with low propensity for pro-oxidant activity (McNulty et al., 2008). In this regard it is important to have in mind that the absorption of carotenoids depends on the presence of dietary fat and that the avocado fruit with its fatty acid content is naturally designed to enhance the absorption of carotenoids (Dreher and Davenport, 2013). Among all fruit and vegetables, avocados are one of the highest in lipophilic total antioxidant capacity (Wu et al., 2004) and may be important for reducing the oxidation of LDL (Hozawa et al., 2007). Avocados are also one of the richest fruit sources of phytosterols (Duester, 2001). The amount of β-sitosterol in this fruit is comparable to that found in soy and olives. Pigments are important contributors to the appearance and healthful properties of both avocado fruit and avocado oil. Ashton et al. (2006) identified the following in the skin, flesh, and oil of avocado fruit: lutein, β-carotene, neoxanthin, violaxanthin, zeaxanthin, antheraxanthin, chlorophylls a and b, and pheophytins a and b, with the highest concentrations of all pigments in the skin. Chlorophyllides a and b were identified in the skin and flesh tissues only.

1.3.5 Stone Fruits

Yellow flesh peaches (Prunus persica L.), such as the cultivar Fay Alberta, contain 54 retinol equivalents (RE) per 100 g of provitamin A carotenoids (USDA, 1982), predominantly as β-carotene and β-cryptoxanthin (Gross, 1987). The two dominant polyphenols in sweet cherries (P. avium L.) are caffeoyltartaric acid and 3-p-coumaroylquinic acid (Robards et al., 1999). However, sweet cherries are characterized to have anthocyanins as the major phenolic compounds, the aglicon cyanidin bound to the glycosides 3-rutinoside and 3-glucoside being the main compounds, with pelargonidin-3-rutinoside, peonidin-3-rutinoside, and peonidin-3-glucoside as minor contributors (Gao and Mazza, 1995; Chaovanalikit and Wrolstad, 2004). Ascorbic acid, total phenolic compounds, and total antioxidant activity decreased during the early stages of sweet cherries fruit development, but exponentially increased coinciding with the stage of anthocyanin accumulation and fruit darkening (Serrano et al., 2005). Prunes (P. domestica) and prune juice were antioxidant toward oxidation of human LDL (Donovan et al., 1998). Prunes ranked highest, with more than twice the level of antioxidants of other high-scoring fruits, when the ORAC assay was used (Wang et al., 1996). The inhibition of LDL oxidation by raw and canned peaches (P. persica) ranged between 56% and 87%, with oxidation activity mainly attributed to the presence of hydroxycinnamic, chlorogenic, and neochlorogenic acids, but not to carotenoids such as β-carotene and β-cryptoxanthin. However, Plumb et al. (1996b) reported that hydroxycinnamic acids do not contribute to the inhibition of lipid peroxidation of liver and cell microsomes by fruit extracts including plums and peaches, although these fruits had the ability to scavenge hydroxyl radicals.

1.3.6 Kiwifruit

Kiwifruit contains high levels of potassium (290 mg/100 g), vitamin C (59 mg/100 g), and lutein (160 μg/100 g), and has high antioxidant capacity (91 mmol/100 g) measured with FRAP. In particular, the kiwifruit is rich in lutein, an oxycarotenoid with high antioxidant capacity (Calvo, 2005; Wolber et al., 2013). Moreover, the kiwifruit has been shown to exert cardioprotective properties (Duttaroy, 2013) and reduce ACE activity (Dizdar- evic et al., 2014) and intake of kiwifruit has shown to up-regulate genes involved in stress defense and DNA repair (Böhn et al., 2010). Intakes of kiwifruits have shown promising effects on BP reduction in smoking men (Karsen et al., 2012) and in men and women with high normal BP (Svendsen et al., 2015). In the study by Karlsen (2012) 102 smoking men were randomized to a kiwifruit group that received three kiwifruit a day, an antioxidant-rich diet group that received about 50% of their dietary intake from antioxidant-rich foods, and a control group that continued with their habitual diet for 8 weeks. Compared to controls, a reduction of 10 mmHg in systolic BP (p = 0.019) and 9 mmHg in diastolic BP (p = 0.016) was seen in the kiwifruit group. In addition, a 15% reduction (p = 0.009) in platelet aggregation and 11% reduction in ACE activity (p = 0.034) was shown in the kiwifruit group. In the antioxidant diet group a reduction in BP was seen only among the hypertensive participants and no effects were seen with regard to platelet aggregation or ACE activity (Karsen et al., 2012). The effect of kiwifruit on BP was investigated in a similar manner among men and women with stage 1 hypertension (Svendsen et al., 2015). In parallel groups, 118 subjects with systolic BP 130–159 mmHg and/or diastolic BP 85–99 mmHg were randomized to daily intakes of three kiwifruits or one apple. After 8 weeks, 24 hour ambulatory BP was lower in
the group assigned to kiwi versus apple intake (between-group difference: −3.6 mmHg, 95% CI −6.5, −0.7, \( P = 0.017 \), and −1.9 mmHg, 95% CI −3.6, −0.3, \( P = 0.040 \), for systolic and diastolic BP, respectively). In this study apple was chosen as the comparing fruit because of the different micronutrient composition with regard to potassium, vitamin C, lutein, and antioxidant capacity measured with FRAP. In these studies, the kiwifruit showed BP lowering effects among subjects that may have higher levels of stress due to smoking and hypertension. In line with this, inflammatory status has been shown to modulate the response of kiwifruit consumption on plasma lipids and inflammatory markers (interleukin-6 and high-sensitivity C-reactive protein), indicating the beneficial effects of regular consumption of kiwifruits among men with higher level of inflammation (Gammon et al., 2013). However, Gammon et al. (2014) did not find any effect of kiwifruit on BP among normotensives.

