

Review

From Foods to Chemotherapeutics: The Antioxidant Potential of Dietary Phytochemicals

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Abstract: Food plants have been recognized for their medicinal properties for millennia, a concept supported by epidemiological studies indicating long-term health benefits for people consuming greater amounts of fruits and vegetables. As our technology and instrumentation advance, researchers have the ability to identify promising phytochemicals, and examine their potential benefits, or detriments, to human health. While results from trials investigating single chemical supplementation have sometimes produced negative health results, studies investigating the synergistic action of phytochemicals—either within our diet or as an adjuvant to radiation or chemotherapy—appear promising. Utilizing phytochemicals as synergistic agents may lower the chemotherapeutic doses needed to incur physiological results, while also using chemicals with fewer toxic effects. This review investigates a variety of plant-produced chemicals humans typically ingest, their impacts on overall health patterns, molecular mechanisms associated with their health impacts, and the potential of their synergistic use for therapeutic purposes.

Keywords: phytochemicals; synergism; antioxidant; chemotherapeutic; adjuvant; dietary prevention; bioavailability; nonenzymatic exogenous antioxidants



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1. Introduction

Defining a plant as “medicinal” encompasses a spectrum of potential interactions between a plant’s phytochemicals (here broadly defined as a plant-produced compound) and the organisms exposed to them. The term “medicinal plant” obviously includes those plants whose phytochemicals are extracted, purified, and used as pharmaceuticals, such as vincristine from the Madagascar periwinkle, *Catharanthus roseus*, or digoxin made by foxglove, *Digitalis purpurea*. The term “medicinal plant” also includes preparations of whole plants or plant parts that are sold as dietary supplements, such as pycnogenol from French Maritime Pine bark, or resveratrol. However, one can also argue that the concept of a “medicinal plant” extends to health benefits provided by plants that are a part of a normal diet. Indeed, much recent work has focused on investigating the chemoprotective and chemotherapeutic value of food-based phytochemicals [1,2].

Investigations of all-cause mortality and the likelihood of developing chronic illnesses clearly indicate that populations consuming plant-based diets (e.g., vegetarians) are less likely to develop chronic diseases such as cardiovascular disease (CVD) [3], type 2 diabetes [4], and ischemic heart disease-related mortality [5]. Meta-analyses also indicate people consuming diets high in fruits, vegetables, or combined fruits plus vegetables, are less likely to develop CVD or cancer, and they have lower all-cause mortality risk. These reduced risks were seen for consuming amounts up to 600 g fruits and vegetables/day for cancer, and 800 g/day for CVD [6]. Investigations of food–plant chemistry were also spurred by epidemiological studies that identified dietary patterns high in fruits, vegetables, legumes, wine, nuts, seeds, and olive oil (e.g., Mediterranean Diet) as protection against the development of chronic diseases. These chemical investigations led to continuing research into the health benefits of phytochemicals such as resveratrol, quercetin, curcumin, and epigallocatechin-3-gallate; although, these studies have had equivocal results, perhaps due

to factors such as dose, bioavailability, and participant health [7]. It is also important to note that while absorbed phytochemicals may benefit human health due to their ability to directly interact with cellular biochemistry, there is ample evidence that phytochemicals can also be metabolized by our gut microbiome. The metabolites resulting from these microbe–phytochemical interactions can also be absorbed/physiologically active within our cells [8,9]. These phytochemicals and their metabolites are often beneficial, at least in part, due to their antioxidant function (Figure 1) [10].

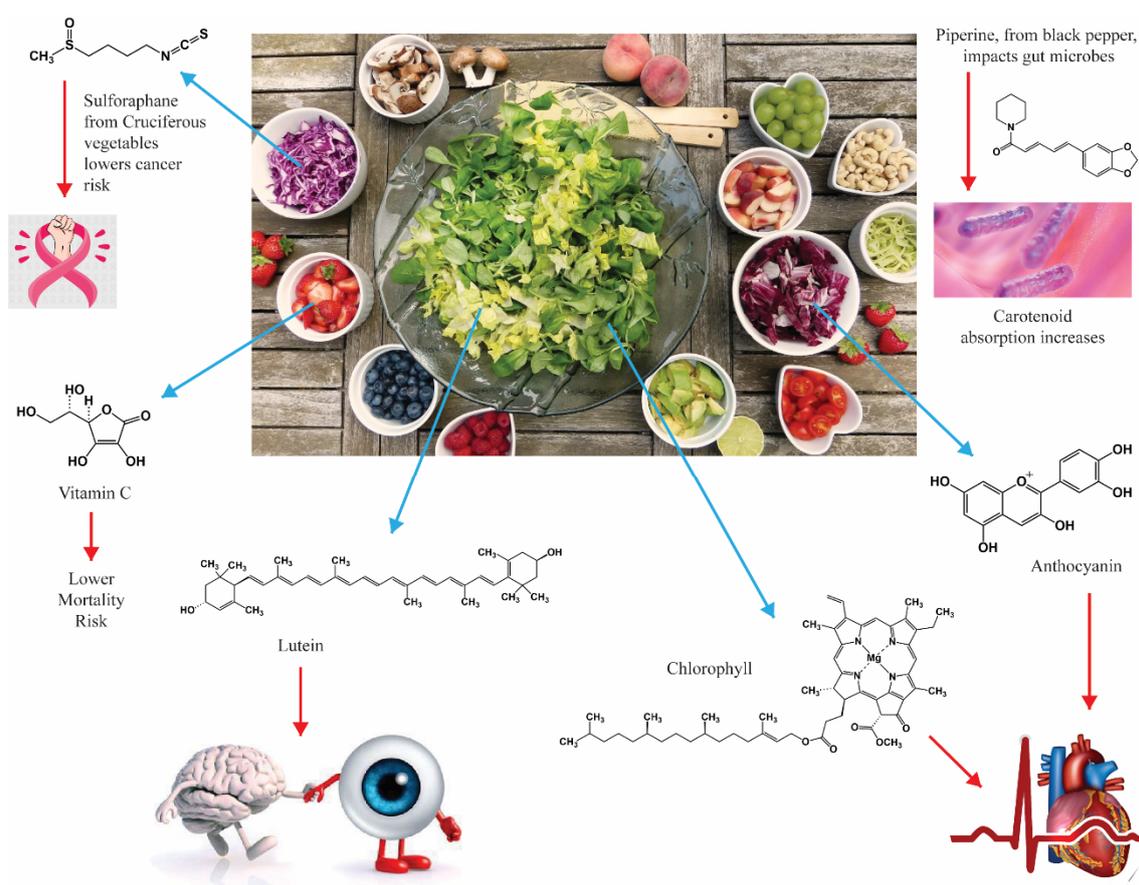


Figure 1. Various phytochemicals and known health benefits.

