# Plants, Diet, and Health

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## Abstract

Chronic disease is a major social challenge of the twenty-first century. In this review, we examine the evidence for discordance between modern diets and those on which humankind evolved as the cause of the increasing incidence of chronic diseases, and the evidence supporting consumption of plant foods as a way to reduce the risk of chronic disease. We also examine the evidence for avoiding certain components of plant-based foods that are enriched in Western diets, and review the mechanisms by which different phytonutrients are thought to reduce the risk of chronic disease. This body of evidence strongly suggests that consuming more fruits and vegetables could contribute both to medical nutrition therapies, as part of a package of treatments for conditions like type 2 diabetes, heart disease, cancer, and obesity, and to the prevention of these diseases. Plant science should be directed toward improving the quality of plant-based foods by building on our improved understanding of the complex relationships between plants, our diet, and our health.

## Contents



## 1. INTRODUCTION

Plants are central to our survival, providing the oxygen we breathe, many of the raw materials for our dwellings, and, directly or indirectly, all of the food that we eat. Diet must be considered an important part of our environment, and it may have significant impacts on our growth and development when we are young and on our risk of disease, particularly chronic disease, throughout our lives.

We can appreciate this relationship easily by considering deficiency diseases. Diets based on staple single crops often lack essential nutrients; polished white rice, for example, is deficient in provitamin A and folate. People dependent on these crops for most or all of their nutrition often suffer from dietary deficiencies. Dietary provitamin A is required by humans for vision and growth, and because consumption of rice as a staple is so prevalent in developing countries, especially in Asia, vitamin A deficiency is estimated to globally affect approximately one-third of children under the age of five, a significant number of whom suffer blindness or die (200).

Deficiency diseases usually result from malnourishment or overdependence on single staple crops. However, many chronic diseases—including diseases arising from metabolic syndrome and obesity, such as type 2 diabetes, cardiovascular disease (CVD), and certain cancers—are also heavily influenced by diet, as a result not of deficiencies in essential nutrients but rather of evolutionary discordance between modern Western diets and the type of diet on which humans evolved, one to which we are presumably physiologically best adjusted. Ideas about the benefits of "Paleolithic diets" have been gaining support since they were first suggested by Eaton & Konnor (55) more than 25 years ago, and increased consumption of unprocessed fruits and vegetables features prominently in many health-promoting dietary campaigns. Over the same period, the list of items in Western diets that increase the risk of chronic disease has grown and now includes many components of modern foods that were absent or of low abundance in Paleolithic diets.

## 2. THE RISE IN INCIDENCE AND MORTALITY FROM CHRONIC DISEASE

Chronic diseases (e.g., CVD, diseases associated with metabolic syndrome, and cancer) account for three-quarters of all disease

worldwide. Approximately half of current deaths from chronic disease can be attributed to modifiable risks, namely tobacco use, physical inactivity, and poor diet (42, 53, 201). As many chronic diseases are related directly to obesity, the global obesity epidemic, which started in the 1980s, underpins much of the projected increase in mortality and the likely prevalence of chronic disease in the near future (199). Predictions about the future incidence of mortality from chronic diseases are based on the risks that current adolescent populations are exposed to, primary among which are the poor Western diets that have fueled the obesity epidemic.

There is now strong evidence for the benefits of fruit and vegetable consumption in terms of protection against chronic disease, and epidemiological studies have linked diets that include abundant consumption of plant-based foods with decreased risk of developing CVD, diseases associated with metabolic syndrome, and various kinds of cancer. Although it has been claimed that the "five-a-day" campaign was the cynical output of a marketing campaign to promote the sales of products from Californian fruit and vegetable companies (75), there is mounting evidence to suggest that the campaign's objective is scientifically sound and that there should be a shift toward increased fruit and vegetable consumption to reduce the risk of chronic disease (13, 14, 28, 35, 68, 69, 82, 91, 102, 117, 129, 157, 158, 177).

## 3. PLANTS IN THE DIET OF HUNTER-GATHERERS

Most of the alleles of the human genome were selected during the Paleolithic era, a period from 2.5 million years ago to approximately 10,000 years ago (150). The Neolithic revolution, which occurred approximately 10,000 years ago, saw the development of both cereal cultivation and animal husbandry, which resulted in fundamental changes in the human diet to include more starches and significantly more fats, respectively. Since the industrial revolution this diet has again changed significantly, accompanied by fundamental changes in lifestyle that mean that people are generally much more sedentary than they were in the past (27). The 10,000 years since these changes began represents a little over 350 generations—not long enough for adaptive change to the new dietary environments. In addition, medical improvements have greatly reduced prereproductive mortality and therefore the selection pressures for adaptive change in humans.

Our Paleolithic ancestors were hunter-gatherers, consuming diets rich in lean wild meat or fish, with relatively high consumption of fruits and green leafy vegetables (**Figure 1*a***). Our modern diets, in contrast, are high in saturated fats and starches, added sugars with high energy load, and "unnatural fats" such as trans fats (**Figure 1*c***). Paleolithic diets, in contrast to those of simians and present-day hunter-gatherers, are estimated to have been approximately 75% fruit (114). In modern US diets, foods unavailable to Paleolithic societies—including dairy products, cereal grains, refined cereal flour, refined sugars, refined vegetable oils, and alcohol—on average make up 70% of total energy consumption. Of this, 50% is in the form of vegetable oils and refined sugars (38). Americans currently consume less than 60% of the US Department of Agriculture recommendations for vegetables and less than 50% of the recommendations for fruits.

Modern hunter-gatherer societies also provide evidence of the benefits of Paleolithic diets compared with modern Western diets. Compared with individuals on Western diets, modern-day hunter-gatherers generally have lower blood pressure, no association between increasing blood pressure and age, excellent insulin sensitivity (especially in older individuals), lower fasting insulin levels in plasma, lower fasting leptin levels, lower body mass indexes, lower waist-to-height ratios, lower tricipital skinfolds, greater maximum oxygen consumption, better visual acuity, better marker levels for bone health, and lower fracture rates (27). Where hunter-gatherers have switched from a traditional diet to a Western one, the incidence of chronic disease has rapidly increased (1, 5, 25, 145, 198). Historical records also establish that

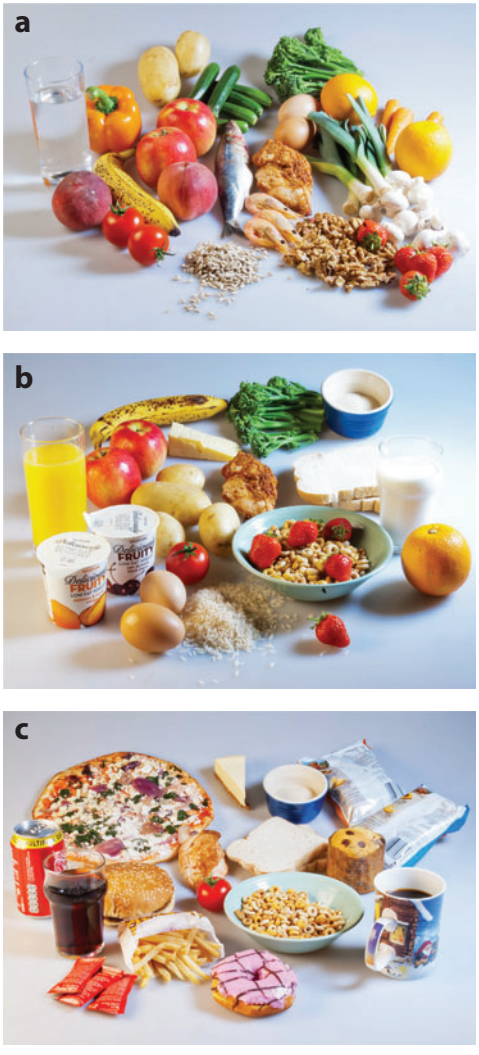


**Figure 1**

Typical diets. (*a*) Food for one day on a Paleolithic-style diet (based on Reference 115). (*b*) Food for one day on a therapeutic diet (based on Reference 90). (*c*) Food for one day on a modern Western diet.

hunter-gatherer societies in the past were fit, lean, and free from the outward signs of chronic disease, including type 2 diabetes, CVD, and cancer (27).

