CHAPTER 2

Contribution of Fruits and Vegetables to Human Nutrition and Health

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2.1 INTRODUCTION

Clinical and epidemiological studies have demonstrated an inverse association between fruit and vegetable consumption and chronic diseases, including different types of cancer, and cardiovascular and neurodegenerative diseases. There is mounting evidence that people who consume sufficient quantities of fruit and vegetables are at lower risk of these diseases. It is estimated that about one-third of cancer cases and up to half of cardiovascular disease (CVD) rates are diet related. Therefore, interest in the health benefits of fruit and vegetable consumption is increasing. In addition, the interest in understanding the type, number, and action mechanism of the different components of fruits and vegetables that confer nutritional and health benefits is also increasing.

Fruits and vegetables are rich sources of some micronutrients (vitamins, minerals), fibers, and a wide array of phytochemicals that individually, or in combination, benefit human health. There are many biologically plausible reasons for this potentially protective association, including the fact that many of the phytochemicals act as antioxidants, anticarcinogens, and immunomodulators.

Phytochemicals, which possess anticarcinogenic properties, are referred to as chemopreventive agents, molecules able to reverse, suppress, or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells of cancer (Fig. 2.1). Based on their mechanisms of action the phytochemicals

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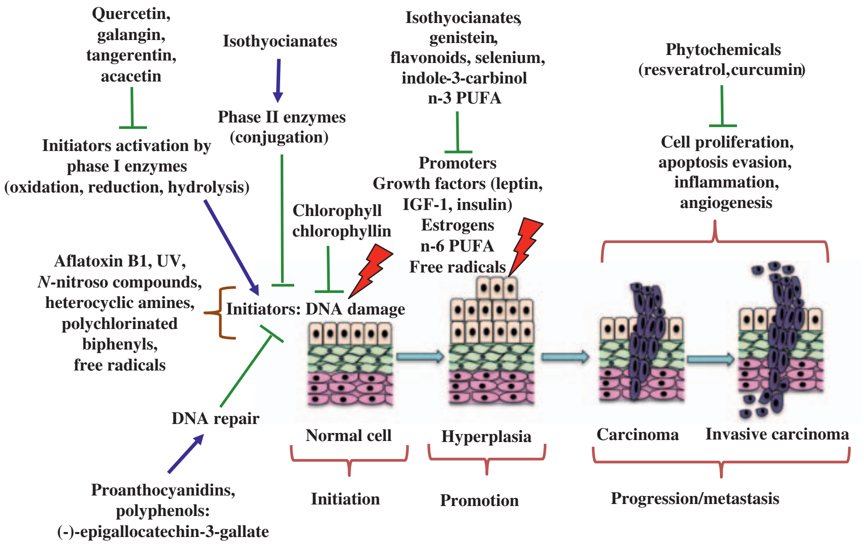

FIGURE 2.1

Schematic representation of inhibition of carcinogenesis by phytochemicals. Carcinogenesis is a multistep process, including: (1) initiation: the first step which consists of a single exposure to carcinogen and appears to involve DNA damage (mutation); (2) promotion: which involves multiple exposure to agents (promoters) that do not damage DNA directly and induce cell proliferation such as growth factors; (3) progression/metastasis: which involves the conversion of benign lesions to malignant and the ability to invade cancer cells. Each step in carcinogenesis can be inhibited by phytochemicals through different mechanisms.

present in a diet rich in fruits and vegetables have been classified in terms of their ability to block the initiation stage of carcinogenesis (cancer-blocking agents) or to suppress (cancer-suppressing agents) the proliferative capacity of preneoplastic lesions in the stages of tumor promotion and progression (Fig. 2.1). 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 (Table 2.1), which account for 60% and 30%, respectively, of the dietary (poly)phenolic compounds, and pigments such as carotenoids, chlorophylls, and betalains. The suppressing agents are able to suppress or eliminate tumor cells by interfering with cell cycle regulation, signal transduction pathways, transcriptional regulation, and inhibition of cyclooxygenase activity, suppression of oncogenes and tumor formation, and induction of apoptosis of cancer cells (Fig. 2.1).

Health authorities worldwide, such as the World Health Organization (WHO), promote high consumption of fruits and vegetables, recommending a daily intake of more than 400 g per person. Many of the putative chemoprotective phytochemicals in fruits and vegetables are colored (due to different pigments). The guidelines are based on selecting 1 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.

Table 2.1 Sources and Potential Effects on Human Health of Some Phytochemicals and Dietary Constituents

Phytochemical	Sources	Potential Effects on Human Health
1. Ascorbic acid (vitamin C)		
Ascorbic acid	Broccoli, cabbage, cantaloupe, citrus fruits, guava, kiwifruit, leafy greens, peppers, pineapples, potato, strawberry, tomato, watermelon	Cardiovascular disease, healthy immune system, scurvy prevention, wound healing
2. Carotenoids		
α-Carotene	Apricots, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, green beans, kale, kiwifruit, lettuce, lima beans, mango, papaya, peaches, peas, prunes, spinach, squash, sweet potato	Atherosclerosis, coronary artery disease, ischemic, stroke, tumor growth
β-Carotene	Dark green vegetables (such as collards, broccoli, spinach, turnip greens, Swiss chard), orange vegetables (such as carrots, pumpkins, sweet potato), orange-flesh fruits (such as apricot, cantaloupe, mango, nectarine, orange, papaya, peach, persimmon, pineapple), red pepper, tomato	Cancer, cataracts, coronary artery disease, chronic fatigue, ischemic stroke, heart disease, night blindness prevention, provitamin A activity, psoriasis
Lycopene	Autumn olive, Brazilian guava, papaya, tomato, watermelon, red grapefruit	Atherosclerosis, breast and prostate cancer, heart disease, male infertility
Xanthophylls (β-cryptoxanthin, lutein, zeaxanthin)	Cantaloupe, corn, okra, spinach, summer squash, turnip greens, sweet corn	Atherosclerosis, cancer, macular degeneration
3. Dietary fiber		
Fiber	Most fruits and vegetables, pulses (legumes), and nuts	Diabetes, heart disease, colorectal cancer
4. Folate		
Folicin or folic acid	Dark green vegetables (such as spinach, mustard greens, butterhead lettuce, romaine lettuce, broccoli, Brussels sprouts, okra), legumes (such as lentils, chickpeas, green peas), asparagus	Birth defects, cancer, heart disease

(*Continued*)

Table 2.1 (Continued)

Phytochemical	Sources	Potential Effects on Human Health
5. Oganosulfur compounds		
Allicin, diallyl sulfide, glucosinolates, indoles, isothiocyanates	Broccoli, Brussels sprouts, chives, garlic, horseradish, leeks, mustard green, onions	Blood pressure, cancer, hypercholesterolemia, diabetes
6. Phenolics		
6.1 Flavonoids		
Anthocyanidins (cyanidin, malvidin, delphinidin, pelargonidin, peonidin, petunidin)	Red, blue, and purple fruits (apple, blueberry, blackberry, cranberry, grape, nectarine, peach, plum, prune, pomegranate, raspberry, strawberry)	Heart disease, cancer initiation, diabetes, cataracts, blood pressure, allergies
Flavan-3-ols (epicatechin, epigallocatechin, catechin, gallocatechin)	Apples, apricots, blackberries, plums, raspberries, strawberries, cherries	Platelet aggregation, cancer
Flavanones (hesperetin, naringenin, eriodictyol)	Citrus such as oranges, grapefruits, lemons, limes, tangerines	Cancer
Flavones (luteolin, apigenin, chrysin)	Artichoke, celeriac, celery, guava, parsley, peppers, rutabaga, spinach	Allergies, cancer, heart disease
Flavonols (kaempferol, myricetin, quercetin, rutin)	Broccoli, cranberry, kale, lettuce, onions, peppers, snap bean, apples, cherry, berries	Cancer initiation, capillary protectant, heart disease
Isoflavonoids (genistein, daizein, glycetein, formonetin)	Soy beans	Breast cancer, cardiovascular diseases, osteoporosis
6.2 Phenolic acids		
Hydroxybenzoic acids (gallic acid, protocatechuic acid, syringe acid, vanillic acid)	Black olive, black raspberry, carrot, dates (dried, fresh), green chicory, kiwi, mushrooms, red chicory, strawberry	Endothelial dysfunction, hypertension
Hydroxycinnamic acids (caffeic acid, ferulic acid, sinapic acid, chlorogenic, acid, coumaric acid)	Apple, blueberry, broccoli, cabbage, carrot, cherry, cranberry, eggplant, grapes, lemon, pear, orange, grapefruit, peach, potato, spinach	Atherosclerosis, antimicrobial effect, antiinflammatory, cancer, osteogenic
6.3 Tannins		
Proanthocyanidins	Apple, cranberry, grape, pomegranate	Cancer