### 1.3.7 Tropical Fruits

Tropical fruits are produced in various tropical countries located in the geographical zone stretching from latitudes 30°S to 30°N, where temperature ranges from 16 °C to 36 °C. The most common are papaya, guava, coconut, pineapple, mango, watermelon, mangosteen, bananas, passion fruit, and feijoa (Dembitsky et al., 2011). Tropical fruits are important sources of nutrients (Yahia, 2006) and bioactive compounds, and are considered potential nutraceutical foods partly because of the antioxidant activity attributed to the content of polyphenols and/or ascorbic acid (Contreras-Calderon et al., 2011; Zapata et al., 2014; Park et al., 2015). The Colombian tropical fruits that have been described as having the highest phenolic content (1011–1018 mg GAE/100 g fresh weight (fw)) and ascorbic acid (AA) (102–257 mg AA/100 g fw) are Brazilian guava, guava apple, and cashew; the last presents a high antioxidant activity (FRAP 125 and ABTS 115 μmol Trolox equivalents (TE) per gram fw) and vitamin C values (228 mg AA/100 g fw). Banana passion fruit (Passiflora mollissima) provides an example of high content of phenolic compounds (1018 mg GAE/100 g fw) and antioxidant activity (FRAP 114 and ABTS 131 μmol TE/g fw) but did not present the highest value of AA (61.5 mg AA/100 g fw) compared to the AA medium value per 100 g fw (26.7–51.1) present in other tropical fruits (giant grana-dilla, pejibaye, mountain papaya, yellow mombina (Contreras-Calderon et al., 2011). Zapata et al. (2014) also determined the phenol content and antioxidant capacity by ORAC assay of Colombian tropical fruits including banana passion fruit, mango ‘Tommy Atkins’, passion fruit, banana, guava apple, pineapple, papaya, guava, and kiwifruit. They found that phenols and ORAC values ranged from 30.5 to 10584.7 mg GAE/100 g dry weight (dw) and from 685.7 to 207850.4 μmol TE/100 g fw; banana passion fruit had the highest phenols content (10584.7 mg GAE/100 g dw) and ORAC value (207850.4 μmol TE/100 g fw), supporting previous studies. It has been proposed that consumption of 100 g or 3000 to 5000 ORAC/day of these fruits could have a positive effect in plasma antioxidant status (Rojano et al., 2012; Prior et al., 2003).

Bananas, plantains, and breadfruit are widely used as a source of starch; acerola fruit contains the highest known ascorbic acid content among all fruits (1000–3300 mg/100 g fw), and some other good sources of vitamin C include guava, lychee, papaya, and passion fruit (Yahia, 2006). Mango and papaya are good sources of vitamin A; breadfruit and cherimoya contain relatively high amounts of niacin and thiamin; and most tropical fruit are good sources of minerals, especially potassium and iron (Yahia, 2006). Tropical fruits are thought to contain more carotenoids compared to temperate fruits, which contain more anthocyanins. Mango and papaya are among the tropical fruits rich in carotenoids (Rivera-Pastarna et al., 2009; Ornelas-Paz et al., 2007, 2008a, 2008b).

Mango fruit is a rich source of vitamin C and carotenoids, some of which function as provitamin A (Sid-dappa and Bhatia, 1954; Thomas, 1975, Yahia et al., 2006). \( \beta \)-carotene (all-trans), \( \beta \)-cryptoxanthin (all-trans and cis), zeaxanthin (all-trans), luteoxanthin isomers, violaxanthin (all-trans and cis), and neoxanthin (all-trans and cis) were identified in several mango cultivars (Mercadante et al., 1997; Ornelas-Paz et al., 2007, 2008a, 2008b). Mango retinol was found to be highly bioavailable by estimating vitamin A and carotene reserves in the liver and plasma of rats. Information on the tocopherol content in mango is very scarce, but it seems to be low (Burns et al., 2003; Ornelas-Paz et al., 2007). The major (poly)phenols in terms of antioxidative capacity identified in mango are mangiferin, catechins, quercetin, kaempferol, rhamnetin, anthocyanins, gallic and ellagic acids, propyl and methyl gallate, benzoic acid, and protocatechuc acid; gallic acid is the most predominant phenolic acid (Dembitsky et al., 2011).