There are many factors, other than direct antioxidant abilities, contributing to the health benefits of consuming more plant-based foods. Higher ingestion of fiber [11], decreased ingestion of saturated animal fats and higher ingestion of plant-based polyunsaturated fatty acids [12], and greater magnesium ingestion [13] all benefit cardiovascular health. However, evidence supporting the beneficial impacts of phytochemicals obtained from consuming a variety of darkly colored or strongly flavored fruits and vegetables continues to accumulate. A study that replicated three different DASH-based (Dietary Approaches to Stop Hypertension) diets using varying combinations of carbohydrates, protein, lipids, fiber, minerals, and vitamins, but lacking in phytochemicals typical of a high fruit/vegetable diet, was unsuccessful in reducing blood pressure in hypertensive rats [14]. However, when hypertensive rats were fed grape phytochemicals at biologically relevant levels along with a high salt diet, the added grape was successful at lowering blood pressure and improving cardiac function, as compared to a high salt diet alone [15]. Adding grape also reduced cardiac hypertrophy and fibrosis, improved diastolic function, and had far-reaching impacts on the cardiac antioxidant transcriptome [16].

A single serving of a fruit or vegetable may contain hundreds of individual phytochemicals that will interact in our gut and, if the original compounds or their metabolites

are absorbed, interact within our cells. Pomegranates, for example, reportedly contain 153 different phytochemicals [17]. These phytochemical interactions are further compounded by consuming the recommended 5 to 10 servings of fruits and vegetables that include a rainbow of colors. When a variety of phytochemicals interact with different aspects of cellular metabolism or gene expression, it is possible for one chemical to enhance, or even suppress, the action of the other. When, for example, the antioxidant activity of two chemicals is monitored both separately and combined, the results could indicate the antioxidant potential of the combined chemicals is less than one would expect from adding the results of the compounds when tested separately. This indicates an antagonistic effect of those chemicals. If the antioxidant potential of the chemicals tested separately was equal to the antioxidant potential when combined, their impact would be additive. However, the impact of adding different chemicals together might also be synergistic. In this case, the antioxidant potential of each when measured separately is less than their antioxidant ability when combined [18].

This paper explores the health impacts of consuming food-based phytochemicals. The antioxidant potential of various phytochemicals, from photosynthetic pigments such as chlorophyll and carotenoids, to plant-based vitamins, and the health-enhancing impacts of other food-borne phytochemicals are also discussed. Protective mechanisms of these phytochemicals at the cellular level are reviewed, and, from food to their use as chemotherapeutic agents, what we are beginning to understand about their synergism is discussed.

2. Oxidants and Endogenous Antioxidants

In order to survive the rigors of an oxidizing environment, all living organisms must either mitigate or repair the damage caused by high concentrations of reactive species, such as oxidants and free radicals. Oxidants are substances that can accept one or more electrons from other substances, while radicals are species that possess an odd number of electrons. Radicals are highly reactive as one of the atoms has an incomplete valence shell of electrons. As the radical seeks a mate for its unpaired electron, it can trigger chain reactions within cells, causing damage to DNA, proteins, lipids, and carbohydrates [19], the molecules that create both the form and function of our cells. Although radicals are not necessarily oxidants, both radicals and oxidants are involved in oxidative stress related to chronic disease [20]. Two biologically important classes of oxidants and radicals are the reactive oxygen species (ROS) and reactive nitrogen species (RNS).

At low concentrations, ROS and RNS can actually benefit cellular health, for example by assisting immune function. Neutrophils, for example, produce a variety of ROS such as superoxide and hydrogen peroxide after they engulf invading microorganisms [21]. Another radical, nitric oxide, is known for its ability to relax endothelial tissue, thus lowering blood pressure; nitric oxide also acts as a messenger in a wide range of cellular functions [22]. However, if ROS and/or RNS reach high concentrations, the body experiences Oxidative Stress [23]. In those situations, our endogenous defense mechanisms against ROS/RNS can actually be involved in the etiology of inflammatory diseases [24], such as cancer [25], heart disease [26,27], and neurodegenerative diseases [28,29]. Within our cells, ROS/RNS arise from a variety of metabolic sources. Major endogenous sources of ROS include the transmembrane NADPH oxidases and the mitochondrial electron transport chain, systems that both produce superoxide [30]. Therefore, cells with greater metabolic rates, including cancer cells, typically produce higher ROS levels. RNS can be produced by the same pathways as ROS; ROS and RNS are also known to interconvert [31]. Exogenous triggers that increase cellular ROS and RNS production include UV radiation, heterocyclic amines, chlorinated compounds, and heavy metals [32,33].

To protect their cells against high levels of ROS and RNS, organisms produce a variety of enzymes and chemicals that act as antioxidants. Antioxidants have been identified in cyanobacteria, probiotic bacteria [34], fungi [35], animals, and plants. Even within organisms classed as obligate anaerobes, 93 of 100 species tested contained at least one enzyme-based antioxidant [36]. Enzymatic antioxidants produced by animal cells to neu-

tralize ROS/RNS include superoxide dismutase, considered the most powerful cellular antioxidant [37], glutathione peroxidase, glutathione reductase, and catalase. These enzymes function in pathways that first convert superoxide (O_2^-) to hydrogen peroxide (via superoxide dismutase), and then breakdown hydrogen peroxide into water and oxygen (via catalase and glutathione peroxidase) [38]. It also appears that many enzymatic antioxidants can regulate redox signaling pathways [39].

Plants, similar to animals, have a variety of enzymatic and non-enzymatic methods they use to reduce the impact of ROS/RNS attacks. Plant compounds that function as non-enzymatic antioxidants include α -tocopherol, ascorbic acid, carotenoids, some alkaloids [40], and polyphenolic compounds such as flavonoids, anthocyanins, and tannins [41]. Flavonoids typically function as antioxidants by scavenging and destroying ROS/RNS, while carotenoids and anthocyanins function as chemical traps to absorb light energy and quench ROS/RNS [42]. Therefore, in addition to an animal's endogenous antioxidants, organisms that consume plant materials, including fruits, vegetables, herbs, and spices, could possibly absorb and utilize these non-enzymatic plant antioxidants as additional ROS/RNS protection.

Animal-produced non-enzymatic antioxidants include organosulfur compounds such as reduced glutathione (GSH); lipoic acid; the dipeptide carnosine; melatonin; bilirubin, a compound resulting from the breakdown of heme; uric acid, a compound derived from purine metabolism that increases as fructose consumption increases [43,44] and coenzyme Q [31]. Other non-enzymatic antioxidants are multi-functional plasma proteins that have the ability to bind and therefore inactivate iron and copper, including albumin, transferrin, ferritin, and ceruloplasmin [45]. Blood serum levels indicate the main human non-enzymatic antioxidants are often absorbed from food sources; these include uric acid, thiol-containing compounds (containing -RSH), ascorbic acid, and vitamin E [46].