(*Continued*)

Table 2.1 (Continued)

Phytochemical	Sources	Potential Effects on Human Health
7. Monoterpenes		
Limonene	Citrus such as grapefruit and tangerine	Cancer
8. Isoprenoids (lipophilic vitamins)		
Vitamin E (tocopherols)	Avocado, nuts (such as almonds, cashew nuts, filberts, macadamia nut, peanuts, pistachio, walnuts), lentils, chickpeas, green leafy vegetables	Cancer, diabetes, heart disease, immune system, LDL oxidation
Vitamin K	Crucifers (such as broccoli, Brussels sprouts, cabbage), green onions, lentils, nuts, leafy greens	Osteoporosis, synthesis of procoagulant factors

2.2 HEALTH-PROMOTING COMPONENTS IN FRUITS AND VEGETABLES

Fruits and vegetables contain thousands of phytochemicals belonging to different classes, such as fibers, pigments (such as chlorophylls, carotenoids, flavonoids, betalains), phenolic compounds, and micronutrients (vitamins and minerals). This section briefly describes the most important phytochemicals, minerals, and vitamins for human health, present in fruits and vegetables.

2.2.1 Dietary Fiber

Dietary fiber is the edible part of plants composed of polysaccharides, oligosaccharides, lignin, and associated plant substances, which are resistant to the activity of human small intestinal enzymes, but are finally fermented by colonic microflora. The plant fiber can be structurally associated to the cell wall such as pectins, celluloses, and hemicellulose. Pectins are abundant in fruits, accounting for up to 40% of the total cell wall polysaccharides. The pectins are a group of polymers rich in galacturonic acid. Cellulose is a cell wall polymer of β-1,4-linked glucose units. Hemicellulose is a crosslinking glycan; the most common hemicellulose polymer is xyloglucan (cellulose of a backbone of β-1,4-linked glucose, but with lateral chains of the pentose xylose: α-1,6 linked). These xylosyl residues can be modified with galactose, arabinose, and/or fucose. There are other types of structural nonpolysaccharide fibers like lignin or nonstructural polysaccharides such as gums and mucilage. Lignin is one of the most abundant biopolymers in nature, present in secondary cell walls, and associated with the xylem vessels, however, in fruits and vegetables, its content is relatively low. This is an aromatic heteropolymer formed by the association of three hydroxycinnamyl alcohol derivatives (*p*-coumaryl, coniferyl, and sinapyl alcohols). The health benefits linked to the formation of a gel matrix that reduces the concentration and absorption of harmful biliary acids and other potential carcinogenic compounds present in feces are based on the increases in fecal mass. This is because there is a soluble fiber form that stimulates intestinal motility, weight and volume of the bolus, and intestinal transit time, contrary to the insoluble fibers like cellulose, hemicellulose, and lignin. Currently the recommendations for adult dietary fiber intake generally fall in the range of 20−35 g/day.

2.2.2 Vitamins

These are considered micronutrients because they are organic molecules required in low or trace amounts for a normal human metabolism and consequently healthy development. These molecules are not synthesized in adequate quantities by humans and must be acquired from the diet, especially from fruits and vegetables, although there are important variations in content among species and cultivars. Vitamins can be classified according to their solubility in water (complex B and vitamin C or ascorbic acid), and in fat (vitamins A or retinol, D, E, and K). The complex B is composed of B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B9 (folate/folic acid), biotin, choline, and B12 (cyanocobalamin). Vitamins B12 and D do not occur in fruits and vegetables.

The B1 vitamin (thiamine) is required as a coenzyme precursor (thiamine phosphate) for the metabolism of carbohydrates. Legumes are an important source of thiamine, and are heat labile, because they can lose between 25% and 40% during cooking. Riboflavin or B2 is a precursor of the coenzymes flavin adenine dinucleotide and flavin adenine mononucleotide, important in bioenergetic processes of mitochondria, and green vegetables are especially rich in it. The B3 vitamin (niacin), also known as nicotinic acid, is the precursor of NADH, NAD, NAD^+, and NADP, and these coenzymes are essential bioenergetics and redox reactions of metabolism. These vitamins can be synthesized by human tryptophan amino acid. Almonds are an important source of B3, but rare in most fruits or vegetables, except Cape gooseberry and avocado. The pantothenic acid (B5) occurs widely in peas, beans, nuts, broccoli, mushrooms, potatoes, and sweet potatoes, and is the precursor to coenzyme-A, which is important for the metabolism of carbohydrates and lipids (triacylglycerides and cholesterol). Vitamin B6 is a precursor of the coenzyme pyridoxal phosphate required in transamination, decarboxylation, and deamination reactions. This vitamin can be found in appreciable amounts in grapes, spinach, beans, bananas, cabbage, cauliflower, sweet potatoes, prunes, and avocados. Biotin acts in metabolic reactions of deamination of amino acids and decarboxylation−carboxylation. It is relatively stable during cooking, processing and storage of fresh, canned and frozen fruits and vegetables. Vitamin B9, or folic acid, is very important for normal reproduction and growth because it is the precursor of constituents for DNA and RNA synthesis, and metabolism of some amino acids like serine, tyrosine, glutamic acid, histidine, and choline. Folic acid is present in green fruits and vegetables.

Vitamin C, or ascorbic acid, has antioxidant and acidic properties due to the presence of a 2,3-enediol moiety. This vitamin is synthesized only by plants using L-galactose or galacturonic acid as precursors. Fruits and vegetables contribute about 90% of the vitamin C requirement depending on the region and the amounts of fruits and vegetables consumed. Fruits, such as tropical species, and leafy vegetables, are rich in vitamin C, including rosehip, jujube and guava, persimmon, strawberry, kiwifruit, peppers, and citrus fruit, among others, and vegetables such as spinach, broccoli and cabbage, etc. This vitamin is heat labile and important losses can occur with heating.

Vitamin E corresponds to tocopherols and tocotrienols that have aromatic rings with a hydroxyl group that can donate hydrogen atoms to reduce reactive oxygen species (ROS), which are considered as antioxidants. The best-known isomers of tocopherols are α, β, γ, and Δ, based on the number and position of methyl groups in the ring, with α-tocopherol being the most active form. The most important sources of this vitamin are oily seeds, nuts, avocados, and olives, but it is also present in low quantities in broccoli and leafy vegetables. Vitamin K is important for blood coagulation and bone health because it promotes the carboxylation of osteocalcin and several proteins involved in coagulation (factors II, VII, IX, and X), and enhances the calcium fixation activity of these proteins. This vitamin is abundant in lettuce, spinach, cauliflower, and cabbage, but can also be produced by intestinal microflora.