Some chemical components of Carica papaya fruit pulp have been reported by Oloyede (2005), suggesting that the astringent action of the plant encountered in numerous therapeutic uses is due to the presence of some phytochemicals like saponins and cardenolides. Liquid chromatography or mass spectrometry analyses of ripe and green papaya showed few candidate phenols, other than catechin conjugates (Mahattanatawe et al., 2006), which is consistent with the small number of compounds reported previously in this fruit (Agrawal and Agrawal, 1982). Quercetin and kaempferol, previously reported in leaves and shoots of C. papaya (Canini et al., 2007), were
found only in trace amounts in fruit peel extracts (Canini et al., 2007; Miean and Mohamed, 2001). Corral-Aguayo et al. (2008) reported that the antioxidant capacity of papaya extract ranked one of the lowest among eight different fruits.

Dopamine, a strong water-soluble antioxidant, was identified in banana fruit (Musa cavendishii) by Kanazawa and Sakakibara (2000). Banana fruit contained high levels in the pulp and peel, at 2.5–10 mg/100 g and 80–560 mg/100 g, respectively. A banana water extract was reported to suppress the autoxidation of linoleic acid by 65–70% after a 5 day incubation in an emulsion system, as determined from peroxide value and thiobarbituric acid reactivity (Kanazawa and Sakakibara, 2000).

Pineapple fiber showed higher (86.7%) antioxidant activity than orange peel fiber (34.6%), and myricetin was the major polyphenol identified in pineapple fiber (Larrauri et al., 1997). On the other hand, the anti-inflammatory and anticarcinogenic properties attributed to the fruit are based on bromelain content—a mixture of different thiol endopeptidases and enzymes of type phosphatase, glucosidase, peroxidase, cellulase, escharase, and several protease inhibitors—and 40% of bromelain is absorbed by the gastrointestinal tract in a functionally intact form (Pavan et al., 2012). Clinical studies have shown that bromelain may be used in cardiovascular diseases by fibrinolytic activity and inhibition of platelet aggregation, and in inflammatory and autoimmune diseases such as rheumatoid arthritis by modulating the activation of TCD4+ macrophages, and natural killer cells and secretion of IL-6, IL-1β and TNF-α. Bromelain induces apoptosis and reduces tumor formation in xenograft human cancer cells in mouse (leukemia, sarcoma, skin, lung, and breast cancer cells) (Pavan et al., 2012).

Ma et al. (2004) isolated and identified seven phenolic compounds in Pouteria campechiana, P. sapota, and P. viridis, namely gallic acid, (+)-gallocatechin, (+)-catechin, (−)-epicatechin, dihydromyricetin, (+)-catechin-3-O-gallate, and myricitrin. The highest level of the seven phenolic compounds was found in P. sapota, the second highest in P. viridis, and the lowest in P. campechiana.

### 1.3.8 Nuts

Nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, and walnuts) and legume seeds (peanuts and baru) are rich sources of unsaturated fatty acids, L-arginine, minerals (magnesium, zinc, selenium, potassium), phenolic compounds, and phytosterols that are consistently shown to have cardioprotective effects (Ros, 2015; Souza et al., 2015). A daily serving of 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts was associated with a reduced incidence of diabetes and stroke of about 50%, in addition to 28% reduction in CVD (Ros, 2015). Several nuts are among the dietary plants with a high content of total antioxidants. Of the tree nuts, walnuts, pecans, and chestnuts have the highest contents of antioxidants. Walnuts contain more than 20 mmol antioxidants per 100 g, mostly in the walnut pellicles. Peanuts also contribute significantly to dietary intake of antioxidants (Blomhoff et al., 2006). Almonds are rich sources of proteins, dietary fats, fibers, and several minerals (Ren et al., 2001; Turnball et al., 1993). Nine phenolic compounds have been identified in almonds by Sang et al. (2002), of which eight exhibited strong antioxidant activity. Almond skins were found to contain high levels of four different types of flavanol glycosides, which are thought to have powerful effects as antioxidants (Frison and Sporns, 2002). Polyphenolic compounds in almonds were reported to be absorbed well in the body, and are active in preventing the oxidation of LDL cholesterol, and vitamin E in almonds acts in synergy with phenolic compounds to reduce oxidation (Millburry et al., 2002). Research has suggested a possible effect of almond consumption on cancer (Davis and Iwahashi, 2001), including colon cancer (Davis et al., 2003).

### 1.3.9 Tomatoes

Tomato and tomato-based products are considered healthy foods because they are low in fat and calories, cholesterol free, and a good source of fiber, vitamins A and C, β-carotene, lycopene, and potassium (Yahia and Brecht, 2012). Interest in the nutritional and health benefits of tomato fruit and their products has increased greatly (Geeson et al., 1985; Giovannucci and Clinton, 1998; Guester, 1997; Yahia and Brecht, 2012). Vitamin C content in tomato (23 mg/100 g) is not as high as in several other fruits, but its contribution is very important due to the common use of tomato in the diet of many cultures. A 100 g tomato can supply about 20% and 40% of the adult US recommended daily intake of vitamins A and C, respectively. The selection of tomato genotypes that are rich in vitamins A and C has been accomplished, and cultivars with very high vitamin A content have been developed, but their orange color was not well accepted by consumers. Epidemiological studies have indicated that tomato fruit has one of the highest inverse correlations with cancer risk and cardiovascular disease, including stroke (Giovannucci et al., 1995). Lycopene, the principal pigment responsible for the characteristic deep red color of ripe tomato fruit and tomato products, is a natural antioxidant that can prevent cancer and heart disease (Shi and Le Maguer, 2000). Although lycopene has no provitamin A activity, as is the case with some other carotenoids, it does exhibit a physical quenching rate constant.
with singlet oxygen almost twice as high as that of β-carotene.