An increasing number of studies have reported improved outcomes for both healthy individuals and patients following a switch to a Paleolithic diet, including both long- and short-term interventions that show improvements in risk factors for type 2 diabetes, CVD, cancer, and obesity (63, 94, 101, 115, 140, 185). So what is it about Paleolithic diets that makes them so good? One suggestion is that the availability of cholesterol, which is essential for lipoprotein transport, bile acid production, and steroid hormone synthesis, was very low in the average Paleolithic diet (90), and consequently human physiology is likely adjusted to extract maximum levels of cholesterol from the diet. Cholesterol levels were low in Paleolithic diets because of low levels of precursors for synthesis and relatively high levels of dietary components that enhance cholesterol elimination via the gut, namely plant fibers, vegetable proteins, and plant sterols. The problems with a physiology tuned to conserve cholesterol occur when the diet contains high levels of fat for the synthesis of cholesterol and also lower levels of components that remove cholesterol.

The reason that Paleolithic diets are beneficial lies in both the food components they contain and the ones they lack.

## 4. PLANTS IN THE MODERN WESTERN DIET

Western diets include basic macronutrients, proteins, fats, and carbohydrates, significant proportions of which are derived directly from plants. On average, it is likely that we consume significantly more food than our Paleolithic ancestors did owing simply to the greater availability of food. However, increased consumption is not the only cause of the current obesity epidemic, and the predicted increase in incidence and mortality from chronic diseases is probably more closely aligned to compositional changes in Western diets compared with traditional diets than it is to the amounts eaten.

### 4.1. Protein

Most international dietary guidelines recommend diets with low energy intake from protein, although high-protein diets have been reported to have beneficial effects on weight

gain and associated metabolic parameters (21, 33, 73). Meta-analysis of such studies has suggested that high-protein diets can lead to more significant weight loss than low-protein diets do (167). The most likely explanation is that high-protein diets are more satiating than low-protein diets and therefore reduce total energy consumption (4). High-protein diets have been suggested to negatively impact bone health, but such suggestions are not supported by clinical data except in the context of inadequate calcium supply (26). High-protein diets may also promote kidney stones and renal disease, but may be deleterious only in patients with preexisting renal dysfunction (26). For these reasons, diets with modest levels of protein (<70 g per day) are likely to have favorable effects on health.

## 4.2. Fats

Fats, derived largely from dairy sources but also from plant oils, are a significant part of Western diets. The so-called lipid hypothesis suggests that low-density lipoprotein (LDL) cholesterol in plasma is the major risk factor for coronary heart disease (CHD) and that LDL levels can be influenced significantly by diet (44). This idea has cast most fats (particularly saturated fats) as negative contributors to a healthy diet, because dietary fatty acids play critical roles in pathogenesis (153). However, dietary fats are not a uniform group of nutrients, play very different physiological roles, and contribute differently to pathogenesis. The current thinking is that total fat intake is significantly less important than fat quality in terms of influencing obesity and the onset and progression of chronic disease (197).

**Table 1** lists the different types of fat available in Western diets. Analyses of populations around the world have identified at least a 10-fold variation in mortality from CHD, a disease that is significantly impacted by environment. Populations with the lowest incidences of mortality from CHD have minimal intake of industrially produced trans fats, high intake of omega-3 (n-3) polyunsaturated fatty acids (PUFAs), and relatively low intake of omega-6 (n-6) PUFAs. Most of these populations also consume relatively low levels of saturated fatty acids and high levels of monounsaturated fatty acids, as in Mediterranean diets (153).

**4.2.1. Trans fats.** Dietary trans fats are produced almost exclusively by the industrial hydrogenation of vegetable oils to produce margarines. Hydrogenation began in earnest at the start of the twentieth century as a means of utilizing soybean oil. Hydrogenated-fat production increased steadily until the 1960s, as processed vegetable fats replaced animal fats in the United States and other developed countries. Controlled intervention studies with relatively large numbers of subjects have shown that trans fats increase plasma levels of LDL cholesterol and reduce plasma levels of high-density lipoprotein (HDL) cholesterol compared with saturated fats and nonhydrogenated oils of equivalent caloric value (131, 136).

Trans-fat consumption has been strongly associated with CHD and promotes three times as many incidents of sudden cardiac arrest as saturated fats do (111). Trans-fat consumption also consistently increases inflammation (137), which may contribute significantly to CHD and metabolic syndrome. Based on the effects of intervention with diets rich in trans fats, Mozaffarian et al. (136) calculated that between 72,000 and 228,000 CHD events in the United States per year could be avoided by the complete elimination of trans fats from the diet. New labeling rules, legislation, and voluntary measures by the food industry are moving developed countries toward complete elimination, but many baked goods and sweets still contain significant levels, as shown in **Table 2**.

**4.2.2. Saturated fats.** Since the 1950s, it has been commonly believed that consuming foods with a high proportion of saturated fatty acids (such as animal fats, milk fat, butter, lard,

**Table 1 Major dietary sources of fats (adapted from Reference 153)**

| Fatty acid | Major sources | Notes | Good or bad? |
|---|---|---|---|
| Trans fats | Household shortenings, margarines, foods fried in partially hydrogenated vegetable oils, baked goods | Beef and dairy products produce small amounts of trans fats, but these are metabolically and nutritionally distinct from partially hydrogenated vegetable oils. | Very bad ☹☹ |
| Saturated fats | Grain-fed animal meats, palm oil (palmitate)<br>Cocoa butter (stearate)<br>Coconut oil, palm kernel oil (laurate and myristate) | | Neutral 😐 |
| Monounsaturated fats | Whole olives, olive oil, canola oil, avocados, nuts | Dairy and other animal fats provide significant amounts of oleate but also palmitate. | Good ☺ |
| Medium-chain n-6 PUFAs (linoleic acid) | Vegetable oil, seed oil (especially safflower, sunflower, corn, cottonseed, and soybean oils) | | Bad ☹ |
| Medium-chain n-3 PUFAs (α-linolenic acid) | Flaxseed oil, canola oil, walnuts<br>Lower amounts from green leafy vegetables | The greatest dietary sources of α-linolenic acid in the United States are soybean-oil salad dressing and mayonnaise, but these are also rich in linoleic acid (a medium-chain n-6 PUFA). | Good ☺ |
| Long-chain n-6 PUFAs (AA) | Eggs, poultry, beef, pork, liver, farmed fish | | Bad ☹ |
| Long-chain n-3 PUFAs (EPA and DHA) | Marine fish (mackerel, herring, salmon, anchovies, sardines, tuna, and oysters)<br>Lower amounts from shrimp, mussels, squid, and scallops<br>Small amounts from meat from wild game and pasture-fed cattle | Meat from grain-fed cattle has much lower n-3:n-6 PUFA ratios than meat from wild game or pasture-fed cattle. | Very good ☺☺ |

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acid.



coconut oil, and palm oil) is less healthy than consuming foods with a lower proportion of saturated fatty acids (such as olive, peanut, canola, safflower, corn, sunflower, and soybean oils). The main saturated fatty acids in Western diets are laurate (from coconut oil and milk), myristate (from milk and animal fat), palmitate (from grain-fed meat and palm oil), and stearate (from grain-fed meat and cocoa butter). In Paleolithic diets, saturated fatty acids constituted approximately 10–15% of the energy intake, whereas in the average US diet before cholesterol-lowering campaigns began, they constituted 16%, mostly from grain-fed meat and dairy. US intake currently averages approximately 11–12% of the total energy intake, mostly as palmitate.