3. Our Exogenous Antioxidants: Vitamin C/Ascorbic Acid

Despite their endogenous antioxidants, it is evident that many animal species benefit by consuming additional antioxidants. Humans, for example, must ingest the antioxidant vitamins C and E; the richest sources of these vitamins are plant sources. If we view a balanced diet as the first defense against disease states, it should be noted that globally, vitamin C deficiency is still a problem [47].

Within plants, ascorbic acid (vitamin C) has multiple metabolic roles, acting in a variety of pathways involved with photosynthesis, cell division, ethylene production, as well as acting as an antioxidant [48]. In humans, vitamin C helps activate enzymes requiring iron or copper as cofactors by keeping these metal cofactors in the reduced, or active, state [49]. Examples of these vitamin C-dependent enzymes include those involved in collagen synthesis and carnitine biosynthesis. Copper-containing enzymes such as those responsible for synthesizing noradrenalin and amidated neuropeptides also require vitamin C, thus impacting mood and stress response [50]. It is important to note that those reactions involving metal cofactors can actually lead to the formation of superoxide and hydrogen peroxide; thus, vitamin C can also function as a pro-oxidant [51,52]. Ascorbate also maintains the active Fe^{2+} state within 2-oxoglutarate-dependent dioxygenases [53], enzymes that influence the demethylation of both DNA and histones, giving vitamin C a role in epigenetics [54].

3.1. Dietary and Supplemental Vitamin C and Health

Randomized controlled trials (RCT's) investigating dietary supplementation with vitamin C do not offer clear evidence of its health benefits. Meta-analyses indicate vitamin C had no association with cancer prevention (Table 1) [55], and no whole-group impacts on several markers of cardiovascular disease (e.g., arterial stiffness, insulin concentration, total cholesterol, or HDL cholesterol) (Table 1) [56]. Interestingly, cardiovascular improvements were observed in a subgrouping of high BMI (body mass index) individuals receiving vitamin C supplementation [56].

Table 1. Parameters and pertinent results from cited studies examining health outcomes associated with vitamin C. RR = Relative risk, CVD = cardiovascular disease.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
Vitamin C	Cancer. (RR 1.00; 95%CI 0.95, 1.05). Subgroup meta-analysis by dose or type of cancer also showed vitamin C supplementation did not effectively prevent cancer.	Supplementation; meta-analysis of seven randomized controlled trials investigating vitamin C's impact on cancer prevention; 62,619 individuals.	[55]
Vitamin C	CVD. Unconvincing evidence that vitamin C supplementation improved CVD risk markers; however, there was weakly significant evidence that vitamin C supplementation improved CVD biomarkers in the elderly, obese, those with low baseline vitamin C status, and those with higher CVD risk.	Supplementation; umbrella review of ten systematic reviews and meta-analyses; 6409 participants.	[56]
Vitamin C	All-cause mortality. Comparison of highest vs. lowest subgroupings based on dietary vitamin C intake RR 0.88 (95%CI 0.83, 0.94); response was U-shaped with higher levels less protective. Comparison of highest vs. lowest subgroupings based on circulating plasma levels of vitamin C, RR 0.61 (95%CI 0.53, 0.69); this response was linear, with higher blood levels being more protective.	Meta-analysis of 41 prospective observational studies including 507,251 participants and 73,965 cases of all-cause mortality.	[57]
Vitamin C	All-cause mortality, total cancer, CVD. Per 100 mg/d increment of dietary vitamin C intake, all-cause mortality (RR 0.89, 95%CI 0.85, 0.94), total cancer (RR 0.93, 95%CI 0.87, 0.99), and CVD (RR 0.89, 95%CI 0.85, 0.94) all had reduced risk. For measures of blood concentrations: Per 50 $\mu\text{mol/L}$ increase in vitamin C, all-cause mortality (RR 0.72, 95%CI 0.66, 0.79), total cancer (RR 0.74, 95%CI 0.66, 0.82), and CVD (RR 0.76, 95%CI 0.65, 0.87) all had lowered risk.	Meta-analysis included 69 prospective cohort studies from Europe, America, and Asia.	[58]

Although RCT's examining vitamin C supplementation often found no significant health benefits, prospective studies examining blood serum levels of ascorbic acid and/or total dietary intake found high levels of vitamin C were protective in nature. The long-term health impacts of dietary suggest those with higher dietary intakes had a 12% lower mortality risk (Table 1). More importantly, subjects with higher plasma levels had a 39% lower mortality risk [57] (Table 1). Aune et al.'s [58] meta-analysis found similar results. For both dietary intakes and circulating plasma levels of vitamin C, there were lower risks for all-cause mortality, as well as total cancer and cardiovascular disease (Table 1).

It is important to note that because prospective studies look for patterns, results are associative in nature (e.g., someone consuming higher amounts of vitamin C-rich foods may also practice other beneficial lifestyle patterns). Micek et al. [59] illustrate the importance of viewing prospective studies in the context of a healthy lifestyle in their meta-analysis of health risk factors associated with flavonoid intake in cohort studies. While it is easy to explain how flavonoid intake could be inversely associated with both BMI and saturated fat intake, while also being positively associated with folate, fiber, and β -carotene, their study also found that total flavonoid intake was inversely associated with current smoking, and positively associated with high physical activity. These factors clearly represent a lifestyle effect more than dietary intake. Therefore, studies that quantify circulating plasma levels are probably a more reliable predictor of health impacts; although, even that measure misses the propensity of certain compounds to concentrate within specific tissues (e.g.,

lutein in the eyes and brain) [60]. More importantly, we also need to recognize that analysis of dietary patterns reflects possible synergistic effects among different phytochemicals. Polyphenols, for example, appear to have a greater physiological impact when ample vitamin C is available [61], so diets or supplements lacking either partner might not reveal benefits.

3.2. Vitamin C as a Chemotherapeutic Agent

Using concentrations beyond those levels that can be achieved by normal intestinal uptake, research indicates that vitamin C may have direct anti-cancer roles when administered intravenously (IV)/intraperitoneally (IP). In a murine system, IP vitamin C modulated tumor infiltration by immune cells, and delayed cancer growth in breast cancer, colorectal, melanoma, and pancreatic cancers [62]. Vitamin C has long been administered IV to some cancer patients as an adjunct treatment. Carr and Cook [63] review the controversies and questions (e.g., how much vitamin C, how often, for how long, etc.) surrounding this practice. Their research suggests that oncology patients typically have compromised levels of vitamin C, and that IV administration is the best method of delivery since it bypasses regulation within the small intestine. While more research is necessary, initial studies indicate lower doses (≤ 10 g/d) may help improve quality of life, while larger doses (≥ 50 g/d) may have direct anti-cancer effects. One possible explanation for increased cancer cell cytotoxicity may be vitamin C's pro-oxidant activity. Normal cells have redundant repair mechanisms that may be impaired or lacking in cancerous cells [24].