2.2.3 Minerals

Minerals are important for the human diet as micronutrients because they are essential in many biological activities for normal cellular functions. They have a role in the synthesis and structural stabilization of proteins and nucleic acids. Vegetables and fruits are sources of manganese (Mn), copper (Cu), iron (Fe), zinc (Zn), sodium (Na), sulfur (S), and selenium (Se). Manganese is a cofactor of superoxide dismutase. At a physiological level it maintains brain function and reproduction, required for glycemia control, and as part of bone structure. Manganese is a cofactor in the function of antioxidant enzymes, such as those in the mitochondria. Spinach is a good source of this mineral. Copper is a metal involved in redox reactions of the oxidative defense system and other enzymes like ceruloplasmin, cytochrome c oxidase, tyrosinase, and dopamine-β-hydroxylase. In addition, it is necessary for the formation of hemoglobin. Grains, legumes, nuts, and soybean are important sources of copper. Iron and copper participate in redox reactions, and structure of heme-containing proteins, electron transport chain, and microsomal electron transport protein. The importance of these minerals in human health is based on the effect of deficiency, reduction of cognitive functions, delayed growth, alterations in bone mineralization, and diminished immune response.

Nuts, vegetables (such as parsley, broccoli, kale, turnip greens, and collards), and legumes are good sources of these minerals. Phytochemicals such as phytic acid, oxalic acid, and tannins reduce their absorption, but vitamin C increases it. The mineral zinc has catalytic functions as enzymatic cofactor, antioxidant functions, modulating immune response, intestinal digestion, reproduction, and wound healing. Fruits are poor sources of zinc; good sources include parsley, pecans, and walnuts. Sodium is important for the regulation of blood pressure (BP) and electrolyte balance. Fruits are poor sources of sodium, but some vegetables such as artichoke, broccoli, carrot, celery, radish, and sweet potato are good sources. Sulfur is a micronutrient important in the synthesis of cysteine and methionine amino acids, where the thiol groups are mediators of redox reactions. The vegetables that contain important quantities of sulfur compounds, like thiocyanates and isothiocyanates, are from the order Brassicales. Selenium is an important mineral present in the metabolites hydrogen selenide, methylselenol, and selenomethionine, that are able to regulate gene expression, protect DNA from damage, and enhance the repair and regulation of the cell cycle and apoptosis.

2.2.4 Carotenoids

This is a group of fat-soluble molecules (terpenoids) responsible for the yellow, orange, and red colors of some fruits and vegetables (such as apricot, mango, citrus, papaya, watermelon, tomatoes, peppers, carrots). They are formed by eight isoprene units and derived from isopentenyl diphosphate. These plant pigments are important for the process of photosynthesis. Carotenoids are either oxygenated like xantophylls (zeaxanthin and lutein) or carotenoid hydrocarbons like lycopene and β-carotene, which differ in thermal stability. Those that have an unsubstituted β-ring with 11-carbon polyene chain have provitamin A activity, like α-carotene, β-carotene, and cryptoxanthin. Carotenoids have conjugated double bonds within their structure, which confer an antioxidant property due to singlet oxygen quenching, which is able to destroy peroxyl radicals. These molecules have received great attention because of their antitumor properties, especially in breast and prostate cancers, involving antioxidant, antiproliferative, and modulation of immune functions.

2.2.5 Phytoesterols

These are molecules structurally similar to cholesterol that reduce the intestinal cholesterol absorption and low-density lipoprotein (LDL)-cholesterol levels in serum due to their low bioavailability and capacity to inhibit the absorption of cholesterol. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III recommended the consumption of 2 g of phytosterols daily for reducing LDL-cholesterol and CVD risk. Phytosterols are found, like glycosides, in ester or free forms, in vegetable oils, nuts, seeds, legumes, wheat germ, bran, fruits, and vegetables.

2.2.6 Phenolic Compounds

Phenolic compounds are the most numerous group of phytochemicals in plants. They include phenolic acids, flavonoids (flavonols, flavones, flavanols, flavanones, and anthocyanins), stilbenes, and lignans, of which flavonoids and phenolic acids account for 60% and 30%, respectively, of the dietary polyphenols. These molecules exert an antioxidant activity and effects on tumor development and carcinogenesis at the cellular level in processes of detoxification, signaling cascades (MAPKinases, p53, NF-κB, PI3K) involved in cell growth and death. Flavonoids are compounds that share the same common skeleton of diphenylpropanes (C6–C3–C6) and contain phenolic hydroxyl groups attached to ring structures that confer antioxidant activity as reducing agents, hydrogen donators, singlet oxygen quenchers, superoxide radical scavengers, and metal chelators. Phenolic acids are composed of hydroxycinnamic and hydroxybenzoic acids. They also present antioxidant activity as chelators and free radical scavengers. The most studied compound is gallic acid, the precursor of many tannins, while cinnamic acid is the precursor of all the hydroxycinnamic acids. Most of the polyphenolic compounds are present as esters, polymers, or glycosides that can be absorbed in these forms or be hydrolyzed by intestinal enzymes or colonic bacteria.

2.3 CONTRIBUTION OF FRUIT AND VEGETABLE CONSUMPTION TO THE PREVENTION OF VARIOUS DISEASES

2.3.1 Cancer

It is estimated, based on epidemiological studies, that improving nutrition and physical activity-related factors can prevent many cancers, around 27% (in low-income countries), 30% (in middle-income countries), to 34%–39% (in high-income countries). The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR), through comprehensive analysis mainly based in systematic literature reviews and meta-analysis of observational epidemiologic studies, case–control studies, and cohort studies, published a second expert panel report in 2007, about food, nutrition, physical activity, and cancer prevention. This expert panel report of WCRF/AICR shows that the evidence about fruit and vegetable consumption probably protects against some cancers (Table 2.2). Nonstarchy vegetables probably decrease risk of cancers of the mouth, pharynx, and larynx, and those of the esophagus and stomach. There is limited evidence suggesting that they also decrease the risk from cancers of the nasopharynx, lung, colorectal, ovary, and endometrium. Allium vegetables probably decrease the risk of stomach cancer. Garlic, an allium vegetable, probably decreases the risk of colorectal cancer. Fruits probably decrease the risk of cancers of the mouth, pharynx, and larynx, and of the esophagus, lung, and stomach. There is limited evidence suggesting that fruits also protect against nasopharynx, pancreas, liver, and colorectal

Table 2.2 Fruit and Vegetable Foods and Phytochemicals That Can Provide Decreased Risk (↓↓) or Convinced Increased Risk (↑↑↑↑) of Several Types of Cancer, According to WCRF/AICR Second Expert Panel Report, 2007

	Type of Cancer						
Foods or Phytochemicals	**Mouth, Pharynx, Larynx**	**Esophagus**	**Lung**	**Stomach**	**Pancreas**	**Colorectal**	**Prostate**
Foods containing dietary fiber						↓↓	
Nonstarchy vegetables	↓↓	↓↓		↓↓			
Allium vegetables				↓↓			
Garlic						↓↓	
Fruits	↓↓	↓↓	↓↓	↓↓			
Foods containing folate					↓↓		
Foods containing carotenoids	↓↓		↓↓				
Foods containing β-carotene		↓↓					
Foods containing lycopene							↓↓
Foods containing vitamin C		↓↓					
Foods containing selenium							↓↓
Selenium supplements							
β-carotene supplements[a]			↑↑↑↑				

[a] *In current smokers.*
Source: Modified from World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR), 2007.

cancers. The chemopreventive properties of vegetables, fruits, and pulses against some types of cancers are attributed to some micronutrients considered as 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 β-carotene and lycopene suggests that they probably protect against esophageal and prostate cancer, respectively. Convincing evidence indicates that β-carotene supplement intake increases the risk of lung cancer among smoking-exposed populations. This paradoxical effect could be explained by at least two reasons generated by experimental data in ferrets: (1) a high dose of β-carotene increases phase I enzyme, which results in reduced retinoic acid and parallel reduced retinoic signaling, and increased cell proliferation; and

(2) eccentric cleavage of β-carotene metabolites facilitating the binding of smoke-derived carcinogens to DNA. It seems that deleterious effects of β-carotene are dose-dependent and supplementation could promote a very high intake of this phytochemical. Therefore, WCRF/AICR recommend, as public health goals, an average consumption of at least 600 g of nonstarchy vegetables and fruits daily, and an average of at least 25 g of nonstarch polysaccharide from relatively unprocessed cereals (grains) and/or pulses (legumes), and other foods that are a natural source of dietary fiber. On the other hand, despite 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, protect against lung cancer.