Early epidemiological data have shown strong positive associations between the average dietary intake of saturated fats, total cholesterol levels in serum, and 25-year death rates from CHD (103). However, longer-term follow-ups have suggested that the association with CHD is not as strong as it is for trans fats (81). Different saturated fats may contribute differentially to increasing LDL cholesterol in plasma, with palmitate raising the LDL level and LDL:HDL ratio whereas stearate and laurate reduce these values and myristate has no effect (131, 153).

**Table 2 Typical trans-fat content of foods produced or prepared with hydrogenated vegetable oils in the United States (adapted from Reference 136)**

| Type of food | Trans-fat content | | | |
|---|---|---|---|---|
| | Amount per serving (g) | Amount per 100g (g) | Total fatty acids (%) | Daily energy intake for 2,000-kcal diet (%) |
| **Fast or frozen foods** | | | | |
| French fries  | 4.7–6.1 | 4.2–5.8 | 28–36 | 2.1–2.7 |
| Breaded fish burger  | 5.6 | 3.4 | 28 | 2.5 |
| Breaded chicken nugget  | 5.0 | 4.9 | 25 | 2.3 |
| Frozen French fries  | 2.8 | 2.5 | 30 | 1.3 |
| Enchilada  | 2.1 | 1.1 | 12 | 0.9 |
| Burrito  | 1.1 | 0.9 | 12 | 0.5 |
| Pizza  | 1.1 | 0.5 | 9 | 0.5 |
| **Packaged snacks** | | | | |
| Tortilla chips  | 1.6 | 5.8 | 22 | 0.7 |
| Popcorn  | 1.2 | 3.0 | 11 | 0.5 |
| Granola bar  | 1.0 | 3.7 | 18 | 0.5 |
| Breakfast bar  | 0.6 | 1.3 | 15 | 0.3 |
| **Bakery products** | | | | |
| Pie  | 3.9 | 3.1 | 28 | 1.8 |
| Danish  | 3.3 | 4.7 | 25 | 1.5 |
| Doughnut  | 2.7 | 5.7 | 25 | 1.2 |
| Cookie  | 1.8 | 5.9 | 26 | 0.8 |
| Cake  | 1.7 | 2.7 | 16 | 0.8 |
| Brownie  | 1.0 | 3.4 | 21 | 0.5 |
| Muffin  | 0.7 | 1.3 | 14 | 0.3 |

**4.2.3. Monounsaturated fats.** Paleolithic diets were rich in monounsaturated fats, which accounted for approximately 16–25% of the energy consumption, with the main sources being wild meat, bone marrow, and nuts. Modern farming practices of feeding animals grain have meant that Western diets contain far more saturated fats, such as palmitate from beef, poultry, and other meats. Some traditional diets, such as Mediterranean diets, are rich in monounsaturated fats because of their high olive and olive-oil content and are associated with improved lipoprotein profiles, improved insulin sensitivity, and reduced thrombogenesis (65, 131, 173).

**4.2.4. Polyunsaturated fats.** Paleolithic diets were also relatively rich in n-3 PUFAs compared with n-6 PUFAs. There has been a decline in consumption of n-3 PUFAs concomitant with increased consumption of cereals (which are low in n-3 PUFAs), exacerbated by animal husbandry practices switching to cereal-based feed (172).

PUFAs are divided into two classes: medium chain and long chain. Medium-chain PUFAs are derived largely from plant sources, whereas long-chain PUFAs are derived largely from marine fish that acquire high levels from the algae on which they feed. Dietary campaigns to reduce saturated-fat consumption recommended replacement with medium-chain PUFAs such as linoleic acid (an n-6 PUFA). On average, linoleic acid would have supplied 1–3% of the total energy intake in a Paleolithic diet, whereas it supplies approximately 6–7% in the modern US diet and 8–12% in some modern European diets. Traditional Mediterranean diets have much lower levels of linoleic acid and are accompanied by lower incidence of CHD. One long-term trial that reduced linoleic acid to levels similar to those in Mediterranean diets reduced CHD events and mortality by 70% (48).

Considerable evidence now exists that it is the composition of long-chain PUFAs, more than the total consumption, that influences disease inception and progression. Long-chain n-3 PUFAs are generally associated with anti-inflammatory effects and combat the effects of long-chain n-6 PUFAs from which signaling molecules (particularly prostaglandins) are synthesized, promoting inflammation and inducing autoimmune responses. This is thought to be the case because n-6 PUFAs are used to form proinflammatory eicosanoids, whereas n-3 PUFAs form anti-inflammatory eicosanoids (172). Animals and humans metabolize dietary linoleic acid to form arachidonic acid (AA, a long-chain n-6 PUFA) and α-linolenic acid to form eicosapentaenoic acid (EPA, an n-3 PUFA) and docosahexaenoic acid (DHA, an n-3 PUFA). However, the conversion of essential fatty acids to AA, EPA, and DHA is inefficient (<5%), so the balance between n-3 and n-6 PUFAs in plasma is determined largely by the dietary levels of EPA and DHA relative to those of AA.

A wealth of data from cell, animal, epidemiological, and intervention studies has shown that higher n-3:n-6 ratios prevent or reduce chronic diseases of different types, probably owing to the promotion of anti-inflammatory activity by n-3 long-chain PUFAs, although they may also influence the properties of cell membranes and modulate gene expression (58, 76, 125). Consequently, current dietary recommendations include the consumption of significant amounts of fatty fish (such as salmon, anchovy, cod, and tuna) to boost EPA and DHA levels. Vegetarians, who must synthesize their own long-chain PUFAs, should be advised to decrease linoleic acid and increase consumption of foods rich in α-linolenic acid (such as flaxseed) to attain higher n-3:n-6 PUFA ratios.

## 4.3. Carbohydrates

Dietary carbohydrates come almost exclusively from plant sources. They are consumed as sugars or polysaccharides and contribute significantly to the energy load of the diet, glucose metabolism, and insulin signaling. As a result of their direct effects on energy balance and lipidogenesis, appetite regulation, body weight, and body composition, they also have a significant impact on the risk of chronic disease.

Indeed, many nutritionists now believe that regulating carbohydrate consumption can have a greater impact on obesity and associated complications than limiting dietary fat intake does.

**4.3.1. Indigestible polysaccharides.** Some dietary carbohydrates are indigestible. Cellulose from plant cell walls is not digested by humans but may provide benefits as dietary fiber (see Section 5.1). Starches are prevalent in Western diets through cereal-based foods but were consumed at much lower levels in Paleolithic diets, before the advent of cereal cultivation.

**4.3.2. Starches.** Starches can be divided into rapidly digested, slowly digested, and resistant. Rapidly digested starch is present in cooked starchy foods, is absorbed in the duodenum, and leads to rapid elevations of blood glucose, and consequently has a high glycemic load. Slowly digested starch is present in uncooked starchy foods such as raw cereals and cooked pulses; it is digested slowly throughout the small intestine to provide a slow and prolonged release of glucose, and has a low glycemic load. Resistant starch is fermented by the colonic microbiota to produce short-chain fatty acids that signal satiety and impact insulin signaling. Dietary sources of resistant starch include underripe bananas, partially milled grains, and retrograded starch in starchy foods that have been cooked and cooled (e.g., potato, whole-wheat bread, and cornflakes).