In a test of synergistic interactions, Vitamin C was administered to cervical cancer cell lines along with the chemotherapeutic drug cisplatin, a drug with several adverse effects including nephrotoxicity. The combination treatment-induced cell death, allowing for a lower dosage of the chemotherapeutic drug [64]. In another example, Vitamin C was administered in conjunction with doxycycline to doxycycline-resistant MCF7 breast cancer cells. Doxycycline reduces cellular respiration by targeting mitochondrial protein translation, while vitamin C inhibits the glycolytic enzyme GAPDH, thus depleting available glutathione and increasing ROS production. Cancer stem cells that were resistant to doxycycline were 4- to 10-fold more susceptible when Vitamin C was administered with doxycycline, thus inhibiting stem cell propagation [65].

4. Our Exogenous Antioxidants: Vitamin E, Tocopherols, and Tocotrienols

Vitamin E is a lipid-soluble vitamin mainly derived from plant sources [66]. It consists of eight isomers (vitamers): four tocopherols (alpha-, beta-, gamma-, and delta-tocopherol) lacking double bonds in their side-chain, and four tocotrienols (alpha-, beta-, gamma-, and delta-tocotrienol) that contain carbon-to-carbon double bonds. Within plants, these compounds protect leaves from oxidative stress associated with intense light or stressful environmental conditions such as salinity, water deficits, or extreme temperature that can trigger excessive excitation energy within chloroplasts [67].

Vitamin E also exhibits antioxidant activity within animal tissues. Some studies found that vitamin E impacts certain transcription factors, such as nuclear factor-erythroid 2-related factor 2 (Nrf2), a transcription factor that induces expression of many antioxidant enzymes [68,69]. Vitamin E supplementation upregulates the antioxidant activity in the musculoskeletal system, slowing osteoarthritis progression [70], and it can also inhibit the NF κ B pathway, suppressing inflammation [71].

4.1. Molecular and Cellular Impacts of Tocopherols

The vitamers of vitamin E vary in their physiological impacts, tissue destinations, and antioxidant abilities. While γ -tocopherol is the main form of dietary vitamin E, α -tocopherol is the most common form of vitamin E in human tissues. After absorption from the small intestine, vitamin E is shuttled within chylomicrons through the lymphatic system, and eventually absorbed by the liver. The liver mainly re-secretes α -tocopherol, to be transported through the bloodstream within various lipoproteins [72]. From those

lipoproteins, γ -tocopherol accumulates in specific tissues such as skin, muscles, and adipose tissue, while less is available in plasma [73]. γ -Tocopherol and its metabolites (e.g., 13'-carboxychromanol) appear to have major anti-inflammatory effects by blocking cyclooxygenases (COX-1 and COX-2) that in turn block prostaglandin production, as well as inhibiting 5-lipoxygenase (5-LOX) activity [73]. Moreover, due to structural differences, γ -tocopherol is able to trap electrophiles that α -tocopherol cannot. It is therefore superior to α -tocopherol in detoxifying nitrogen dioxide, peroxynitrite, and copper–zinc superoxide dismutase, thus protecting mitochondrial function. However, because α -tocopherol is the major form released by the liver, some Vitamin E supplements often include mostly/only α -tocopherol, even though γ -tocopherol is absorbed and quickly metabolized by the body [73]. It also appears that large doses of α -tocopherol can replace γ -tocopherol in plasma and tissues, suggesting that vitamin E should be consumed from foods rather than supplements containing a single form of vitamin E [74,75]. This also points out a need for specificity when reporting food sources and/or vitamers present during studies involving vitamin E.

4.2. Health Impacts of Tocopherols

When vitamin E was ingested as food, or as supplements high in both γ - and δ -tocopherols, it appeared to help prevent cancer [76]; although, not all studies support γ -tocopherol's protective role [73]. One possible factor in these mixed results from food-based vitamin E studies could relate to the fatty acid content of different plant sources. Plant oils high in n-6 fatty acids (e.g., corn) are often high in γ -tocopherols [73]. While γ -tocopherols should have an anti-inflammatory effect, the impact of fatty acid metabolism may overwhelm any positive impact of γ -tocopherols. n-6 Fatty acids are known to feed into inflammatory metabolic pathways when they are not balanced with n-3 fatty acids [77]. However, olive oil, while still containing a majority of PUFA in the form of n-6 fatty acids, also contains low amounts of n-3 PUFA (usually a 10:1 ratio) [78], as well as phenolic compounds and components such as monounsaturated fatty acids that are associated with decreased inflammation [79,80]. Therefore, negative aspects of consuming a diet containing, for example, more corn oil than olive oil may overwhelm any benefits of γ -tocopherol [73].

4.3. Tocotrienols

As compared to the tocopherols, some studies indicate tocotrienols could be more potent antioxidants [81,82]; although, this is not supported by all studies [83]. Regardless of which are more effective antioxidants, tocotrienols clearly play important roles in cellular metabolism. For example, while all vitamers of vitamin E can scavenge free radicals, tocotrienols are thought to be better scavengers due to uniform distribution within membranes, a high number of double bonds, and greater redox cycling efficiencies [84]. Nor Azman et al. [85] conducted a study examining vitamin E's ability to increase endogenous antioxidants in healthy older adults (50–55 y) by supplementing with either α -tocopherol or a tocotrienol-rich fraction, relative to a placebo. Compared to baseline levels, six months of tocotrienol-rich supplements significantly increased superoxide dismutase levels of the entire population; α -tocopherol, however, had no impact on this measure. When examined by gender, females had significant increases in both superoxide dismutase and glutathione peroxidase after six months of tocotrienol-rich-fraction supplementation. α -Tocopherol only had a significant impact when examining the ratio of reduced glutathione to oxidized glutathione in females; the tocotrienol-rich fractions also significantly impacted this measure. The authors suggest this greater ratio of reduced glutathione to oxidized glutathione indicates improved cellular health, since a lower ratio is associated with chronic diseases such as diabetes, high blood pressure, and Alzheimer's Disease. While males showed similar patterns, the impact was not significant [85].