2.3.1.1 CHEMOPREVENTION OF CARCINOGENESIS BY PHYTOCHEMICALS

Carcinogenesis is a very complex process, defined by the course in which a normal cell becomes malignant. It can be summarized in three steps: (1) initiation, (2) promotion, and (3) progression/metastasis (Fig. 2.1). In the first step, initiation occurs when either chemical (as polycyclic hydrocarbon) or physical (as ultraviolet (UV) radiation) stimuli damage cell DNA which can produce mutations in genes involved in proliferation (oncogenes) or in DNA repair, cell death, and inhibition of proliferation (tumor suppressor genes). After initiation, the promotion step consists of the proliferation of cells with mutations. Finally, the progression/metastasis step consists of the acquisition of several characteristics that permit the tumor to survive and invade adjacent tissue (progression) and even far away tissues through blood and lymph (metastasis). As is shown in Fig. 2.1, phytochemicals could act in each step of carcinogenesis.

In the first step of carcinogenesis, initiation, the activation of chemical carcinogens (initiators) (aflatoxin B1, benzo(a)pyrene, 2-naphthylamine) by cytochrome P450 phase I enzymes is a key point of this process. Carcinogens bind DNA and form adducts which distort DNA structure and disrupt its replication, and this could cause mistranslation. Carcinogens can also break DNA, and thus they can generate mutation and deletion of genetic material. Flavonols such as quercetin, galangin, and targerentin (flavone) inhibit phase I enzymes such as CYP1A2 and thus inhibit initiator activation.

On the other hand, it is well documented that organosulfur compounds, such as isothiocyanates, found in Brassica vegetables, increase liver phase II detoxification enzymes, catalyze the conjugation of chemical carcinogens, and promote their elimination through urine or bile. Main phase II enzymes are NAD(P)H:quinone oxireductase, UDP-glucoronosyl transferases, glutathione *S*-transferases, and sulfotransferases. Phase II enzyme expression genes are regulated by erythroid-2-related factor 2 (Nrf2), which binds antioxidant response element present in the promoter sequence of phase II genes.

Another mechanism of phytochemicals against the initiation process is the activation of DNA repair. UV-induced DNA damage consists of the formation of pyrimidine dimers, which is contrasted by epigallocatechin-3-gallate (EGCG) through nucleotide excision repair and interleukin 12-mediated mechanisms. Finally, some phytochemicals, such as chlorophyll and its food-grade derivative chlorophyllin, interact directly with carcinogens such as aflatoxin B and benzo(a)pryrene and form a complex. This complex reduces carcinogen bioavailability. Chlorophyll and chlorophyllin can also inhibit the initiation process through inhibition of phase I enzymes and induction of phase II enzymes.

Different events occur in the promotion and progression/metastasis steps of carcinogenesis that could be regulated by phytochemicals. The hallmark characteristic in the promotion step is cell proliferation which is stimulated by hormones, growth factors, free radicals, and other environmental agents called promoters. In this step, phytochemicals can act as modulators of hormones such as genistein and isothiocyanates that modulate estrogen receptors α and β, a key factor in the promotion of premenopausal breast cancer. In some cases phytochemicals act on cell-signaling pathways, such as curcumin blocking phosphorylation of tyrosine kinases, and serine/threonine kinases, key proteins in promoting cell growth.

In the progression/carcinogenesis step, cancer cells have different strategies to grow, invade, and survive. Cancer cells promote their own uncontrolled proliferation, inflammation, and angiogenesis, evade cell death, invade other tissues, and become multidrug resistant, and phytochemicals can act in all these different processes. As an example, resveratrol, the most important stilbene, mainly present in red wine and grapes, and curcumin, the major yellow pigment present in turmeric, both with demonstrated chemopreventive properties, are able to inhibit the proliferation of a wide range of human cancer cells (ovarian, breast, prostate, liver, uterine, leukemia, lung, gastric, colorectal), and to suppresses carcinogenesis in several organ sites (head and neck, liver, thyroid, stomach, colorectal, pancreas, prostate, renal, bone, skin, breast, lung), by controlling cell cycle progression, apoptosis, inflammation, angiogenesis, invasion, and metastasis.

2.3.2 Cardiovascular Disease

CVD is the number one cause of death in developed and developing countries, and prevention is at the top of the public health agenda. In 2008, 17 million deaths worldwide were due to CVD, which represents 48% of noncommunicable disease deaths. Numerous epidemiological studies around the world have demonstrated evidence that diets rich in fruits and vegetables prevented CVD and reduced mortality from CVD. The positive effect has been accomplished by 3 servings of vegetables and fruits, and the relative risk (RR) can be minimized to a great extent by enhancing the vegetable and fruit consumption by up to 10 servings/day. The inverse relationship between vegetable intake and CVD was more evident with smokers consuming at least 2.5 servings of fruits and vegetables per day in comparison with less than 1 serving/day. A high fruit and vegetable intake has shown a significant inverse association with CVD risk factors such as systolic BP, total cholesterol and LDL-cholesterol, and explained 48% of the protective effect. Legume consumption was also significantly and inversely associated with CVD, lowering the risk by about 11%. In the Mediterranean Diet Prevention (PREDIMED) study, a randomized, controlled trial including 7447 obese men and women with a mean age of 67 years at high risk for CVD, 50% of the participants had type II diabetes mellitus (T2DM), 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 the incidence of CVD (myocardial infarction, stroke, or cardiovascular death) by 30% in the olive oil group (hazard ratio adjusted [HR_{adj}] = 0.70, 95% confidence interval [CI] 0.54−0.92) and 28% in the nut group (HR_{adj} = 0.72; 95% CI 0.54−0.96) compared to the control group that was instructed to eat a low-fat diet (Estruch et al., 2013). Moreover, in the prospective part of the PREDIMED study, the baseline intake of fruit was inversely associated with all causes of 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 other causes of death (Buil-Cosiales et al., 2014).

On the other hand, it is well documented that high consumption of fruits and vegetables is inversely associated with the risk of coronary heart disease (CHD). A meta-analysis that included 23 cohort studies involving 937,665 participants and 18,047 patients with CHD, concluded that a fruit and vegetable intake of more than 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 RR 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 vegetable, respectively (Gan et al., 2015).

It has been reported that death attributed to CVD and CHD showed strong and consistent reductions with increasing nut/peanut consumption. Moreover, ischemic heart disease (IHD) is inversely associated with 28 g of nut consumption 4-weekly (reduction of 24%) and nonfatal IHD (reduction of 22%). Likewise, a 27% reduced risk of all-cause mortality for 1 serving of nuts per day and a 39% risk for CVD mortality per daily serving of nuts (Grosso et al., 2015). However, as the authors pointed out, confounding factors such as body mass index, smoking status, increased intake of fruits and vegetables, as well as intake of alcohol, have to be taken into account when considering the findings.

Nuts and peanuts have beneficial effects on lipids, lipoproteins, and various CHD risk factors, including oxidation, inflammation, endothelial function, and arterial stiffness. Daily nut consumption decreased by 5% and 7%, total cholesterol and LDL-cholesterol, respectively, and improved LDL-cholesterol to high-density lipoprotein (HDL)-cholesterol ratio. Moreover, pistachio consumption reduced LDL-cholesterol in patients with prediabetes.