Foods with higher levels of resistant or slowly digested starch have been reported to impact short-term responses, reducing glucose and insulin responses and conferring enhanced satiety (16, 79), and to have longer-term effects that reduce potential risk factors for type 2 diabetes and metabolic syndrome (57). The beneficial effects of switching from diets rich in rapidly digested starch to those rich in slowly digested starch and resistant starch (**Figure 1*b***) could impact obesity and associated chronic diseases, but the outcomes of epidemiological and intervention studies have been inconsistent (3).

**4.3.3. Sugars.** Sugars were reasonably abundant in Paleolithic diets through fruits and occasionally honey. However, these types of sugars (largely fructose in fruits) are classified as intrinsic sugars and are not subject to dietary recommendations because they are not present at levels that are high enough to constitute a health risk. In Western diets, the levels of free (added) sugars are high, and consumption has increased more than fivefold over the past 60 years (rising from an average of 7.1 kg per person per year in 1966 to 37.6 kg per person per year in 2002 for the US population). This large rise is attributable to increased consumption of beverages sweetened with high-fructose corn syrup, which consists of approximately 55% fructose and 45% glucose. Bray et al. (20) first pointed out the strong correlation between the rise in obesity and increased consumption of high-fructose corn syrup. Intervention studies have shown that diets high in free sugars give rise to greater body-weight gains than do isoenergetic diets high in fats or high-glycemic-index starches (22, 152). Studies in children have shown that the odds ratio for obesity increases 1.6-fold for each additional can of sugar-sweetened drink consumed per day (124).

The evidence linking obesity to increased consumption of beverages sweetened with high-fructose corn syrup is compelling. Part of the causal relationship involves the consumption of more added sugars in beverages, which for US children is now at close to or more than their total recommended daily levels (124). However, the high fructose content in these beverages may also contribute specifically to obesity, because fructose is metabolized differently from glucose. Fructose consumption is more likely to lead to insulin resistance, type 2 diabetes, lipogenesis, and obesity than equivalent levels of glucose consumption because fructose metabolism lacks tight regulation of glycolysis. In addition, calories consumed in soft drinks do not satiate to the same extent as those consumed in foods (45, 128).

## 5. GOOD THINGS FROM PLANTS IN THE DIET

### 5.1. Fiber

Paleolithic diets were richer in fiber than Western diets, and this was largely viscous fiber in fruits rather than fiber from processed cereal grains, which is the best source in Western diets. Viscous fiber lowers the glycemic index of foods and has a beneficial impact on type 2 diabetes, risk factors for CVD, and obesity (108, 132), whereas whole-grain cereal fiber has been correlated to reduced risk of type 2 diabetes, CVD, and obesity, and no metabolic experiments have shown an impact on glycemic index (97). Dietary fiber can reduce appetite and so contribute to weight loss because it is not digested in the upper part of the gastrointestinal tract but rather is fermented in the colon to form short-chain fatty acids (acetate, butyrate, and propionate), which are important in signaling satiety. All dietary fiber comes from plants, but vegetables such as Jerusalem artichoke, chicory, eggplant, okra, asparagus, garlic, leek, and onion are particularly good sources (97, 193).

Resistant starch has properties similar to those of dietary fiber. Although it is metabolized to some extent (it has half the caloric value of rapidly digested starch), it induces both beneficial changes in the colonic microbiome composition and production of short-chain fatty acids to modulate immune function and lower pH, creating an environment less conducive to cancer cell proliferation. The average Western diet includes 3–6 g of resistant starch each day, and good sources are starchy fruits like banana and mango. Because of these beneficial effects on gut health and chronic disease, resistant starch and dietary fiber are being promoted for their prebiotic functionalities (64).

### 5.2. Antioxidants: Polyphenols, Carotenoids, and Tocotrienols

Many compounds present in foods from plants can be classified as antioxidants. Although the antioxidant capacities of many phytonutrients have been claimed to explain their health-promoting properties (161), many dietary phytonutrients have a low bioavailability, making it highly unlikely that, once absorbed, they operate directly as antioxidants to promote health. Phytonutrients with strong antioxidant activity can be subdivided into hydrophilic and lipophilic antioxidants. The current dietary advice is to include both types of antioxidant to reduce the risk of chronic disease (54).

### 5.3. Hydrophilic Antioxidants

Hydrophilic dietary antioxidants such as uric acid, ascorbic acid, and glutathione protect cellular constituents against oxidation. Many hydrophilic antioxidants in the diet are metabolized in the gut or once absorbed, although their metabolites may also have significant antioxidant activity.

**5.3.1. Anthocyanins.** Anthocyanins are plant pigments belonging to a subset of flavonoids with a particularly high antioxidant capacity and concomitantly strong health-promoting effects. As part of the human diet, they offer protection against cancer, inhibiting the initiation and progression stages of tumor development (192); they also reduce inflammatory inducers of tumor initiation, suppress angiogenesis, and minimize cancer-induced DNA damage in animal disease models. Anthocyanins also protect against CVD and age-related degenerative diseases associated with metabolic syndrome (2, 157, 158). As anthocyanins are often present at relatively high levels in fruits such as blueberry, blackberry, cranberry, strawberry, and raspberry, they were present at relatively high levels in Paleolithic diets.

**5.3.2. Flavonols.** High levels of flavonols, another group of flavonoids, are present in vegetables like onion and fruits like apple. Dietary flavonols inhibit LDL oxidation and so reduce the primary risk factor for atherosclerosis and related diseases. Longer-term dietary administration of flavonols offers cardioprotection and

improves the levels of CVD risk factors in animals (189), and the animal studies are supported by human epidemiological studies, which show inverse correlations between the occurrence of CVD, certain cancers, and age-related degenerative diseases and the consumption of flavonol-rich diets (133, 168, 174).

Flavonols have been linked to protective effects against several specific cancers, including leukemia and pancreatic, breast, cervical, prostate, uterine, and urinary tract cancers. Subjects with regular flavonol intake have a 10–60% lower incidence of these types of cancer compared with subjects with low flavonol intake. This protective activity results from both the action of flavonols as stimulators of antioxidant defenses and their direct inhibitory effects on cellular proliferation. Quercetin consumption has been reported to be inversely associated with breast cancer incidence (61).

**5.3.3. Isoflavonoids.** Isoflavonoids are polyphenols produced almost exclusively by members of the legume family. Inclusion of isoflavonoids in the diet is linked to reduced incidence of CVD, breast and prostate cancers, osteoporosis, and associated complications. The major sources of dietary isoflavonoids for humans are soybean products such as tofu. Other legumes, such as the common bean and pea, contain 10–100-fold lower levels of the major isoflavonoid, genistein (46). Western diets generally have a 100-fold lower level of isoflavonoids compared with Asian diets, and epidemiological studies have shown this difference in isoflavonoid intake to be inversely correlated with breast cancer incidence in these two groups. Animal studies have also shown the beneficial effects of isoflavonoids in preventing CVD, breast and prostate cancers, and postmenopausal ailments (39, 51). As legumes entered the human diet only after the Neolithic revolution, isoflavonoid consumption is unlikely to have been significant in Paleolithic times.

**5.3.4. Resveratrol.** Resveratrol is a stilbene phytoalexin produced by specific plant species in response to biotic and abiotic challenges. It is thought to be one of the principal agents in the health-promoting effects of red wine (12). Dietary resveratrol has been reported to have a number of beneficial health effects, including anticancer, antiaging, and anti-inflammatory activities (12). Although resveratrol exhibits potent anticancer activities against transformed cells, its effectiveness is limited by its poor bioavailability, and as a dietary phytonutrient it is most effective against tumors with which it comes in direct contact, such as skin cancers and tumors of the gastrointestinal tract. Because of the restricted number of crop species that synthesize resveratrol, it is unlikely to have featured strongly in Paleolithic diets.