4.4. Vitamin E Supplementation Studies

Given the differing antioxidant abilities of vitamers, interactions with other dietary components, as well as a tendency for the more common vitamer to replace the less avail-

able form, perhaps the wide spectrum of results from vitamin E studies should not surprise us. At the negative end of the spectrum, a prospective study (SELECT) supplementing with α -tocopherol actually increased the likelihood of developing prostate cancer by 17% (Table 2) [86], while a meta-analysis determined that supplementation with vitamin E significantly increased overall mortality rates (Table 2) [87]. In the middle of the spectrum, some studies indicated that neither dietary vitamin E nor blood α -tocopherol levels protected against cardiovascular disease, total cancer, or all cause-mortality [58]. At the positive end of the spectrum, some studies have found vitamin E generally improved the inflammatory status in healthy subjects, and also in those with diabetes and metabolic syndrome [88]. Another meta-analysis reports that vitamin E alone might be effective, but not when administered in conjunction with other antioxidants (e.g., multivitamins, vitamin A, Vitamin C, β -carotene, selenium, or PUFA) that apparently nullify any positive effects (Table 2) [89]. Ashor et al. [90] performed a meta-analysis on 46 RCTs examining endothelial function, and found similar results; endothelial function was significantly improved when either vitamin C or vitamin E were administered singly, but not then they were administered together. Given the high variability, as well as potential negative effects, obtaining vitamin E via dietary sources such as nuts and olive oil appears to be the most prudent dietary advice.

Table 2. Parameters and pertinent results from cited studies examining health outcomes associated with vitamin E. RR = Relative risk, HR = Hazard risk, CVD = cardiovascular disease.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
Vitamin E	Prostate cancer. Compared to the placebo group, Hazard ratios for developing prostate cancer for the vitamin E treatment were HR 1.17 (99%CI 1.004, 1.36, $p = 0.008$); for selenium HR 1.09 (99%CI 0.93, 1.27; $p = 0.18$); for selenium plus vitamin E HR 1.05 (99%CI 0.89, 1.22, $p = 0.46$).	Selenium and Vitamin E Cancer Prevention Trial (SELECT). Analysis of 34,887 men randomly assigned to one of four treatment groups (selenium: 200 $\mu\text{g}/\text{d}$ from L-selenomethionine plus vitamin E placebo; vitamin E: 400 IU/d of all rac- α -tocopheryl acetate plus selenium placebo; both selenium and vitamin E; placebo).	[86]
Vitamin E	Mortality rates. Supplementation with vitamin E significantly increased overall mortality rates (RR 1.03, 95%CI 1.00, 1.05).	Meta-analysis of 46 supplementation trials with low bias risk; included 171,244 participants.	[87]
Vitamin E	CVD. When comparing high vs. low intake groups, there was no significant protective role of vitamin E against CVD (RR 0.90, 95%CI 0.78, 1.03), total cancer (RR 1.01, 95%CI 0.92, 1.10), or total mortality (RR 0.98, 95%CI 0.93, 1.04).	Meta-analysis of dietary vitamin E and risk of CVD (eight studies), total cancer (five studies), total mortality (nine studies).	[58]
Vitamin E	Myocardial infarction. Compared to controls, vitamin E given alone significantly decreased myocardial infarction (3.0% vs. 3.4%) (Risk Ratio 0.82, 95%CI 0.70, 0.96; $p = 0.01$).	Meta-analysis of 16 randomized controlled clinical trials examined vitamin E's impact on myocardial infarction. Dose ranged from 33–800 IU, with follow-up ranging from 0.5 to 9.4 years.	[89]

5. Plant Antioxidants beyond Vitamins

5.1. Chlorophyll and Its Metabolites

It is apparent that when humans consume a diet high in fruits and vegetables, they experience health benefits that greatly outweigh just the presence of vitamins C and E. Plant chemicals exhibiting in vitro antioxidant activity include chlorophyll and its metabolites. During in vitro digestion of chlorophyll, pheophytins, a Mg-chelated form of chlorophyll, are typically created [91]. Both chlorophyll and pheophytins exhibit antioxidant properties [92]. Pheophytins are further metabolized by gut microbes to create pheophorbides, compounds associated with even higher antioxidant activity [91]. During fruit ripening,

chlorophyll is enzymatically converted into phyllobilins; these compounds may be yellow or pink, adding to the visual signals of ripened fruit. Several phyllobilins are known to inhibit lipid auto-oxidation [93]. There is evidence that chlorophyll metabolites are found within human serum after supplementation with chlorophyllin [94]. These chlorophyll metabolites catalyze the reduction in ubiquinone and generate ubiquinol. Ubiquinol-10 is a lipid-based antioxidant that helps modulate α -tocopherol; although, ubiquinol is thought to be a more effective antioxidant than α -tocopherol, β -carotene, or lycopene [95]. At the molecular level, chlorophyll A metabolites are retinoic X receptors, and thus can alter insulin signaling [96], perhaps reducing the chance of diabetes.

Health Impacts of Consuming Leafy, Green Vegetables

In a meta-analysis of prospective studies, comparing high- and low-intake groups suggests green, leafy vegetables were inversely related to the development of CHD, CVD, total stroke risk, ischemic stroke, and all-cause mortality. In dose-response analyses, however, green leafy vegetables and salads were only significantly associated with lower all-cause mortality (Table 3) [6]. Ingestion of green leafy vegetables is also associated with significantly slower cognitive decline. In the Memory and Aging Project, the decline rate in the highest intake group was the equivalent of 11 years slower (i.e., eleven years younger) than those with the lowest intake [97]. However, while green, leafy vegetables are a good source of chlorophyll, they also provide many other nutrients such as folate, vitamin K (phylloquinone), vitamin E (α -tocopherol), carotenoids such as lutein and β -carotene, and flavonoids such as kaempferol. All the afore-mentioned nutrients, except for β -carotene, were also significant in predicting the slower memory decline rate [97].

Table 3. Parameters and pertinent results from cited studies examining health outcomes associated with consuming leafy green vegetables. RR = Relative risk, CVD = cardiovascular disease, CHD = coronary heart disease.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
Green, leafy vegetables	In high vs. low comparison, green, leafy vegetables were inversely related to development of CHD (RR 0.83, 95%CI 0.75, 0.91), CVD (RR 0.84, 95%CI 0.71, 0.99), total stroke risk (RR 0.88, 95%CI 0.81, 0.95), ischemic stroke (RR 0.88, 95%CI 0.78, 0.99), and all-cause mortality (RR 0.92, 95%CI 0.86, 0.97). In dose-response analyses, green leafy vegetables and salads were only significantly associated with lower all-cause mortality (per 100 g/d RR 0.78, 95%CI 0.71, 0.86).	Meta-analysis of ten prospective studies comparing high vs. low intake groups; analysis of nine studies investigating dose-response, in increments of 100 g/day.	[6]

5.2. Carotenoids and Their Metabolites

Carotenoids include a diverse array of colorful tetraterpene compounds, the carotenes (hydrocarbons), and xanthophylls (oxygenated products of carotenes) [98]. Within plants, they function to not only absorb some light wavelengths that chlorophyll cannot, but also to protect chlorophyll from photooxidation, a process causing permanent bleaching of chlorophyll. Carotenoids can also be cleaved to create several plant growth-regulating compounds, such as abscisic acid and strigolactones [99]. While many carotenoids are common in land plants, some carotenoids such as astaxanthin are present only in microalgae (e.g., *Haematococcus*, Chlorophyceae), and in marine animals (e.g., salmon) that consume them [100]. In humans, about 50 carotenoids can be cleaved to form vitamin A; although, only three are a major dietary source (β -carotene, α -carotene, and β -cryptoxanthin [101]. Besides vision, Vitamin A is essential for the formation and maturation of epithelial tissue and keratin formation [102], organism growth and development, and innate immunity [103]. Within human tissues, the carotenoid profile typically includes α -carotene, β -carotene, β -cryptoxanthin, lycopene, lutein, and zeaxanthin [104].