The LDL-cholesterol-lowering response of nut and peanut consumption studies is not only from changes in the fatty acid profile of the diet. Thus, nuts and peanuts contain other bioactive compounds that explain their multiple cardiovascular benefits such as plant protein, arginine, fiber, potassium, calcium, magnesium, tocopherols, phytosterols, phenolic compounds, and resveratrol. Nuts and peanuts are food sources of cardioprotective components and if routinely incorporated in a healthy diet, the population risk of CHD would therefore be expected to decrease markedly. Some biological mechanisms have been proposed to explain these protective effects by using in vivo models such as inhibition of lipid oxidation, increase of antioxidant capacity of serum or plasma, protection against oxidation of cholesterol and other lipids in cell membrane, reduction in oxidative stress, antiinflammatory effect, prevention of platelet aggregation, reduction of vascular tone, synthesis induction of glutathione, endothelial NO synthase, and inducible NO synthase.

The consumption of avocado, a food rich in mono-unsaturated fatty acids, reduces both total cholesterol and LDL-cholesterol while preserving the level of HDL.

Lycopene from tomato fruit was found to prevent the oxidation of LDL-cholesterol and to reduce the risk of developing atherosclerosis and CHD disease, and 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. Lycopene has also been reported to increase gap-junctional communication between cells and to induce the synthesis of connexin-43.

Anthocyanin, proanthocyanidin, flavanone, flavone, and flavanol consumption is inversely associated with the risk of CVD. An average increase of 10−20 mg/day of flavonol intake was associated with 5%−14% decrease in the risk for developing CVD. The biological mechanisms by which flavonoids may exert this effect are antioxidant, antiinflammatory, and vasodilatory properties.

2.3.2.1 HYPERTENSION

High blood pressure is a continuous, consistent, and independent risk factor for CVD that is modifiable through lifestyle. Indeed, a moderate average BP reduction of 3.5 and 2.0 mmHg for systolic and diastolic BP, respectively, was associated with a 24% reduction in stroke. It is consistently shown that diet plays a major role in BP control. Several studies clearly showed that consumption of vegetables, fruit, and low-fat dairy products lowered BP. Nut consumption reduces systolic BP among participants without T2DM (−1.3 mmHg, 95% CI −2.3 to −0.22 mmHg), whereas pistachios had the strongest effect on systolic (−1.8 mmHg, 95% CI −3.0 to −0.7 mmHg) and diastolic BP (−0.8 mmHg, 95% CI −1.4 to −0.2 mmHg). Even more, it was shown that a vegetarian diet is associated with a reduction in mean systolic BP (−4.8 mmHg, 95% CI −6.6 to −3.1 mmHg) and diastolic BP (−2.2, 95% CI −3.5 to −1.1 mmHg) (Mohammadifard et al., 2015).

The BP-lowering effects of fruits and vegetables may involve several mechanisms. Oxidative stress could a play a role in the pathogenesis of hypertension and antioxidants may increase the bioavailability of NO by decreasing endogenous oxidant formation. Another possibility may be the increased intake of potassium. Potassium has been shown to promote vasodilation, decrease renin and renal sodium reabsorption, reduce reactive oxygen production, and reduce platelet aggregation. In addition, the inhibition of angiotensin-converting enzyme activity by fruit and vegetables is another possibility.

2.3.2.2 CHRONIC HEART FAILURE

Chronic heart failure (CHF) has a prevalence of about 80% among individuals of more than 80 years of age worldwide, and is seen as the end stage of CVD and the final pathway of diseases such as hypertension and CVD. CHF has many causes, but oxidative stress has also been proposed as a risk factor. Furthermore, the total antioxidant capacity measured in the diet is inversely associated with CHF. A diet rich in fruit and vegetables has been associated with reduced incidence of CHF by up to 22%.

2.3.3 Diabetes Mellitus

The prevalence of T2DM is increasing worldwide. In 2013, 382 million cases were reported, and this number is expected to rise to 592 million by 2035. Because T2DM is characterized by either resistance to the blood glucose-regulating hormone insulin or its relative deficiency, it has been proposed that antioxidants may play a role in increasing insulin sensitivity. Thus, fruit and vegetable consumption in patients with T2DM improve glucose and glycated hemoglobin levels, and increase serum antioxidant compounds (vitamin C and reduced glutathione), and reduce markers of oxidative stress and inflammation such as DNA oxidation and lipid peroxidation and IL-6 serum levels. Moreover, several studies have shown that the consumption of fruit, vegetables, nuts, and whole grain intake of antioxidants reduce the RR of T2DM by 13%−15% (Wu et al., 2015; Bazzano et al., 2008; Hamer and Chida, 2007). However, fruit and vegetable consumption and its effects on T2DM risk are inconsistent (Villegas et al., 2008). It has been proposed that this inconsistency between studies examining the association between fruit and vegetable intake and the risk of T2DM could be due to the extent of measurement error associated with the food frequency questionnaire overestimating fruit and vegetable consumption. In addition, these studies include consumption of fruit juices that contain important sugar content, especially fructose that contributes to the development of T2DM and insulin resistance (Bazzano et al., 2008).

Experimental evidence showed that consumption of prickly pear cladodes (nopal) could decrease blood glucose levels (Frati et al., 1990). The intake of broiled *Opuntia* stems for 10 days improved glucose control in a small group of adults with T2DM (Frati-Munari et al., 1990). 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 if the sugar was ingested alone (Frati et al., 1990). In patients with T2DM, the ingestion of some species of nopal (*Opuntia streptacantha*, *Opuntia ficus-indica*) in fasting conditions 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 by *Plantago psyllium* or other sources of dietary fibers (Frati, 1992). Ingestion of raw and cooked *Opuntia ficus-indica* extracts resulted in beneficial effects on total cholesterol, without any secondary effect on glucose and lipoprotein amounts in blood (Cárdenas Medellín et al., 1998).

Some flavonoids, such as procyanidins, have antidiabetic properties because they improve altered glucose and oxidative metabolism of diabetic states (Pinent et al., 2004). Extract of grape seed procyanidins administered orally to streptozotocin (STZ)-induced diabetic rats resulted in an antihyperglycemic effect, which was significantly increased if procyanidin administration was accompanied by a low insulin dose (Pinent et al., 2004). The antihyperglycemic effect of procyanidins may be partially due to the insulinomimetic activity of procyanidins on insulin-sensitive cell lines. Similar results have been reported using guava leaves that have an antihyperglycemic, antihyperlipidemic, and antioxidant activity attributed to their phenolic compounds such as flavones, gallic, and ellagic derivatives, cyanidin-glucoside, pentacyclic triterpenoids, guiajaverin, and quercetin (Díaz de Cerio et al., 2016). The leaf extract of guava has traditionally been used for the treatment of diabetes in East Asia and Africa. In Japan there is a guava leaf tea containing the aqueous leaf extract from guava which has been approved as one of the "foods for specified health uses" and which is now commercially available. This has been shown to reduce postprandial blood glucose and to improve hyperglycemia, hyperinsulinemia, hypoadiponectinemia, hypertriglyceridemia, and hypercholesterolemia using STZ-induced "type I diabetes mellitus (DMI)" murine models (50–800 mg/kg) (Ojewole, 2005; Deguchi and Miyazaki, 2010). Moreover, the leaf aqueous extract of *Psidium guava* exhibits a hypotensive property as observed in the hypertensive Dahl salt-sensitive rats which were used to investigate the antihypertensive effect of the plant's extract (50–800 mg/kg). Intravenous administration was administered producing dose-dependent, significant reductions ($P < .05 - .001$) in systemic arterial BP and heart rates (Ojewole, 2005). In spite of these findings using guava plant, little is known regarding the therapeutic activity in human clinical trials as well as its underlying mechanism of action and safety using guava leaves.

One of the possible mechanisms involved in the protective effect of flavonoids on T2DM is their antioxidant activity to protect tissues against ROS and lipid peroxidation. In addition, flavonoids are able to activate pathways that lead to antiinflammation, improvement of endothelial function, and reduction in blood cholesterol concentrations.