Increasing clinical evidence supports the role of lycopene as a micronutrient with important health benefits, due to its role in protection against a broad range of epithelial cancers (Shi and Le Maguer, 2000). The serum level of lycopene and the dietary intake of tomatoes have been inversely correlated with the incidence of cancer (Helzlsouer et al., 1989; Van Eenwyk et al., 1991).

Fresh tomato fruit contains about 0.72 to 20 mg of lycopene per 100 g of fresh weight, which accounts for about 30% of the total carotenoids in plasma (Stahl and Sies, 1996). Yellow tomato species are less rich in lycopene, with a content of only about 0.5 mg/100 g (Holzapfel et al., 2013). In contrast to other pigments such as β-carotene, lutein, violaxanthin, auroxanthin, neoxanthin, and chlorophylls a and b, which accumulate in inner pulp and in the outer region of the pericarp, lycopene appears only at the end of the maturation period, and almost exclusively in the external part of the fruit (Laval-Martin et al., 1975). Other tomato components that can contribute to health include flavonoids, folic acid, and vitamin E (Doraïs et al., 2001a, 2001b).

Absorption of lycopene is in the cis conformation; this occurs through dietary lipid micelles passing into the mucosa of the small intestine, then being transported by chylomicrons to the liver in the lymph system, from where they are distributed to their target organs (testes, prostate, and adrenal glands). By contrary, all-trans isomers have a greater disposition to aggregate in the intestine, building crystals, which may reduce their uptake through micelles (Parker, 1996; Boileau et al., 2002).

Tomato was reported to exert antioxidant activity in some studies (Vinson et al., 1998; Kahkonen et al., 1999), but to show no antioxidant activity or even to act as pro-oxidant in others (Gazzani et al., 1998). In serum samples from individuals fed with tomato products or tomato extracts, there was observed a delay chemically induced in LDL oxidation. This effect was not observed with lycopene supplementation alone (30 mg/day). However, lymphocyte DNA damage was reduced (Devaraj et al., 2008; Neyestani et al., 2007; Zhao et al., 2006). Thus, the antioxidant effect of tomato is most probably due to synergism between several compounds and not due to lycopene content alone, as pure lycopene and several other carotenoids act as pro-oxidants in a lipid environment (Al-Saikhani et al., 1995; Haila et al., 1996). On the other hand, lycopene has biological effects independent of antioxidant activity such as apoptosis, arrest of cycle, inhibition of androgen and estrogen activity, induction of hepatic phase II enzymes, and decrease in C reactive protein and serum cholesterol levels (Erdman et al., 2009).

1.3.10 Cruciferous Vegetables

Sulfur-containing phytochemicals of two different kinds are present in all Brassica oleracea (Cruciferae) vegetables (cabbage, broccoli, cauliflower, Brussels sprouts, kale). They are glucosinolates (previously called thioglucosides) and S-methyl cysteine sulfoxide. These compounds, which are derived in plant tissue by amino acid biosynthesis, show quite different toxicological effects and appear to possess anticarcinogenic properties (Stoewand, 1995). Glucosinolates have been extensively studied since the mid nineteenth century. They are present in plant foods other than Brassica vegetables, with especially high levels in a number of seed meals fed to livestock. About 100 different kinds of glucosinolates are known to exist in the plant kingdom, but only about 10 are present in Brassica. The first toxic effects of isothiocyanates and other hydrolytic products from glucosinolates that were identified were goiter and a general inhibition of iodine uptake by the thyroid. Numerous studies have indicated that the hydrolytic products of at least three glucosinolates, 4-methyl-sulfinylbutyl (glucoraphanin), 2-phenethyl (glucoturrtiin), 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-Methyl cysteine sulfoxide and its metabolite methyl methane thiosulfonate have been 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-methyl cysteine sulfoxide).

The effect of consumption of Brussels sprouts on levels of 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG) in human urine was investigated in 10 healthy, male, non-smoking volunteers by Verhagen et al. (1995). Following a 3 week run-in period, five volunteers continued on a diet free of cruciferous vegetables for a subsequent 3 week intervention period (control group), while the other five (sprouts group) consumed 300 g of cooked Brussels sprouts per day, at the expense of 300 g of a glucosinolate-free vegetable. In the control group there was no difference between the two periods in levels of 8-oxodG (P = 0.72), but in the sprouts group the levels of 8-oxodG were decreased by 28% during the intervention period (P = 0.039); these results support the results of epidemiologic studies that consumption of cruciferous vegetables may result in a decreased cancer risk.