**5.3.5. Catechins.** Epidemiological, clinical, and experimental studies have established an inverse correlation between green tea/epicatechin consumption and CVD and cancer (6, 19). Epicatechins are the major polyphenolic compounds in green tea, and the most significant active component is thought to be epigallocatechin gallate (EGCG). In breast cancer cell lines, EGCG inhibits cell shedding (indicative of metastasis), hepatocyte growth factor signaling, and cell motility; causes cell arrest in S phase; modulates NO signaling; induces killer caspases; and inhibits NF-κB signaling (24). Catechins, epicatechins, and condensed tannins accumulate in seed coats and are present in many fruits, including grape and blueberry, and they may have been a significant component of Paleolithic diets. However, their bitter tastes (as experienced in tea) may have meant that they were not a large part of Paleolithic diets before tea drinking became popular (the earliest records of medicinal use of tea date from 12,000 years ago).

**5.3.6. Caffeoylquinic acids.** Another important group of plant-based bioactive polyphenols are the caffeoylquinic acids, of which chlorogenic acid is the major soluble phenolic in solanaceous species such as potato, tomato, and eggplant as well as in coffee. Chlorogenic acid

is one of the most abundant polyphenols in the human diet and is the major antioxidant in the average US and European diets. It is also found in strawberry, blueberry, and pineapple. Caffeoylquinic acids have significant antioxidant activity and can limit LDL oxidation. Other caffeoylquinic acids, such as dicaffeoylquinic acid and tricaffeoylquinic acid, offer even greater protection than chlorogenic acid (84).

**5.3.7. Vitamin C.** Vitamin C (ascorbic acid) is an essential nutrient for humans, protecting the body against oxidative stress (142) and acting as a cofactor in enzymatic reactions. Dietary vitamin C acts to lessen oxidative stress, which impacts diabetes, CVD, hypertension, and chronic inflammatory diseases (71).

## 5.4. Lipophilic Antioxidants

Common lipophilic antioxidants in the diet are carotenoids, tocopherols, and tocotrienols. They protect lipids in the body from oxidation and so reduce membrane damage in particular.

**5.4.1. Lycopene.** Lycopene is a potent lipophilic antioxidant, with greater antioxidant activity than other carotenoids such as α-tocopherol, β-carotene, and lutein. Dietary lycopene is believed to confer protection against CVD, specifically protecting against LDL oxidation and reducing the risk of cerebral infarction, acute coronary events, and stroke (163). It is also believed to protect against prostate, breast, lung, and stomach cancers, possibly through its ability to impact cell growth regulation by inhibiting apoptosis and the cell cycle, stimulating the immune system, or lowering the production of inflammatory mediators (169). Lycopene has been granted a limited health claim by the US Food and Drug Administration as offering protection against prostate cancer. The richest dietary source of lycopene is tomato, which contains 8–40 μg per gram fresh weight, although it is also consumed in ruby grapefruit, papaya, guava, and watermelon. The recommended daily intake for protection against CVD is 7–20 mg per day (154).

**5.4.2. β-Carotene.** Dietary carotenes (α, β, and γ) from plants can be converted into vitamin A (retinol). Dietary provitamin A is required for synthesis of retinal (a hormone-like growth factor) and for scotopic and color vision by the retina. Both intervention and epidemiological studies have linked β-carotene consumption to enhanced protection against CVD, including cerebral infarction (159). However, the inconclusive or detrimental effects of β-carotene supplementation have detracted from programs aiming to enhance β-carotene intake, although no detrimental effects have been reported from β-carotene consumption in food as opposed to supplements (15).

**5.4.3. Lutein.** Lutein is a carotenoid synthesized only by plants; it is found in high quantities in green leafy vegetables such as spinach and kale. In humans, it is concentrated in the macula, a small area of the retina responsible for central vision, where it is thought to keep the eyes safe from oxidative stress. Several studies have shown that an increase in macular pigmentation decreases the risk of eye diseases such as age-related macular degeneration (162), and some studies support the view that supplemental lutein helps protect against age-related macular degeneration (166).

**5.4.4. Vitamin E (tocotrienols).** α-Tocopherol is the most biologically active form of vitamin E. It is a fat-soluble antioxidant that limits the activity of reactive oxygen species formed when fat undergoes oxidation (77, 141). The mechanisms of action of vitamin E are not well understood, but it has been classified as a lipid-soluble antioxidant protecting against LDL and PUFA oxidation. Vitamin E deficiency is seen only under severe malnutrition and in humans with genetic disorders affecting α-tocopherol transport or lipid absorption from the diet. However, suboptimal levels of vitamin E are associated with CVD (70) and some cancers (88). The dietary reference intake is 15 mg per day, but only a minority of people achieve these levels, even in developed countries (67).

### 5.5. Plant Sterols

The principal plant sterols are β-sitosterol, campesterol, and stigmasterol, and only relatively low levels of cholesterol accumulate in plants. Dietary phytosterols can reduce cholesterol levels in the blood by competing for uptake mechanisms in the gut (93). Their action is complementary to that of anticholesterol statins (139), and clinical trials indicate that a daily intake of 0.8 g leads to a significant reduction in LDL and total cholesterol in the blood (135, 187). There is also evidence that phytosterols protect against certain cancers, notably breast and prostate cancers (9).

Most Western diets contain relatively low levels of phytosterols (typically 150–450 mg per day) compared with more traditional plant-based diets (more than 1 g per day; 91). Some vegetables contain high levels of sterols; for example, broccoli contains 367–390 mg per gram fresh weight, carrot contains 153–160 mg per gram fresh weight, and cauliflower contains 310–400 mg per gram fresh weight.

## 6. IMPACT OF THE FOOD MATRIX

Many health-benefit studies have been confounded because purified phytochemicals fail to have the same effects as they do in food (47, 56, 120, 121, 149, 180). Three explanations can be offered for these observations:

1. Bioactives may function in cooperation with other food components, giving rise to synergistic effects on animal physiology that are observed only in a whole-food context.
2. The food matrix may significantly impact bioavailability. As an example, carotenoid emulsification and micellization steps, important for their absorption through the gastrointestinal tract, are hugely affected by the food matrix and other dietary components. Carotenoids are more easily absorbed from food if the food matrix contains fat (203).
3. Supplements allow the consumption of very high levels of phytonutrients, which may reach toxic levels (100, 118). For example, one study in which human subjects took daily 500-mg supplements of vitamin C showed that rather than protecting against oxidative stress, this overconsumption caused the vitamin C to act as a pro-oxidant in vivo (148).

Recently, the concept of food synergy has been proposed to help people consume healthy compounds in a safe and efficient way (85–87, 120). One of the best examples of food synergy is the recent recommendation to consume whole-grain cereals (170). Research indicates that there are large health benefits from compounds present in cereal bran and germ, which are normally removed during processing, and that there is a direct correlation between whole-grain dietary patterns and lower risk of chronic diseases (8, 36, 170).

## 7. PHYTONUTRIENT MECHANISMS OF ACTION AGAINST CHRONIC DISEASES

Food is a complex system impacted by multiple factors that collectively influence our metabolism, physiology, and health. The absorption of different phytonutrients varies across the different compartments of the gastrointestinal tract. Most phytonutrients are subject to metabolism by the enzymes of the gastrointestinal tract and by the gut microbiota, and are usually metabolized further once absorbed.