2.3.4 Overweight and Obesity

WHO estimates that more than 1.9 billion adults and more than 42 million of children under 5 years old are overweight worldwide, indicating its prevalence in all age groups. 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 for its wide spread across population groups, as well as its contribution to the development of chronic diseases, particularly CVDs, T2DM, some types of cancer (i.e., colorectal, breast) resulting from a sedentary lifestyle, unhealthy dietary practices, high energy intake, and low energy expenditure.

Despite the alarming increase in the prevalence of obesity in the world, epidemiologic studies on the relation between fruit and vegetable consumption and weight gain (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. In fact, a recent analysis from the National Health and Nutrition Examination Survey 2005–10 showed that nut consumers who ate a mean of 44 g of nuts per day had lower body mass index and waist circumference than nonnut consumers (P for both $<.01$) (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 increased fruit and vegetable intake, together with other dietary recommendations, might promote satiety and weight loss in overweight and obese individuals, because of low-fat but high in water content, indigestible fiber, and soluble dietary fiber, which contribute to reducing the energy intake of meals, reducing the energy 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 diminishes partly the activity of enzymes involved in the digestion of macronutrients and absorption, prolonging the contact of the nutrients with receptors in the small intestine, such as fructose, causing the release of putative satiety peptides, and causing a hyperosmolar environment in the colon leading, for example, to a decrease in insulin secretion and improved glucose control, attraction of fluids into the gut lumen, and lost interest in further food consumption (Mirmiram 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 assay.

He et al. (2004) examined the changes in intake of fruits and vegetables in relation to risk of obesity and WG 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 CVD, cancer, and T2DM 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% of 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 WG ($\geq$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.

Low fruit consumption is considered an important contributor to the global disease burden, and an important attributable risk factor because many clinical studies have evidenced that increased daily consumption of fruits is inversely correlated to WG. However, these researches pointed to the possible obesity effects of fruits in the form of juices, which are low in fiber and rich in simple sugars (sucrose, glucose, or fructose), stimulating hepatic de novo triacylglycerides biosynthesis and very-low-density lipoproteins that increase circulation in blood and augment fat mass.

The following possible antiobesity mechanisms proposed are attributable to consumption of whole fruit:

1. Reduction of energy consumption, because adding fruit daily to the diet will reduce overall energy consumption, restricting WG, reduction of fat mass, and control obesity;
2. Presence of fruit micronutrients able to downregulate genes involved in adipocyte generation and differentiation such as vitamins A, E, and C and minerals such as zinc, iron, and calcium;
3. A diet rich in fiber and polyphenols leads to a prevalence of Bacteroidetes and Actinobacteria, which are characteristics of lean individuals, whereas in obese people the presence of Firmicutes and Proteobacteria is increased, however the specific mechanisms responsible for modulatory effects of gut microbial ecology related to fruit consumption on obese individuals are unknown (Sharma et al., 2016);

4. Fruit provides prolonged satiety attributed to dietary fiber. Bes-Rastrollo et al. (2006) assessed the association between fiber intake and fruit and vegetable consumption with the likelihood of WG 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/vegetable consumption and WG, but only among men, and 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 fruit and vegetables.

De Carvalho et al. (2006) evaluated the dietary fiber intake of adolescents in the metropolitan area of São Paulo City (Brazil), and the association between low dietary fiber intake with constipation and overweight. The study included 716 adolescents, and evaluation of fiber intake was based on a 24-h daily intake record and a frequency questionnaire. Adolescents who did not eat beans on more than 4 days/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.

2.3.5 Pulmonary Health

Several studies have shown a positive association between fruit and vegetable intake and pulmonary function. Fruit and vegetable consumption has been suggested to maintain a healthy pulmonary function in well-adult populations, and improve lung function in those with established pulmonary disorders. Phytochemicals, especially of antioxidant potential, have been suggested to be important in protecting the lungs from oxidative stress. Higher fruit intake was found to be consistently associated with lowered mortality from chronic obstructive pulmonary disease (COPD)-related causes. 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.

It has been suggested that reduced antioxidant intake is one critical factor associated with increased susceptibility to asthma, and therefore fruit and vegetable intake has been suggested to reduce it by improving ventilatory function and respiratory symptoms. Fruits and vegetables 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). Moreover, the consumption of fruit and vegetables is associated with reduced occurrence of wheezing and shortness of breath in schoolchildren.

2.3.6 Bone Health

The loss of bone mass is a global epidemic associated with osteoporosis. Fruit and vegetable consumption has been suggested to improve bones. Higher fruit and vegetable intake was associated with improved markers of bone status in males and females ranging between 16 and 83 years old. Tylavsky et al. (2004) showed that fruit and vegetable intake might be important in bone health in white girls ages 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 vegetable) in the low group. Girls in the high fruit and vegetable intake group had significantly larger bone area of the whole body and 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 concluded that fruit and vegetable intake is positively correlated with bone health. In a study conducted with 85 boys and 67 girls, ages 8–20 years in Saskatchewan, Canada, fruit and vegetable intake was reported to be an important independent predictor of accrued total body bone mineral content (BMC) in boys but not in girls. In a study with adolescents ages 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.

Oxidative stress contributes to the etiology of osteoporosis through the inhibition of osteoblastic differentiation via extracellular signal-regulated kinases (ERK) and ERK-dependent nuclear factor-κB signaling pathways. Thus antioxidants in fruits and vegetables, including β-carotene, are able to reduce oxidative stress on bone mineral density (BMD), in addition to the potential role of some nutrients such as vitamins C and K that can promote bone cell and structural formation.

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 bones. Potassium intake was significantly and linearly associated with markers of bone turnover and femoral BMD. 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 of 40 healthy men and women, with an average age of 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 "urinary N-telopeptide (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 BMD and 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) reported that a daily increase of 100 g/kcal total fruit intake was associated with 4.5% and 6.4% increases of BMD at whole body, and 3.9% and 4.8% increases at the femoral neck in Honk 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 a significant association between vegetable intake and bone mass.

Shen et al. (2012) proposed a potential osteoprotective mechanism of most commonly consumed fruits and their phytochemicals, such as tomato (lycopene), grape (resveratrol), citrus fruits, berry fruits, dried plum, and apple (polyphenols, flavonoids, phloridzin, and pectin), via antiinflammatory and antioxidant mechanisms, leading to osteoblast mineralization and osteoclast inactivation. They proposed that fruit intake promotes osteoblastogenesis by upregulating RunX2 and osteocalcin, specific genes for osteoblast formation. This process also involves activation of the Wnt signaling pathway through β-catenin that, together with BMP-2 protein, promotes osteoblast differentiation. In addition, IGF-I is correlated positively with bone formation by inhibiting collagen degradation.

Fruits and phytochemicals also downregulate RANKL, a key protein responsible for differentiating monocytes/macrophage precursors into osteoclasts, because RANKL stimulates the expression of osteoclast-specific genes (TRAP, cathepsin K [CATK], calcitonin receptor, and β3-integrin) that consequently degrade bone minerals and collagen matrices. In addition, the inhibition of RANKL will reduce the matrix metalloproteinase (MMP-2 and MMP-9) activity that degrades bone collagen. Finally, downregulation of RANKL can inactivate NFATc1, a calcineurin- and calcium-regulated transcriptional factor that promotes osteoclastogenesis (Shen et al., 2012).

2.3.7 Cataracts and Eye Health

Oxidative mechanisms have been implicated in the etiology of cataracts in humans, and fruit and vegetable intake has been associated with this problem. A study involving 35,724 healthy professional women over the age of 45 years in the United States 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. RR 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. 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, used macular pigment optical density (MPOD) as a marker to correlate diet and serum carotenoid levels with the amount of molecular pigment in the retina and showed that a high (≥5 servings/day) intake of fruit and vegetables was associated with significantly higher MPOD compared to measurement in subjects with lower (<3 servings/day) intake.