Extracts from broccoli (B. oleracea L. ’Italica’), Brussels sprouts (B. oleracea L. ’Rubra’), white cabbage (B. oleracea L. ’Alba’) and cauliflower (B. oleracea L. ’Botrytis’) showed significant antioxidant properties against lipid
peroxidation (Plumb et al., 1996a). However, it is thought that most of the direct antioxidant action of the crucifer vegetables is not due to the glucosinolate content, but probably involves the hydroxylated phenols and polyphenol content, as has been identified in broccoli (Plumb et al., 1997b). Cabbage, cauliflower, and Brussels sprouts were reported to be pro-oxidants toward lipid peroxidation in microsomes containing specific cytochrome P450s (Plumb et al., 1997a). Kale (B. oleracea L. ‘Acephala’), Brussels sprouts, and broccoli were found to exert higher antioxidant activity than cauliflower and some other vegetables (Al-Saikhan et al., 1995; Cao et al., 1996; Ramarathnam et al., 1997; Vinson et al., 1998).

### 1.3.11 Leafy Vegetables

Some contradictory results have been reported regarding the antioxidant activities of leafy vegetables. For example, among 23 vegetables, spinach (Spinacia oleracea) ranked 18th and head lettuce (Lactuca sativa L. ‘Capita’) 22nd when assayed for inhibition of LDL (Vinson et al., 1998). However, the ORAC antioxidant activity of spinach was reported to be very high, while that of leaf lettuce and iceberg lettuce was poor (Cao et al., 1996).

### 1.3.12 Root and Tuberous Vegetables

Carrots (Daucus carota) are excellent sources of β-carotene and vitamin A, although they have been reported to exert low antioxidant activity compared to some other vegetables (Al-Saikhan et al., 1995; Cao et al., 1996; Ramarathnam et al., 1997; Vinson et al., 1998; Beom et al., 1998). However, boiling carrots for 30 minutes significantly improved their antioxidant activity towards coupled oxidation of β-carotene and linolenic acid (Gazzani et al., 1998).

In addition to being an excellent source for some carbohydrates, potatoes (Solanum tuberosum) are considered a source for some antioxidants such as ascorbic acid, α-tocopherol, and polyphenolic compounds (Al-Saikhan et al., 1995; Velioglu et al., 1998). Potato peels have been reported to show high antioxidant activity (Rodriguez de Siotillo et al., 1994). Purple potatoes and peel have been shown to exhibit greater antioxidant activity than the white and yellow varieties (Velioglu et al., 1998), which is due to the presence of anthocyanins such as pelargonidin-3-rutinoside-5-glucoside (Rodriguez-Saona et al., 1998). Potato is not considered to be a rich source of carotenoids, but some have been identified. Pendlington et al. (1965) tentatively identified eight carotenoids (e.g. β,β-carotene, lutein) as most abundant in most cultivars, although Muller (1997) reported that violaxanthin is the main potato carotenoid, followed by lutein, antheraxanthin, and others. Iwanzik et al. (1983) compared the carotenoid content between 13 potato cultivars in the same habitat, and reported violaxanthin as the main carotenoid, followed by lutein, lutein-5,6-epoxide, and neoxanthin. Breithaupt and Bamedi (2002) investigated the pattern of four yellow-fleshed and four white-fleshed potato cultivars, and reported that it is dominated by violaxanthin, antheraxanthin, lutein, and zeaxanthin, whereas neoxanthin, β-cryptoxanthin, and β,β-carotene generally are only minor constituents. The color of orange-fleshed potato was suggested to originate from large amounts of zeaxanthin (Brown et al., 1993).

In addition to having some important phytochemicals such betalains, beetroot (Beta vulgaris L.) and sugar beet (B. vulgaris subsp. esculenta) peels showed remarkably high antioxidant activities (Kalkonen et al., 1999). For example, beet ranked eighth among 23 vegetables assayed for inhibition of LDL oxidation (Vinson et al., 1998).

### 1.3.13 Peppers

Fresh peppers are excellent sources of vitamins A and C, as well as neutral and acidic phenolic compounds (Howard et al., 2000). Levels of these can vary by genotype and maturity, and are influenced by growing conditions and processing (Mejia et al., 1988; Howard et al., 1994; Lee et al., 1995; Daoed et al., 1996; Simmone et al., 1997; Osuna-García et al., 1998; Markus et al., 1999; Howard et al., 2000). Peppers have been reported to be rich in the provitamin A carotenoids β-carotene, α-carotene and β-cryptoxanthin (Minguez-Mosquera and Homero-Mendez, 1994; Markus et al., 1999), as well as xanthophylls (Davies et al., 1970; Markus et al., 1999). Bell peppers have been shown to exert low antioxidant activity (Al-Saikhan et al., 1995; Cao et al., 1996; Vinson et al., 1998), or may even act as pro-oxidants (Gazzani et al., 1998).