### 7.1. Phytonutrient Impacts on Signaling and Metabolic Pathways

Phytonutrients may have beneficial effects on health by modulating cell signaling and thereby impacting the activity of metabolic pathways and bioenergetic regulation. Such effects may be general, such as the effects of dietary antioxidants on redox status; specific to particular

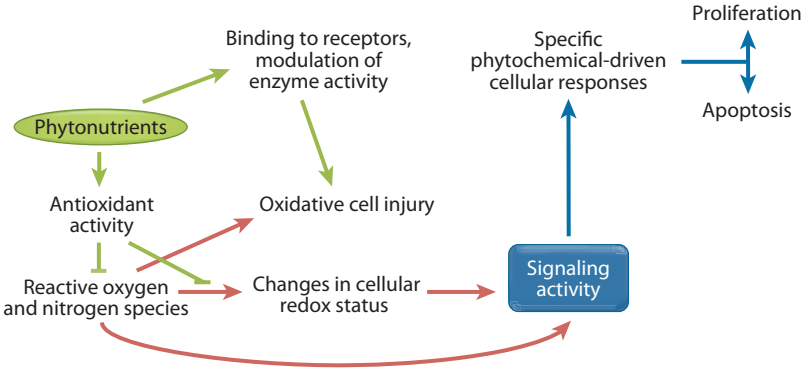


**Figure 2**

Influence of phytonutrients on cell signaling. Phytonutrients interact with cell signaling through mechanisms independent of their antioxidant properties, by directly affecting the activities of a wide spectrum of cellular targets, including key enzymes, membranes, and nuclear receptors. Adapted from Reference 190.



phytonutrients; or a combination of both general and specific effects.

**7.1.1. Influence on cellular redox status.** Reactive oxygen and nitrogen species are considered major determinants of many degenerative pathologies, including CVD, certain cancers, neurodegenerative diseases, chronic inflammation, and tissue aging (34, 186). Essentially, these molecules can act by damaging biological structures and molecules, but can also influence cell signaling either indirectly (by changing the redox cellular status) or directly (by participating in intracellular signaling) (190). Although the antioxidant properties of phytonutrients have been a major focus of research, there is an emerging view that they may act not only by scavenging reactive oxygen and nitrogen species or suppressing their production but also by enhancing the endogenous antioxidant capacity of cells/tissues (e.g., glutathione synthesis) or by influencing signaling pathways through interaction with proteins, enzymes, and nuclear receptors (**Figure 2**) (190).

Red wine contains varying levels of resveratrol, flavonols, anthocyanins, and catechins (EGCG), which are all effective antioxidants. However, the cardioprotection afforded by these polyphenols is likely the result of multiple biological activities independent of their antioxidant activities, including improvement of endothelial function, reduction in LDL uptake, reduction in LDL oxidation and aggregation, reduction of blood pressure, and inhibition of platelet aggregation (17). Interestingly, dietary polyphenols have been suggested to prevent LDL oxidation by direct binding to oxidizable sites in LDLs (194).

**7.1.2. Chemopreventive signaling.** The chemopreventive activity of phytonutrients has been suggested to be associated with the ability to block the progression of latent tumors through four different mechanisms (13):

1. Some phytonutrients modulate enzymes that detoxify carcinogens or proteins that export them from cells (37, 178).
2. Other phytonutrients, such as isothiocyanates from cruciferous plants, curcumin from turmeric, and resveratrol from grapes, directly induce or indirectly promote apoptosis and cell death of tumor cells (89, 95, 96).
3. Some phytonutrients inhibit the vascularization of microtumors by blocking the vascular endothelial growth factor 2 receptor (for example, EGCG from green tea) and the platelet-derived growth factor receptor (for example, ellagic acid from raspberry and strawberry and delphinidin from blueberry) (105–107).

4. Other phytonutrients, such as EGCG, curcumin, and resveratrol, reduce inflammation by inhibiting cyclooxygenase 2 (2, 177).

Other phytonutrients, known as phytoestrogens, interact with the estrogen receptors (ERα and ERβ). Isoflavonoids (daidzein, genistein, and equol) and other polyphenols (such as resveratrol) interact with ERs and regulate estrogen-responsive genes (126, 164). In general, phytoestrogens can act as estrogen agonists, mimicking estrogen effects in the bone, brain, and cardiomyocytes and thus protecting against osteoporosis, neurodegeneration, and CVD, or they can act as estrogen antagonists in other tissues, like breast and uterus tissues, thereby preventing breast and endometrial cancers (18). The interaction of isoflavonoids with ERs may thus explain the significantly lower incidence of steroid hormone–responsive cancers (25% lower incidence of prostate cancer and 10% lower incidence of breast cancer) in Asian communities that consume large amounts of soy products, which are rich in genistein and daidzein isoflavones. The protective effects of isoflavones against breast cancer are also associated with the downregulation of the oncogenic Wnt-signaling pathway, which occurs coincidently with increased apoptosis, enhanced differentiation, and lower tumor invasiveness (43). An alternate mechanism by which phytoestrogens may prevent breast cancer is by inhibiting the activity of enzymes involved in estrogen synthesis (for example, aromatase) in breast tissue (160, 171).

Recent studies have established that people suffering from Laron syndrome do not develop cancer, type 2 diabetes, or acne (72, 176). Laron syndrome involves congenital dwarfism resulting from a mutation in the growth hormone receptor. This impairs insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS), and it is thought that IIS promotes chronic diseases such as type 2 diabetes and cancer in later adult life. IIS declines as people get older, but consumption of a Western diet promotes IIS, which may underpin the positive effects of these diets on chronic diseases like type 2 diabetes and epithelial cell cancers (130). Diets that reduce IIS—such as Paleolithic diets, which were rich in fruits and vegetables and low in foods that stimulate IIS, such as milk and dairy—may promote health in later life (66, 130).

**7.1.3. Modulation of energy metabolism.** Polyphenols have been shown to modulate energy metabolism and consequently reduce insulin resistance, type 2 diabetes, and metabolic syndrome (74). AMP-activated protein kinase (AMPK) is an evolutionarily conserved sensor of cellular energy (99). Low energy stores determined by caloric restriction increase the AMP/ATP ratio and activate AMPK activity, which in turn activate sirtuin 1 (SIRT1), a class III histone deacetylase (HDAC), and influence glucose/lipid metabolism and age-related diseases (179). Therefore, activation of AMPK has been proposed as a strategy for treating metabolic syndrome and delaying aging (41).

Recent studies have demonstrated that many dietary polyphenols can act as mimics of caloric restriction and activate AMPK, thus suppressing hepatic gluconeogenesis, inducing hepatic fatty-acid β-oxidation, and stimulating glucose transporters in muscle and adipose tissues, with an overall reduction of the glucose level in the blood and the lipid content of the liver as well as an improvement in insulin sensitivity (74, 83). Some polyphenols (e.g., resveratrol, quercetin, and anthocyanins) also extend life span in different species (12). Resveratrol directly inhibits cAMP-degrading phosphodiesterases, leading to an increase in cAMP and subsequent activation of AMPK (144).

## 7.2. Effects on n-3 PUFA Metabolism

Preclinical studies with an infarction/reperfusion animal model have shown that dietary anthocyanins are cardioprotective (182). Comparison of the plasma of animals fed high- or low-anthocyanin diets showed elevated levels of n-3 PUFAs in animals on the high-anthocyanin diet (41% EPA and 16% DHA). The differing EPA and DHA increases

suggest that dietary anthocyanins may alter endogenous PUFA metabolism by promoting the conversion of α-linolenic acid present in corn into the n-3 PUFAs, EPA, and DHA (183). Recent epidemiological studies have shown that EPA and DHA levels are elevated in the blood and cells of red wine drinkers and that components of red wine other than alcohol, probably flavonoids, are responsible for this difference (49, 50).

Considering that a high n-3:n-6 PUFA ratio is known to prevent not only CVD but also other chronic diseases, such as diabetes, cancer, and neurodegenerative diseases, the diverse effects of anthocyanins on different chronic diseases (23, 180, 182, 188) may result primarily from their modulation of plasma n-3 PUFA levels.