5.2.1. Carotenoid Bioavailability—Impacts on Diet

Studies assessing the bioavailability of different carotenoids indicate that gentle cooking generally increases carotenoid bioavailability [105], most likely through the disruption of cell walls. The food source of carotenoids also impacts their bioavailability; ingestion of carotenoids from fruit sources increases carotenoid absorption relative to absorption from vegetables. In a study of 7–11 y anemic children in Indonesia, the children who consumed fruits showed a mean change in serum carotene concentration of 0.52 mol/L. However, the children who consumed vegetables only showed a mean change in serum carotene concentration of 0.14 (Table 4) [106]. This greater availability from fruits is thought to be due to changes in fruit cell walls during the ripening process [107]; although, other aspects of plant chemistry such as pectin and fiber content [108,109] could potentially interfere with absorption. The physical state of carotenoids within chromoplasts can also impact their release from the food matrix during digestion; β -carotene is present as crystals in carrots and tomatoes, while it is typically dissolved in lipids within mango and papaya, a form that increases its absorbability [110]. In dark-green, leafy vegetables, however, carotenoids are complexed with proteins within chloroplasts, making their absorption more difficult [111]. Further, the combination of carotenoids one ingests may also impact their absorbability; lutein, for example, interferes with the absorption of β -carotene, reducing its bioavailability [109]. Considering all the variables, it is no surprise that both in vivo and in vitro studies indicate the bioaccessibility of carotenoids is often low, unrelated to carotenoid concentration within the food [111], and varies based on preparation methods. For example, the availability of lycopene was 0.1% from raw tomatoes, and 1.5% from tomato puree; for β -carotene, 4% was available from carrot puree, 14% from carrot juice; and for lutein, 37% was available from raw spinach leaves, while 48% was available from boiled spinach [112].

Table 4. Parameters and pertinent results from cited studies examining health outcomes associated with various carotenoids.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
Carotenoids	Mean changes in serum retinol concentrations after consuming retinol-rich foods 0.23 micromol/L (95%CI 0.18, 0.28), fruit 0.12 micromol/L (95%CI 0.06, 0.18), vegetable 0.07 micromol/L (95%CI 0.03, 0.11), and low-retinol, low-carotene groups 0.00 micromol/L (95%CI −0.06, 0.05). Mean changes in serum beta-carotene concentrations in the vegetable group was 0.14 micromol/L (95%CI 0.12, 0.17) while the increase in the fruit group was 0.52 micromol/L (95%CI 0.43, 0.60).	Anemic school children (7–11 y) in West Java, Indonesia were randomly assigned to 1 of 4 groups. Children consumed two meals/day, six days/week for nine weeks. Group 1 ($n = 48$) consumed 556 retinol equivalents (RE)/d from retinol-rich food; Group 2 ($n = 49$) consumed 509 RE/d from fruit; Group 3 ($n = 45$) consumed 684 RE/d from dark-green, leafy vegetables and carrots; Group 4 ($n = 46$) consumed 44 RE/d from low-retinol, low-carotene food.	[106]
Beta-carotene plus alkaloid piperine	Significantly greater serum beta-carotene increases were observed during supplementation with beta-carotene plus piperine ($49.8 \pm 9.6 \mu\text{g/dL}$) as compared to beta-carotene plus placebo ($30.9 \pm 5.4 \mu\text{g/dL}$), ($p < 0.0001$).	Double-blind cross-over study with healthy adult males. Examined serum beta-carotene levels after 16 days of oral supplementation with 15 mg beta-carotene either with 5 mg 98% pure piperine, the main alkaloid of <i>Piper nigrum</i> , black pepper, or with a placebo control.	[113]
Carotenoids—Lutein and Zeaxanthin	The study investigated the association between age-related macular degeneration and lutein. Participants with higher plasma lutein had a significantly lower risk of developing age-related macular degeneration (Hazard Ratio 0.63 per 1-SD increase, 95%CI 0.41, 0.97). Zeaxanthin, however, was not significantly associated with reduced risk.	A prospective, population-based cohort study (Alienor: Antioxydants Lipides Essentiels Nutrition et Maladies Oculaires) followed 963 residents of Bordeaux, France, for eight years. Subjects were 73 years or older at baseline.	[114]

5.2.2. Carotenoids as Chemotherapeutic Agents

The low bioavailability and solubility of carotenoids have limited their potential use as a chemotherapeutic agent. Encapsulating carotenoids within nanocarriers is currently under investigation for potential use in cancer therapy [115,116]. Co-ingestion with lipophilic spices or spice extracts also appears to increase absorption. For example, carotenoid absorption increased 60% in the presence of piperine, an alkaloid from black pepper (Table 4) [113]. In animal studies, ingestion of carotenoids with a lipophilic spice such as capsaicin from *Capsicum annuum*, gingerol or gingerone from *Zingiber officinale* also resulted in increased carotenoid absorption, presumably due to altered permeability of the intestinal brush border [111]. In a rat intestine study, black pepper increased β -carotene uptake by 59%, while its purified alkaloid piperine increased uptake by 147%. Similarly, red pepper increased β -carotene absorption by 27%, while a red pepper extract, capsaicin, increased its absorption by 50%. Dietary ginger also increased β -carotene absorption by 59% [117]. Adding spices to fruit and vegetable dishes appears to increase their health benefits, and may also be useful in the development of oral chemotherapeutics.

5.2.3. Molecular and Cellular Impacts of Carotenoids

Beyond the importance of certain carotenoids to act as a vitamin A source, carotenoids appear to benefit our health through a variety of mechanisms. For example, they are known to quench free radicals [118], upregulate antioxidant enzymes via Nrf2 [119], regulate signal cascades that impact gene expression associated with inflammation and oxidative stress (e.g., suppress NF κ B) [119,120], protect against DNA damage, and interfere with estrogen in cancerous breast cells [121]. When human neutrophils were subjected to high levels of glucose (30 mM) or free fatty acids (0.1 mM), they exhibited increased ROS and RNS production as well as decreased phagocytic capacity. However, when these compromised neutrophils were also exposed to the carotenoid astaxanthin, their phagocytic capacity was partially restored, and ROS/RNS production was lowered [122]. When colon adenocarcinoma cells of the LS-180 line were treated for 24 h with astaxanthin, they increased the expression of BAX and Caspase3 genes while decreasing Bcl2 expression, leading to apoptosis and growth inhibition of cancer cells. The astaxanthin-treated cells also had lower malondialdehyde levels, and elevated superoxide dismutase, catalase, and glutathione peroxidase activity [123]. These varied antioxidant responses suggest astaxanthin may be an important player in our arsenal of cancer prevention, and perhaps even cancer treatment.