### 1.3.14 Alliums

Edible alliums, especially onions and garlic, have been an important part of the daily diet of several cultures for hundreds of years. In many cultures alliums were thought to have medicinal properties. Allium vegetables, such as onions, garlic, scallions, chives, and leeks, include high concentrations of compounds such as diallyl sulfide and allyl methyl trisulfide (Steinmetz and Potter, 1996). These compounds have been shown to inhibit cell proliferation and growth, enhance the immune system, alter carcinogen activation, stimulate detoxification enzymes, and reduce carcinogen–DNA binding (Hattori et al., 1996; Lin et al., 1994; Lee et al., 1994; Amagase and Miller,
Fruit and Vegetable Phytochemicals

1.3.15 Prickly Pear Fruit and Cladodes

Prickly pear fruit and cladodes are valued because of their high nutrient content, vitamins, and other health components (Yahia, 2012a; Hegwood, 1990).

Cladodes (called nopal in Mexico) are low in calories and high in fiber, and are traditionally consumed as a vegetable in Mexico and the southern region of the USA. Nopal contains about 920 g/kg water, 40–60 g/kg fiber, 10–20 g/kg proteins, and about 10 g/kg minerals, primarily calcium. Vitamin C content is about 100–150 mg/kg and β-carotenes (provitamin A) are about 300 μg/kg. Cladodes are used in various pharmaceutical applications for their therapeutic, dermatological, and medical properties. Ethanol extract of Opuntia ficus-indica shows potential analgesic and anti-inflammatory effects (Park et al., 1998). Galati et al. (2001) reported preventive and curative effects of O. ficus-indica cladodes preparations on rats affected by ethanol-induced ulcers. The cactus consumption gives rise to cytoprotection phenomena by breaking up the epithelial cells and stimulating an increase in mucus production. When O. ficus-indica cladodes are administered as a preventive therapy, they keep the gastric mucosa in the normal condition by preventing mucus dissolution caused by ethanol and favoring mucus production. An increase of mucus production is also observed during the course of the curative treatment. The treatment with O. ficus-indica cladodes provokes an increase in the number of secretory cells. Probably, the gastric fibroblasts are involved in the anti-ulcer activity.

The consumption of prickly pear cactus fruit is recommended for their beneficial and therapeutic properties (Yahia, 2012a). Aqueous extracts of cactus pear fruit (O. ficus-indica L. Mill.) were reported by Butera et al. (2002) to possess a high total antioxidant capacity, expressed as Trolox equivalents, and to exhibit a marked antioxidant capacity in several in vitro assays, including the oxidation of red blood cell membrane lipids and the oxidation of human LDLs induced by copper and 2,2’-azobis(2-amidinopropane-hydrochloride). Antioxidant components reported by these authors included vitamin C, negligible amounts of carotenoids, and vitamin E. However, Corral-Aguayo et al. (2008) reported that the antioxidant capacity of extracts of prickly pear fruit ranked the lowest compared to seven other fruits. Some prickly pear fruit contain two betalain pigments, the purple-red betanin and the yellow indicaxanthin, both with radical-scavenging and reducing properties (Forni et al., 1992; Fernandez-Lopez and Almela, 2001; Stintzing et al., 2002; Castellanos-Santiago and Yahia, 2008). Qualitative and quantitative analysis of betalains pigments in 10 cultivars and lines of prickly pear (Opuntia spp.) fruit were conducted with reverse phase high-performance liquid chromatography with diode array detection (HPLC-DAD) coupled with electrospray mass spectrometry (ESI-MS) (Castellanos-Santiago and Yahia, 2008). Betacyanins and betaxanthins were identified by comparison with UV/Vis and mass spectrometric characteristics as well as the retention times of semi-synthesized reference betaxanthins. Carotenoids and chlorophylls were also identified and quantified based on their molecular mass determined by applying HPLC-DAD coupled with positive atmospheric pressure chemical ionization mass spectrometry (APCI-MS). A total of 24 known and unknown betalains were present in the studied prickly pear fruit, including 18 betaxanthins and 6 betacyanins. The ratio and concentration of betalain pigments are responsible for the color in the different cultivars; the highest betalains content is shown in fruit of purple color, comparable to that found in red beet (Beta vulgaris L. ‘Pablo’). All cultivars/lines had a similar carotenoid profile; lutein was the most abundant compound in ‘Camuesa’, while neoxanthin was the most abundant compound in the line ‘21441’. Chlorophyll a was the most abundant in all cultivars/lines, with the highest quantity in ‘21441’. Daily supplementation with 500 g cactus fruit (O. ficus-indica)
pulp for 2 weeks greatly improved the oxidation stress status of healthy humans (Tesoriere et al., 2004). The effects included remarkable reduction in plasma markers of oxidative damage to lipids, such as isoprostanes and malondialdehyde (MDA), an improvement in the oxidative status of LDL, considerably higher concentrations of major plasma antioxidants, and improvement in the redox status of erythrocytes. The fruit also enhances renal function (Cacioppo, 1991).