2.3.8 Arthritis

Dietary antioxidants and antiinflammatory 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. A study of 29,368 married women from the United States, predominately white, average age 61.4 years, for 11 years, indicated that total fruit consumption (> 83 servings per month) was associated with reduced risk of RA. Oranges were the only individual fruit linked to a 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) indicated that lower but not statistically significant intake of fruits and vegetables was weakly associated with higher incidence of inflammatory polyarthritis (IP). 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). In a related study to determine the relationship with carotenoid intake, the diets of 88 cases were compared to those of 176 controls (mean age 61 years; 69% women), and it was 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.

2.3.9 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. 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%–27% after short-term feeding experiments with fruits and vegetables and red blood cell folate also increases with increasing fruit and vegetable intake (from 1 to 7 servings/day).

2.3.10 Diverticulosis

Diverticulosis affects 50% or more of the population over the age of 60 years in several countries. Fruit and vegetable consumption is inversely associated with the risk of diverticulosis and fiber-rich food intake is an important aspect of its therapy.

2.3.11 Skin Diseases

Skin is the largest organ and is exposed constantly to environmental factors able to induce oxidative stress, such as UV radiation, air pollutants, and chemical oxidants favoring skin aging, an inevitable normal process. However, premature skin aging may occur due to nonhealthy lifestyle (smoking, imbalanced nutrition, excessive caloric restriction, and mental stress). 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 to human skin after irradiation with UV light.

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 at 2 atmospheric pressure (atm) for 2 h with hyperbaric oxygen. The animals were supplemented for 8 weeks, reducing significantly "reduced glutathione (GSH)" levels compared to placebo-fed rats. In addition, vascular endothelial growth factor (VEGF) expression induced in keratinocytes by treatment with H_2O_2 and tumor necrosis factor-alpha, an inflammatory cytokine), was inhibited after 12 h of treatment with OptiBerry; and pretreatment of cells with OptiBerry inhibited ROS- and inflammation-induced VEGF protein expression.

Promising results have been obtained to prevent UV-induced skin alterations and premature skin aging by using extracts of pomace from Riesling grapes that showed a dose-dependent inhibitory activity against both enzymes with IC_{50} values of 20.3 and 14.7 μg/mL for collagenase and elastase activity, respectively, with the free phenolic acids fraction being the most active. Human dermal fibroblasts incubated with strawberry extract at 0.5 mg/mL and stressed with H_2O_2 showed an increase in cell viability, a smaller intracellular amount of ROS, and a reduction in membrane lipid peroxidation and DNA damage, which was also able to improve mitochondrial functionality, increase the basal respiration of mitochondria, and promote a regenerative capacity of cells after exposure to prooxidant stimuli. 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 analogues, and flavonoids are currently incorporated into a variety of antiaging 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.

2.3.12 Neurodegenerative Diseases

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. Animal and human studies have suggested that consumption of fruits and vegetables has the potential to decrease some age-related processes, primarily due to the antioxidant and antiinflammatory properties of several phytochemicals. In vitro studies have 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.

Fruit and vegetable extracts have been demonstrated to reverse or retard various age-related cognitive and motor deficits in rats. 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. Examination of the brain tissue from these animals showed evidence of reduced inflammatory and oxidative processes in the supplemented groups. A transgenic mice model of Alzheimer's disease fed blueberry extract exhibited cognitive performance equivalent to that of normal nonsupplemented mice and was significantly improved compared to nonsupplemented transgenic mice. Blueberry supplementation in the transgenic mice increased the 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 that is also known to be important in cognitive function. Aging rats provided with Concord grape juice at low concentration (10%) for 9 weeks improved cognitive performance, while a high (50%) concentration improved motor performance. 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.

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 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, 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 flavonoids and β-carotene intake was protective in smokers but not in nonsmokers.

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, improving learning and memory. Epigallocatechin gallate is able to protect neuronal cell lines submitted to glucose or glutamate toxicity and age-associated oxidative damage in rat brain by increasing activities of superoxide dismutase, catalase, glutathione peroxidase, and glucose-6-phosphate dehydrogenase. Another mechanism observed with epigallocatechin gallate, genistein, kaempferol, and quercetine, is the inhibition of cholinesterase activity, which improves cognitive functions, like learning and memory. It has also been observed that curcumin grape extracts and resveratrol and epigallocatechin gallate have the capacity to reduce amyloid-β (Aβ) deposition and Aβ protein in preclinical in vitro and animal models.

There are a growing number of evidences about the potential of natural polyphenols against neurodegenerative diseases, despite the application into clinical routine being limited because it is necessary to understand the systemic metabolism, pharmacokinetics, brain bioavailability, local metabolism, and modification in the central nervous system.

2.4 SUMMARY AND CONCLUSIONS

Accumulating evidences demonstrate that fruit and vegetable consumption has health benefits. These benefits of fruits and vegetables are associated with their content of thousands of phytochemicals of diverse classes. Therefore, health organizations recommend the consumption of at least 400 g of fruits and vegetables daily. Intensive research activity is dealing with the identification of the phytochemicals in fruits and vegetables, and their role in human nutrition and health through controlled clinical intervention trials, as well as studies to reveal the mechanisms behind the effect of the different phytochemical components.

REFERENCES

Bagchi, D., Roy, S., Patel, V., He, G., Khanna, S., Ojha, N., et al., 2006. Safety and whole-body antioxidant potential of a novel anthocyanin-rich formulation of edible berries. Mol. Cell Biochem. 281, 197–209.

Bazzano, L.A., Li, T.Y., Joshipura, K.J., Hu, F.B., 2008. Intake of fruit, vegetables, and fruit juices and risk of diabetes in women. Diabetes Care 31, 1311–1317.

Bes-Rastrollo, M., Martínez-González, M.A., Sánchez-Villegas, A., de la Fuente Arrillaga, C., Martínez, J.A., 2006. Association of fiber intake and fruit/vegetable consumption with weight gain in a Mediterranean population. Nutrition 22, 504–511.

Buil-Cosiales, P., Zazpe, I., Toledo, E., Corella, D., Salas-Salvadó, J., Diez-Espino, J., et al., 2014. Fiber intake and all-cause mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. Am. J. Clin. Nutr. 100, 1498–1507.

Cárdenas Medellín, M.L., Serna Saldívar, S.O., Velazco de la Garza, J., 1998. Efecto de la ingestión de nopal crudo y cocido (*Opuntia ficus indica*) en el crecimiento y perfil de colesterol total, lipoproteína y glucosa en sangre de ratas. Arch. Latinoam. Nutr. 48, 316–323.

De Carvalho, E.B., Vitolo, M.R., Gama, C.M., Lopez, F.A., Taddei, J.A., de Morais, M.B., 2006. Fiber intake, constipation, and overweight among adolescents living in Sao Paulo City. Nutrition 22, 744–749.

Deguchi, Y., Miyazaki, K., 2010. Anti-hyperglycemic and anti-hyperlipidemic effects of guava leaf extract. Nutr. Metab. 7, 9.

Díaz de Cerio, E., Verardo, V., Gómez-Caravaca, A.M., Fernández-Gutiérrez, A., Segura-Carretero, A., 2016. Exploratory characterization of phenolic compounds with demonstrated anti-diabetic activity in guava leaves at different oxidation states. Int. J. Mol. Sci. 17, 699.

Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M.I., Corella, D., Arós, F., et al., 2013. Primary prevention of cardiovascular disease with a Mediterranean diet. N. Engl. J. Med. 368, 1279–1290.

Fogelholm, M., Anderssen, S., Gunnarsdottir, I., Lahti-Koski, M., 2012. Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. Food Nutr. Res. 56. Available from: https://doi.org/10.3402/fnr.v56i0.19103.

Frati A., 1992. Medical implication of prickly pear cactus. In: Felker, P. Moss, J.R. (Eds.), Proceedings of the Third Annual Texas Prickly Pear Council, Kingsville, TX, pp. 29–34.