5.2.4. Beneficial Health Impacts of Dietary Carotenoids

Eye and Brain Health

Only two carotenoids are known to cross the blood–retina barrier to create macular pigments—lutein and zeaxanthin. Within the macula, lutein and zeaxanthin are known to absorb blue light, preventing photo-oxidation that could damage the retina [119]. A study of elderly subjects indicates that those with higher plasma lutein had a significantly lower risk of developing age-related macular degeneration; zeaxanthin, however, was not significantly associated with reduced risk (Table 4) [114].

Lutein and zeaxanthin are also known to cross the blood–brain barrier. Lutein, even when it is not the dominant dietary carotenoid, preferentially accumulates within the human brain. It appears to be important for brain development and cognition early in life, and cognitive health throughout life [60]. Nouchi et al. [124] completed a systematic review of randomized controlled trials to examine the effects of carotenoid intake on cognitive functions in humans. Lutein consumption (10 mg/d over 12 months) was significantly related to improved performance in tests of visual episodic memory in young and middle-aged adults. For measures of inhibition, middle-aged and older adults consuming lutein showed significant improvement in performance.

Other studies have investigated tissue concentrations of several nutrients to determine if they were correlated with cognitive function. In the Georgia Centenarian Study, results of

pre-mortem cognitive tests and measures of depression were compared with post-mortem brain tissue levels of carotenoids, tocopherol, and retinol. Researchers found significant relationships between carotenoids and a variety of separate cognitive functions including memory, executive function, and language. Cortical lutein concentrations were positively correlated with cognitive function and language, while being negatively associated with depression. Cortical zeaxanthin was positively correlated with verbal fluency, and tocopherol was significantly associated with cognitive and executive functions [124]. While the mechanisms related to how these carotenoids influence brain health remain unclear, there are several hypotheses revolving around lutein's antioxidant function. Lutein is known to localize in membrane regions that are high in polyunsaturated fatty acids, such as DHA [125,126]. Because polyunsaturated fatty acids are in greater danger of oxidation, lutein may block those destructive reactions, helping preserve membrane fluidity and stability, and conserving DHA for biochemical processing [60].

Cancer and Heart Disease

In a meta-analysis of prospective studies [121], researchers examined the relationship between reported dietary carotenoid intake and breast cancer risk, as well as the relationship based on blood concentrations. In the analysis of questionnaire-reported dietary intakes, only β -carotene was significantly associated with reduced breast cancer risk. However, the relationships between blood carotenoid concentrations and breast cancer risk were significant for a wider array of carotenoids, and with a greater probability. While these results highlight the inconsistencies of questionnaire-based intake data relative to actual blood concentrations, they also suggest the potential use of carotenoids as a marker associated with breast cancer risk [121]. Other meta-analyses examined for associations between health status (CVD, CHD, mortality, and total cancer) and various dietary carotenoid intakes or blood carotenoid levels. When comparing the highest with the lowest group, measures of blood β -carotene levels were inversely associated with (i.e., protective against) CHD, CVD, total cancer, and mortality [58]. It is also important to note that while carotenoids are generally protective in nature, different types of carotenoids do not mirror each other in their effectiveness. For example, neither dietary nor blood levels of lycopene or lutein were significantly associated with a decreased risk of CVD, CHD, total cancer, or total mortality [58], while other studies found a reduced all-cause mortality risk for β -carotene and lycopene, but not for either zeaxanthin or lutein [57].

5.2.5. Negative Health Impacts of High Carotenoid Concentrations

Similar to other antioxidants, carotenoids also have pro-oxidant capabilities; in cancer cells with high ROS, carotenoids such as astaxanthin, β -carotene, and lycopene act as pro-oxidants, triggering ROS-mediated apoptosis [127]. While those actions are beneficial, carotenoids can also negatively impact human health. Oxidative carotenoid metabolites are thought to be associated with the deleterious effects seen in those taking high-dose supplements. This was evident in the CARET trial where lung cancer risk increased in those participants taking β -carotene combined with vitamin A [128], or in the ATBC trial where participants taking β -carotene had a greater risk of developing lung cancer [129]. Haider et al. [130] found that although β -carotene itself acts as an antioxidant and only causes cytotoxic effects at high concentrations (50 M), β -carotene cleavage products at concentrations as low as 1 μ M caused significant increases in DNA strand breaks in stressed primary pneumocyte type II cells.

5.3. Flavonoids

Flavonoids are phytochemicals containing two benzene rings, one of which is fused to a pyran-derived ring (Figure 2). Flavonoid subclasses vary based on substitution patterns on the pyran ring, while another subclass of flavonoids, the isoflavonoids, differ in where the benzene ring attaches to the pyran ring [131]. Within plants, flavonoids absorb UV light, while others create floral UV patterns to signal insect pollinators. While some flavonoids

appear colorless in the visible spectrum, others act as visual attractants to pollinators and seed dispersers by adding red and blue hues to fruits and flowers (anthocyanins). Among other plant functions, flavonoids act as signal molecules, play a role in temperature acclimatization, and act as phytoalexins, protective chemicals that are produced after a pathogen attack [132]. In addition to the above functions, flavonoids, especially the dihydroxy B-ring-substituted flavonoids such as quercetin 3-O and luteolin 7-O-glycosides, are also highly effective scavengers of ROS. Within plants, these dihydroxy B-ring substituted flavonoids are typically found in locations such as the chloroplast, and the nucleus of leaf mesophyll cells, where ROS generation is common [133].

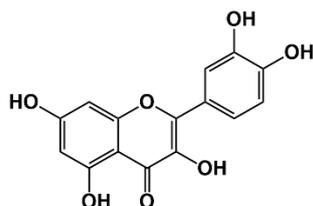


Figure 2. Quercetin, a typical flavonoid.