Reports indicate that other parts of prickly pear cactus are also used in folk medicine as emollient, moisturizing, cicatrizant, hypcholesterolemic, and hypoglycemic agents, and in gastric mucosa diseases (Hegwood, 1990; Frati et al., 1990a, 1990b; Cruse, 1973; Meyer and McLaughlin, 1981; Harvala et al., 1982; Camacho-Ibanez et al., 1983; Brutsch, 1990; Fernandez et al., 1992, 1994; Yahia, 2012a). In Sicilian folk medicine, a flower infusion has an effect generally defined as depurative, and in particular it is used because of its diuretic and relaxant action on the renal excretory tract (Arcoleo et al., 1961, 1966; Sisini, 1969). Therefore, it is stipulated that a flower infusion may help the expulsion of renal calculi. Galati et al. (2002) reported that flower infusion shows a modest increase in diuresis and natriuresis. Treatment with cladode infusions increases diuresis but does not significantly influence the uric acid pattern. The fruit infusion instead had diuretic and anturiaic activity. The diuretic action observed may depend on stimulation of the urinary tract and is linked to the activation of the neurohumoral mechanism, mediators of stimuli acting on glomerulus, and tone acid on the pylouretical peristalsis. These effects might be due to the influence that the electrolytes, present in considerable quantities in the plant, exert on the renal epithelium. In particular, $O_fi_nus-indica$ is rich in K$^+$ ions, which are present at concentrations of 548 mg/kg in the cladodes, 21.7 mg/kg in the flowers, and 18 mg/kg in the fruit (D’Aquino, 1998).

### 1.3.16 Mushrooms

Some types of mushrooms contain moderate quantities of good quality protein and are good sources of dietary fiber, vitamins C and B, and minerals (Breene, 1990). Extensive clinical studies have demonstrated that some species have medicinal and therapeutic value, by injection or oral administration, in the prevention and treatment of cancer, viral diseases (influenza, polio), hypercholesterolemia, blood platelet aggregation, and hypertension (Breene, 1990). It has been reported that the inclusion of cultivated mushrooms, particularly shiitake and enokitake, in the diet is likely to provide some protection against some manifestation of cancer (Mori et al., 1987).

### 1.3.17 Pickled Vegetables

Roussin’s red (dimethylthiethanitrosodiiron) has been identified as a non-alkylating N-nitroso compound present in pickled vegetables from Linxian County, a high-risk area for esophageal cancer in China (Cheng et al., 1981). In vitro experiments showed that Roussin’s red had no significant mutagenic and transforming activities at the doses used, but it did enhance transformation in C3H/10T1/2 cells initiated with 3-methylcholanthrene (0.1 μg/mL), and it reduced the number of sebaceous glands and increased the epidermal thickness in short-term skin tests. This indicated that Roussin’s red resembled 12-O-tetradecanoyl-phorbol-13-acetate and may be a new naturally occurring tumor promoter. Examination of dietary data in relation to incidence rates specific to place of birth showed positive associations of stomach cancer with consumption of rice, pickled vegetables, and dried/salted fish, and a negative association with vitamin C intake (Kolonel et al., 1981); the results are consistent with the particular hypothesis that stomach cancer is caused by endogenous nitrosamine formation from dietary precursors, and that vitamin C may protect against the disease. Extracts of pickled vegetables commonly consumed in Linhsien County, a high-incidence area for esophageal cancer in northern China, were studied for mutagenicity (Lu et al., 1981). The liquid residue from ethereal extracts produced a dose-dependent increase of mutants in Salmonella typhimurium TA98 and TA100 strains; mutagenicity required the presence of a fortified liver microsomal activation system induced by Aroclor 1254 in adult male BD VI inbred rats. An amount of extract equivalent to 2.8 g fresh pickled vegetables produced sixfold (75 revertants/g) and twofold (45 revertants/g) increases in revertant frequencies in strains TA98 and TA100, respectively. Roussin’s red methyl ester, a tetratinosro compound $[(NO)2Fe(CH3S)]_2$, was isolated and identified from the ethereal extracts, and shown to be mutagenic in strain TA100 in the presence of a liver activation system, producing 25 revertants/mmol. A type of Japanese mixed vegetable pickle was found to be mutagenic to S. typhimurium strains TA100 and TA98 with S9 mix (Takahashi et al., 1979). Its activity was one-sixth that of a similar Chinese pickle from Linhsien County, China. Mutagens in the Japanese pickle were isolated, purified, and identified; the main component was kaempferol and a minor component was isorhamnetin. As flavonoids are ubiquitous in vegetables, kaempferol and isorhamnetin do not seem to be specific to the pickle. Whole pickles of each kind of vegetable used in the Japanese pickle were extracted with methanol and subjected to mutagenicity tests; extracts of all vegetables except carrots were slightly mutagenic, with green leaves.
of vegetables and yellow chrysanthemum flowers showing the highest specific activity.

1.4 Enhancement of Phytochemicals in Fruits and Vegetables

In addition to increasing the consumption of fruits and vegetables, the enhancement of the nutritional and health quality of fruits and vegetables is an important goal in the effort to improve global health and nutrition. Erbersdobler (2003) and Boeing et al. (2004) advocated the intake of functional foods that are enriched with phytochemicals.

A number of crop production techniques have been reported to enhance phytochemical content in several fruits and vegetables (Schreiner, 2005). Various postharvest practices and techniques can also affect the content of phytochemicals (Beuscher et al., 1999; Goldmann et al., 1999; Huyskens-Keil and Schreiner, 2004).