Frati, A.C., Gordillo, B.E., Altamirano, P., Ariza, C.R., Cortes-Franco, R., Chavez-Negrete, A., 1990. Acute hypoglycemic effect of *Opuntia streptacantha* Lemaire in NIDDM. Diabetes Care 13, 455–456.

Frati-Munari, A.C., Licona-Quesada, R., Araiza-Andraga, C.R., Lopex-Ledesma, R., Chavez-Negrete, A., 1990. Acción de *Opuntia streptacantha* en individuos sanos con hiperglucemia inducida. Arch. Invest. Med. 21, 99–102.

Gan, Y., Tong, X., Li, L., Cao, S., Yin, X., Gao, C., et al., 2015. Consumption of fruit and vegetable and risk of coronary heart disease: a meta-analysis of prospective cohort studies. Int. J. Cardiol. 15 (183), 129–137.

Grosso, G., Yang, J., Marventano, S., Micek, A., Galvano, F., Kales, S.N., 2015. Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. Am. J. Clin. Nutr. 101, 783–793.

Hamer, M., Chida, Y., 2007. Intake of fruit, vegetables, and antioxidants and risk of type 2 diabetes: systematic review and meta-analysis. J. Hypertens. 25, 2361–2369.

He, K., Hu, F.B., Colditz, G.A., Manson, J.E., Willett, W.C., Liu, S., 2004. Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. Int. J. Obes. Relat. Metab. Disord. 28, 1569–1574.

Jajoo, R., Song, L., Rasmussen, H., Harris, S.S., Dawson-Hughes, B., 2006. Dietary acid-base balance, bone resorption, and calcium excretion. J. Am. Coll. Nutr. 25 (3), 224–230.

Li, J.J., Huang, Z.W., Wang, R.Q., Ma, X.M., Zhang, Z.Q., Liu, Z., et al., 2013. Fruit and vegetable intake and bone mass in Chinese adolescents, young and postmenopausal women. Public Health Nutr. 16, 78–86.

Liu, Z.M., Leung, J., Wong, S.Y., Wong, C.K., Chan, R., Woo, J., 2015. Greater fruit intake was associated with better bone mineral status among Chinese elderly men and women: results of Hong Kong Mr. Os and Ms. Os studies. J. Am. Med. Dir. Assoc. 16, 309–315.

Mattes, R.D., Kris-Etherton, P.M., Foster, G.D., 2008. Impact of peanuts and tree nuts on body weight and healthy weight loss in adults. J. Nutr. 138, 1741S–1745S.

Mirmiram, P., Holsseinni-Esfahani, F., Azizi, F., 2013. Fruit and vegetable consumption and risk of noncommunicable diseases. In: Ross, R., Preedy, V.R. (Eds.), Bioactive Food as Dietary Interventions for Cardiovascular Disease. Elsevier, Tucson, AZ.

Mohammadifard, N., Salehi-Abargouei, A., Salas-Salvadó, J., Guasch-Ferré, M., Humphries, K., Sarrafzadegan, N., 2015. The effect of tree nut, peanut, and soy nut consumption on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. Am. J. Clin. Nutr. 101, 966–982.

Ojewole, J.A., 2005. Hypoglycemic and hypotensive effects of *Psidium guajava* Linn. (Myrtaceae) leaf aqueous extract. Methods Find. Exp. Clin. Pharmacol. 27, 689–695.

O'Neil, C.E., Fulgoni 3rd, V.L., Nicklas, T.A., 2015. Tree Nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. Adults: NHANES 2005–2010. Nutr. J. 14, 64.
Pinent, M., Blay, M., Bladé, M.C., Salvadó, M.J., Arola, L., Ardévol, A., 2004. Grape seed-derived procyanidins have an antihyperglycemic effect in streptozotocin-induced diabetic rats and insulinomimetic activity in insulin-sensitive cell lines. Endocrinology 145, 4985–4990.
Sharma, S.P., Chung, H.J., Kim, H.J., Hong, S.T., 2016. Paradoxical effects of fruit on obesity. Nutrients 8, 633.
Shen, C.-L., von Bergen, V., Chyu, M.-C., Jenkin, M.R., Mo, H., Chen, C.-H., et al., 2012. Fruits and dietary phytochemicals in bone protection. Nutr. Res. 32, 897–910.
Svendsen, M., Blomhoff, R., Holme, I., Tonstad, S., 2007. The effect of an increased intake of vegetables and fruit on weight loss, blood pressure and antioxidant defense in subjects with sleep related breathing disorders. Eur. J. Clin. Nutr. 61, 1301–1311.
Tylavsky, F.A., Holliday, K., Danish, R., Womack, C., Norwood, J., Carbone, L., 2004. Fruit and vegetable intakes are an independent predictor of bone size in early pubertal children. Am. J. Clin. Nutr. 79, 311–317.
Villegas, R., Shu, X.O., Gao, Y.T., Yang, G., Elasy, T., Li, H., et al., 2008. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in Chinese women. J. Nutr. 138, 574–580.
Vioque, J., Weinbrenner, T., Castelló, A., Asensio, L., Garcia de la Hera, M., 2008. Intake of fruits and vegetables in relation to 10-year weight gain among Spanish adults. Obesity (Silver Spring) 16 (3), 664–670.
Wu, Y., Zhang, D., Jiang, X., Jiang, W., 2015. Fruit and vegetable consumption and risk of type 2 diabetes mellitus: a dose–response meta-analysis of prospective cohort studies. Nutr. Metab. Cardiovasc. Dis. 25, 140–147.

FURTHER READING

Geleijnse, J.M., Hollman, P., 2008. Flavonoids and cardiovascular health: which compounds, what mechanisms? Am. J. Clin. Nutr. 88, 12e3.
Pavan, A.R., Silva, G.D., Jornada, D.H., Chiba, D.E., Fernandes, G.F., Man Chin, C., et al., 2016. Unraveling the anticancer effect of curcumin and resveratrol. Nutrients 8, E628.
Signh, B.N., Singh, H.B., Singh, A., Naqvi, A.H., Singh, B.R., 2014. Dietary phytochemicals alter epigenetic events and signaling pathways for inhibition of metastasis cascade. Cancer Metastasis Rev. 33, 41–85.
Wang, X., Ouyang, Y.Y., Liu, J., Zhao, G., 2014. Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. Brit. J. Nutr. 111, 1–11.
Wang, Z.M., Zhao, D., Nie, Z.L., Zhao, H., Zhou, B., Gao, W., et al., 2015. Flavonol intake and stroke-risk: a meta-analysis of cohort studies. Nutrition 30, 518–523.
World Cancer Research Fund/American Institute for Cancer Research, 2007. Food, nutrition, physical activity and the prevention of cancer: a global perspective. AIRC, Washington DC.
World Cancer Research Fund/American Institute for Cancer Research, 2009. Policy action for prevention for food, nutrition, physical activity and the prevention of cancer: a global perspective. AIRC, Washington DC.
Yahia, E.M., 2009. The contribution of fruit and vegetable consumption to human health. In: Benkeblia, N. (Ed.), Postharvest Technology for Horticultural Crops. Research Signpost Publisher, Kerala, pp. 139–163.
Yahia, E.M., 2010. The contribution of fruits and vegetables to human health. In: De la Rosa, L., Alvarez-Parrilla, E., Gonzalez-Aguilar, G. (Eds.), Fruit and Vegetable Phytochemicals: Chemistry, Nutritional Value and Stability. Wiley-Blackwell Publishing, Oxford, UK, pp. 3–51.
Yahia, E.M. (Ed.), 2018. Fruit and Vegetable Phytochemicals: Chemistry and Human Health. second ed. Wiley-Blackwell, Oxford, UK.
Yahia, E.M., Maldonado-Celis, M.E., Svensen, M., 2018. The contribution of fruit and vegetable consumption to human health. In: Yahia, E.M. (Ed.), Fruit and Vegetable Phytochemicals: Chemistry and Human Health., second ed. Wiley-Blackwell, Oxford, UK, pp. 3–52.