## 7.3. Effects on the Gut Microbiome

Each part of the gastrointestinal tract has a different microbiome and differs between individuals. However, in healthy adult individuals, the taxonomic composition of the microbiome at most anatomical sites is stable over time. The exceptions are differences in microbial composition in the stomach with and without the presence of *Helicobacter pylori* following dietary changes or during aging (30).

The human gut microbiome is subject to major changes in early life and is established by the age of three (202). It can be considered a metabolic "organ" that processes indigestible components of the diet, such as plant polysaccharides. It is dominated by anaerobic bacteria belonging to three major phyla: in order of prevalence, Bacteroidetes, Firmicutes, and Actinobacteria (7). Based on the most prevalent Bacteroidetes genera, humans are divided in two enterotypes. The *Bacteroides* enterotype is prevalent in US individuals, associated with high levels of protein and saturated fat (meat) in the diet, and characterized by activities involved in the degradation of glutamine and other amino acids and in the catabolism of simple sugars. The *Prevotella* enterotype is prevalent in Malawians and Amerindians, associated with high levels of carbohydrates and simple sugars in the diet, and characterized by genes encoding glutamate synthase (typical of herbivorous mammals) and α-amylase for starch degradation (202).

Variant microbial populations occur in specific disease states and change over the course of a disease or with dietary change. Studies in germ-free mouse models have revealed that the microbiome is essential for using plant polysaccharides as energy sources and for promoting the storage of triglycerides (10). Obesity is associated with a 50% reduction in the abundance of Bacteroidetes and an equivalent increase in Firmicutes, especially Mollicutes. This change can be induced by a Western diet and is correlated with an increased capacity for energy harvest (112, 184). Firmicutes (i.e., Mollicutes) is also increased in obese human subjects and reduced on carbohydrate- or fat-restricted low-calorie diets (112).

These findings have supported a drive to identify phytonutrients that influence the composition of the gut microbiome for beneficial effects on host energy metabolism (prebiotics). Several chronic diseases, such as cancer, inflammatory bowel disease, psoriasis, asthma, and possibly autism, are associated with changes in the microbiota of the gastrointestinal tract (40, 146). Beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* contribute to human health at different levels by enhancing the gut barrier function, stimulating host immune function, preventing diarrhea or allergies, activating provitamins, and modulating lipid metabolism (80). Other bacteria, such as *Clostridium difficile*, are associated with inflammatory bowel disease (155). One promising compound is berberine, the major component of the Chinese herb *Coptis chinensis*. Some dietary polyphenols have antimicrobial or bacteriostatic activities whereas others have prebiotic activity because they promote the growth of beneficial bacteria and inhibit the growth of pathogens. Anthocyanins and their gut metabolites enhance the growth of *Bifidobacterium* and *Lactobacillus* (78). Consumption of red wine or pomegranate polyphenols promotes *Bifidobacterium* in the

microbiome and has been demonstrated to reduce inflammatory markers and improve lipid profiles (138, 151).

## 7.4. Epigenetic Effects

Epigenetic phenomena involve differential gene expression and phenotypes between individuals, without changes in DNA sequence. Epigenetic phenomena result from DNA methylation, histone modifications (methylation, acetylation, phosphorylation, etc.), and posttranscriptional gene regulation by noncoding RNAs. Epigenetic changes can be modulated by environmental factors, including diet, most notably during fetal and neonatal development but also in adults (92).

The epigenome is most susceptible to diet during fetal development, because early embryogenesis in mammals is the most critical period for its establishment. During gametogenesis, parental genomes undergo a demethylation and remethylation cycle, which is thought to erase previous paternal imprints and reestablish sex-specific imprints. Between fertilization and implantation, the zygote genome is widely demethylated (except imprinted genes) to restore the totipotency of the fertilized egg, and then remethylated at implantation to allow the establishment of different cell lineages (156).

The influence of maternal diet on epigenome establishment during fetal development and on the health status of offspring has been demonstrated using the agouti viable yellow ($A^{vy}$) mouse. The *Agouti* wild-type gene encodes a signaling molecule that is transiently expressed in hair follicles, where it promotes melanocytes to produce yellow pheomelanin instead of black eumelanin, thus resulting in the agouti fur color. The $A^{vy}$ allele is a metastable allele caused by insertion of the IAP retrotransposon upstream of the *Agouti* gene, which determines a constitutive and ectopic expression of *Agouti*, resulting in yellow fur, obesity, and tumorigenesis (134). Ectopic *Agouti* expression is inversely correlated with the methylation level of CpG sites present in IAP, with isogenic $A^{vy}/a$ mice showing wide variation in coat color, ranging from yellow (unmethylated) to pseudoagouti (fully methylated). When ectopically expressed, Agouti binds the melanocortin 4 receptor in the hypothalamus and antagonizes the satiety signaling cascade, thus leading to obesity in $A^{vy}$ mice owing to hyperphagia. Maternal dietary supplementation with folate, vitamin $B_{12}$, choline, and betaine shifts the coat color distribution of the offspring toward the pseudoagouti phenotype, which results from increased methylation of CpG sites in IAP (195) and prevents the transgenerational amplification of obesity observed in $A^{vy}$ mice (196). A similar change in DNA methylation of IAP, coat color, and obesity has been obtained with dietary genistein supplementation (52).

An example of human DNA methylation being affected by nutrition occurred during the Dutch famine. By the end of the Second World War, the Dutch population was exposed to famine for five months owing to limited food supply. Individuals whose mothers were exposed to famine during early gestation showed a greater weight and length at birth and a higher risk of diabetes, CVD, and obesity once they reached 50–60 years old (143). DNA methylation of *IGF-2*, a maternally imprinted gene, was lower in individuals periconceptionally exposed to famine compared with those exposed late in gestation, and this was correlated with higher birth weight and length (143). DNA methylation was increased for other genes involved in satiety signaling, cholesterol transport, and HDL formation, thus linking early nutrition to adult metabolic diseases (181).

Recent studies in rats have suggested that diet also influences the epigenome during neonatal development, because neonatal overfeeding of rats increases methylation of the hypothalamic insulin receptor promoter, thus advancing the onset of metabolic syndrome and obesity (147). Studies of monozygotic twins have indicated that whereas 3-year-old twin pairs are epigenetically very similar, 50-year-old twin pairs—particularly those who were separated early and lived in different environments—have major differences in

global DNA methylation, histone acetylation, and gene expression, indicating that changes in the epigenome can also occur throughout life (62). Such differences may also result from differences in diet, as shown by long-term feeding experiments in isogenic animal models under different dietary regimes (191).

DNA methylation is affected by diet in essentially three ways (**Figure 3**): (*a*) Methyl donors acquired through the diet (i.e., folate, choline, betaine, and methionine) enter into one-carbon metabolism and are important precursors for the synthesis of *S*-adenosylmethionine (SAM), the universal methyl donor for both DNA and protein methyltransferases; (*b*) vitamins $B_6$ and $B_{12}$ (from plants) are essential cofactors for two enzymes of one-carbon metabolism; and (*c*) phytonutrients, mainly polyphenols, directly or indirectly inhibit DNA methyltransferases (DNMTs). Some polyphenols, such as EGCG and curcumin, have been shown to directly inhibit DNMT1 by covalent binding within its catalytic pocket (**Figure 3*b***) (109, 122). Other polyphenols with a catechol group, such as coffee polyphenols (chlorogenic acid and caffeic acid) and green tea polyphenols (catechins, epicatechin, and EGCG), are methylated by catechol-*O*-methyltransferase using SAM as methyl donor, thus releasing *S*-adenosylhomocysteine (SAH), which is a potent feedback inhibitor of DNMT (110, 111). The dual inhibitory mechanism of EGCG may explain its potent demethylating activity and chemopreventive properties against breast cancer, prostate cancer, and other tumors (109, 110). Treatment of different types of cancer cell lines with EGCG has been associated with demethylation and consequent reactivation of tumor suppressor genes (60, 109, 123).