Genetic engineering can make a substantial contribution to improved nutrition in crops. The most famous example of using biotechnology to improve nutrition is the development of vitamin A enriched “golden” rice (Ye et al., 2000). Biotechnology has also been applied to improvements in the nutritional quality of a range of fruit and vegetables (Dalal et al., 2006), targeting protein quality and quantity, desirable fatty acids, vitamins, minerals, and antioxidants. Many vegetables and fruits contain significant amounts of protein, but are deficient in particular amino acids, such as potato which is deficient in lysine, tyrosine, methionine, and cysteine, and therefore the introduction of a transgene encoding a seed albumin protein into potato resulted in tubers with sufficient quantities of all essential amino acids (Chakraborty et al., 2000). Cassava has also been improved by introducing an artificial protein encoding a maximal content of all essential amino acids (Sautter et al., 2006). Conventional breeding has resulted in similar successes, such as maize with higher-quality protein that is enriched for lysine and tryptophan (Hoisington, 2002). Polyunsaturated fatty acids have been implicated as being beneficial to human health. Enhancement of the γ-linoleic acid content of tomato was achieved through introduction of a gene encoding a Δ⁶ desaturase enzyme (Cook et al., 2002).

Plants, including fruits and vegetables, naturally contain a large array of antioxidants, including carotenoids, vitamins C and E, and flavonoids, and efforts to increase the antioxidant content of fruits and vegetables have taken both breeding-based and transgenic approaches. Natural high-pigment mutants are available in tomato that can be used in breeding strategies (Long et al., 2006) and wild accessions of tomato exhibit substantial metabolic diversity that may similarly be exploited (Fernie et al., 2006). A series of introgression lines has been generated in cultivated tomato containing genomic segments of a wild tomato relative, and the population exhibited a broad range of phenotypes, including characteristics that have potentially important attributes related to health and nutrition. Analysis of these lines identified more than 800 quantitative trait loci (QTL) underlying levels of various metabolites including ascorbate and γ-tocopherol (Schauer et al., 2006). Using structural flavonoid genes (encoding stilbene synthase, chalcone synthase, chalcone reductase, chalcone isomerase, and flavone synthase) from different plant sources, Schijlen et al. (2006) were able to produce transgenic tomatoes accumulating new phytochemicals. Biochemical analysis showed that the fruit peel contained high levels of stilbenes (resveratrol and piceid), deoxychalcones (butein and isoliquiritigenin), flavones (luteolin-7-glucoside and luteolin aglycon) and flavonols (quercetin glycosides and kaempferol glycosides). They have demonstrated that, due to the presence of the novel flavonoids, the transgenic tomato fruits displayed altered antioxidant profiles. In addition, total antioxidant capacity of tomato fruit peel with high levels of flavones and flavonols increased more than threefold. These results on genetic engineering of flavonoids in tomato fruit demonstrate the possibilities for changing the levels and composition of health-related polyphenols in a crop plant (Fraser et al., 2007). Introduction of transgenes has been shown to increase antioxidant content (Bovy et al., 2002; Fraser et al., 2002). QTL for lycopene content and β-carotene content have been identified in carrot (Santos and Simon, 2002) and varietal differences in antioxidant content of onion suggest the presence of genetic diversity that could be exploited by selective breeding (Yang et al., 2004).

Diaz de la Garza et al. (2004) used genetic engineering to generate a 10-fold increase in the folic acid content of ripe tomatoes. Substantial improvements can be made using marker-assisted and traditional breeding. The use of a non-transgenic approach such as targeted induced local lesions in genomes (TILLING) can allow for relatively easy identification of novel alleles in either mutagenized or natural populations. This technology was initially used in reverse genetic studies by plant biologists and it is now being applied to crop improvement (Slade and Knauf, 2005). Naturally occurring germplasm can provide a rich source of genetic variation, and it is likely that new strategies for improving the nutritional value of fruits and vegetables will result from screening for variation in nutritional and health composition in wild crops and the broadest possible spectrum of existing cultivars.

1.5 Conclusions

Accumulating evidence demonstrates that fruit and vegetable consumption has health-promoting properties.
Fruits and vegetables are rich sources of diverse phytochemicals. The majority of evidence linking fruit and vegetable intake to health continues to be observational, and data in some areas are still contradictory. Therefore, although it is evident that fruit and vegetable consumption is important for health, there is still a need for further controlled clinical intervention trials in order to investigate and to confirm the effect of the consumption of fruits and vegetables on different diseases, as well as for studies to reveal the mechanisms behind the effects of the different phytochemical components of fruits and vegetables.

References

Aptekmann NP, Cesar TB. 2013. Long-term orange juice consumption is associated with low LDL-cholesterol and apolipoprotein B in normal and moderately hypercholesterolemic subjects. Lipids Health Dis 12:119.


Gammon CS, Kruger R, Conlon CA, von Hurst PR, Jones B, Stonehouse W. 2013. Inflammatory status modulates...


Minguez-Mosquera MI, Hornero-Mendez D. 1994. Comparative study of the effect of paprika processing on the carotenoids in peppers (*Capsicum annuum*) of the


Ornelas-Paz JJ, Yahia EM, Gardea-Bejar A. 2008a. Relationship between fruit external and internal color...