Histone methylation is controlled by the opposing activities of histone methyltransferases and histone demethylases and may be influenced by dietary methyl donors through SAM availability (**Figure 3*a***). Histone acetylation can be influenced by phytonutrients through their modulation of the activity of three groups of enzymes (116, 175): histone acetyltransferases (HATs), class I and II HDACs, and class III HDACs (sirtuins). Several studies have revealed that many phytonutrients affect both DNA methylation and histone modification as well as microRNA expression (**Figure 3*b***) (92, 116, 175). Among phytonutrients, EGCG is a potent inhibitor of different HAT enzymes (31). Changes in DNA methylation caused by genistein are associated with increases in histone acetylation and HAT activity in renal and prostate cancers (165). Other studies have shown that genistein causes a decrease in HDAC activity in renal and esophageal cancer cells (59, 165). HAT activation and HDAC inhibition by genistein are associated with activation of tumor suppressor genes (*p21*, *p16*, *FOXA3*, and *PTEN*) and inhibition of oncogenes (*bTERT*) (116). Curcumin is an inhibitor of both p300 HAT and several HDACs, suppressing proliferation and inducing apoptosis of cancer cells (29, 119). Resveratrol and quercetin are both activators of SIRT1 (a class III HDAC), which deacetylates several proteins, including histones (32). Sirtuins influence aging, apoptosis, and energy efficiency, and through these functionalities their activities may impact the risk of chronic disease.

## 8. CONCLUSIONS

Scientific evidence strongly supports the idea that adopting Paleolithic diets could significantly reduce the risk of chronic disease. However, wide-scale adoption of these diets would be impractical for reasons of cost, sustainability, and time spent eating (90). However, it should be possible to reduce the risk of a significant proportion of chronic disease by encouraging diets that encompass more of the good things from Paleolithic diets, particularly increased consumption of fruits and vegetables, reduced consumption of meats (particularly high-fat meats) and saturated fats, significantly reduced amounts of added sugars (particularly high-fructose corn syrup), and elimination of trans fats. These recommendations are central to the guidelines of the American Cancer Society on nutrition for cancer prevention (104) and

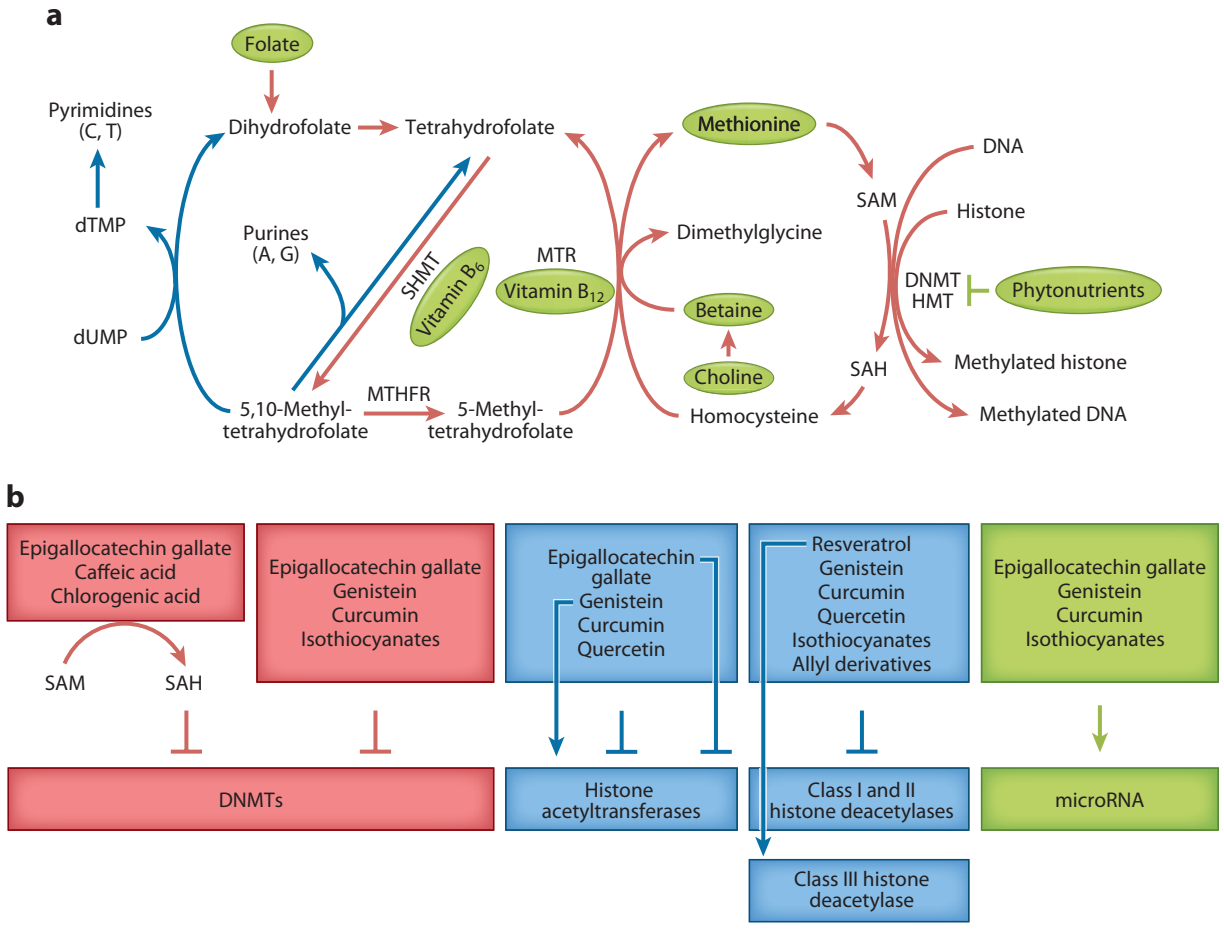


**Figure 3**

Phytonutrient mechanisms of action. (*a*) One-carbon metabolism and its implications for nucleotide synthesis (*blue arrows*) and DNA/histone methylation (*red arrows*). Methyl donors, cofactors, and phytonutrients acquired through the diet are highlighted with green ovals. (*b*) Epigenetic modifications mediated by phytonutrients. Enzyme abbreviations: DNMT, DNA methyltransferase; HMT, histone methyltransferase; MTHFR, methylenetetrahydrofolate reductase; MTR, 5-methyltetrahydrofolate-homocysteine methyltransferase; SHMT, serine hydroxymethyltransferase. Metabolite abbreviations: SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine.

are consistent with those of the American Heart Association (113) and the American Diabetes Association (11). To accomplish these objectives, societies need to ensure greater access to fruits and vegetables at reasonable prices.

Government policies could be directed more toward supporting the crops that should form a greater part of our diet. However, US data show far greater expenditures on meat and dairy and the crops used to feed animals than on cultivation of fruits and vegetables. Similarly, consumption of the phytonutrients that promote health and protect against chronic disease might be encouraged if more research were invested in improving the phytonutrient content of fruits and vegetables, improving our understanding of their mechanisms of action (127) and improving their taste and attractiveness to consumers so that they can compete more effectively with the junk processed foods that are underpinning the global obesity epidemic and the rising incidence of chronic disease.

## DISCLOSURE STATEMENT

C.M. is a director of Norfolk Plant Sciences, an SME for the development of phytonutrient-enriched fruits and vegetables.

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**Errata**

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