5.3.1. Flavonoid Bioavailability

Within plant cells, flavonoids are typically attached to sugars that increase their solubility within the plant's vacuole. Those sugars need to be removed by brush-border enzymes prior to human absorption, leaving lipophilic aglycones that are easily absorbed into enterocytes. Some glycosylated flavonoids can also be absorbed in their entirety via the sodium-dependent glucose transporter present in enterocyte membranes; these glycosides are then converted to aglycones within the enterocyte [134]. Flavonoids that are not absorbed in the small intestine interact with the colonic microbiome, producing metabolites that could be absorbed or eliminated; colonic uptake is thought to play a major role in flavonoid absorption [135]. Structural aspects can also impact flavonoid uptake. For example, the amount of quercetin absorbed from onions is four times greater than quercetin absorbed from tea or apples, presumably because of different sugar moieties attached to quercetin in these different plant sources [134]. Structural differences are most likely the reason that quercetin and catechin have some of the highest flavonoid bioavailabilities, while anthocyanins and pro-anthocyanidins have among the lowest [136].

Other dietary constituents can also impact their bioavailability; proteins appear to decrease flavonoid absorption while concomitant dietary fat increases flavonoid absorption from the gut. For example, there was a 45% increase in absorption when 1095 mg of quercetin aglycone was consumed in a high fat (15.4 g) muffin as compared to a non-fat muffin [137]. While fruits and vegetables are typically lower protein food sources, thus improving absorption, they are often lower in fat as well, suggesting ingestion with an olive oil-based dressing would improve bioavailability. After their absorption, flavonoids are typically conjugated with glucuronide or sulfate, increasing their solubility to aid in excretion through bile or urine [138]; although, there is evidence that flavonoids such as anthocyanins have a longer residence time in tissues, including the brain, than in plasma [139].

5.3.2. Health Impacts of Flavonoids

The absorbed and conjugated flavonoids, prior to their excretion, can exhibit antiviral, anti-bacterial, anti-fungal, and anti-protozoan properties [140]. Several flavonoids, especially those with greater lipophilic characteristics, have also been shown to cross the blood–brain barrier. For example, the permeabilities of hesperetin and naringenin are greater than those of either anthocyanins or the glucuronide conjugates of hesperetin and naringenin. This ability to cross the blood–brain barrier could explain the beneficial impacts of dietary flavonoids against diseases of the aging brain [141]. Flavonoids are also anti-cancer, due to impacts that can often be linked to their antioxidant/pro-oxidant abilities.

Flavonoids can arrest the cell cycle, induce apoptosis, and suppress cancer cell invasiveness through a wide variety of mechanisms [142]. Within various animal systems, flavonoids protected mitochondrial function through ROS scavenging and chelating transition metal ions. The scavenger/chelation effects of flavonoids, however, might actually be insignificant relative to their ability to increase the transcription of antioxidant enzymes and trigger the destruction of damaged mitochondria (mitophagy). A variety of flavonoids such as catechins, kaempferol, naringenin, and quercetin also inhibit apoptosis in a variety of animal systems challenged with ischemia or toxins. Many flavonoids appear to preserve mitochondrial function, and help regulate redox potential by upregulation of Bcl-2. This can lead to an increased ratio of anti-apoptotic Bcl-2 proteins relative to pro-apoptotic BAX proteins [143], helping preserve damaged tissues.

5.3.3. Impacts of Dietary Flavonoids on Health

A meta-analysis of RCTs investigated the impacts of different high flavonoid foods and beverages on cardiovascular disease and associated risk factors, such as blood pressure, lipoproteins, and flow-mediated dilatation [144]. When these physical measures were analyzed relative to the common food flavonoids, there was often significant heterogeneity between different flavonoid subclasses (e.g., flavanols, anthocyanins), again suggesting flavonoid structure impacts health benefits. Similarly, different flavonoid-rich foods varied in their impacts on the cardiovascular system. When intake as food was examined, chocolate intake increased flow-mediated dilatation after both acute (up to 6 h after ingesting) and chronic exposure (greater than two weeks). Chocolate was also associated with a significant reduction in systolic and diastolic blood pressure. Green tea, however, was cardio-protective due to reductions in LDL cholesterol. Another flavonoid-rich beverage, black tea, did not appear cardio-protective with regard to blood pressure. When measured up to six hours after ingestion, black tea increased both systolic and diastolic blood pressure (Table 5). While this increase could be due to caffeine, several of the included studies controlled for the effects of caffeine. The authors also suggest theobromine was unlikely to cause the changes in blood pressure, since it is also present in chocolate, but chocolate was not associated with acute rises in blood pressure. However, the different phytochemical profiles of chocolate and black tea may cause one chemical to act very differently depending on the phytochemical combination.

Table 5. Parameters and pertinent results from cited studies examining health outcomes associated with dietary flavonoids and isoflavonoids. HR = Hazard risk, OR = Odds Ratio, CVD = cardiovascular disease, CHD = coronary heart disease.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
High flavonoid foods and beverages	CVD, blood pressure, lipoproteins, flow-mediated dilatation. Chocolate intake increased flow-mediated dilatation after both acute (up to 6 h after ingesting; 3.99%; 95%CI 2.86, 5.12) and chronic exposure (greater than two weeks; 1.45%; 95%CI 0.62, 2.28). Chocolate was associated with a significant reduction in systolic (−5.88 mm Hg; 95%CI −9.55, −2.21) and diastolic (−3.30 mm Hg; 95%CI −5.77, −0.83) blood pressure. Green tea reduced LDL cholesterol (−0.23 mmol/L; 95%CI −0.34, −0.12). When measured up to six hours after ingestion, black tea increased both systolic (5.69 mm Hg; 95%CI 1.52, 9.86) and diastolic (2.56 mm Hg; 95%CI 1.03, 4.10) blood pressure.	Meta-analysis of 133 randomized controlled trials.	[144]

Table 5. Cont.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
Anthocyanins	CHD and CVD mortality. Dietary anthocyanins were associated with reduced risk of CHD (RR 0.91, 95%CI 0.83, 0.99) and CVD mortality (RR 0.92, 95%CI 0.87, 0.97). No relationship was observed between intake of high anthocyanin food and a reduced risk of myocardial infarction, stroke, or total CVD. Subgroup analysis indicates reduced risks were more prevalent for anthocyanidin intake, as compared to consumption of anthocyanin or berries.	Meta-analysis of prospective cohort studies. Nineteen studies involving 602,054 participants and more than 22,673 cases of non-fatal or fatal cardiovascular disease were included.	[145]
Flavonoids	Type 2 diabetes. Flavonoids were associated with reduced risk of Type 2 diabetes; for total flavonoid intake, RR 0.89 (95%CI 0.82, 0.96).	Meta-analysis of eight prospective cohort studies that included 312,015 participants. Of these, 19,953 developed type 2 diabetes mellitus during the follow-up periods, ranging from 4 to 28 years.	[146]
Flavonols, anthocyanins	Alzheimer's Disease and related dementias. Results indicate participants with the greatest intakes of flavonols, anthocyanins, and flavonoid polymers had the lowest health risk of Alzheimer's Disease and related dementias, relative to those with the lowest intakes. Significant protective relationships were seen for flavonols (health risk 0.54, 95%CI 0.32, 0.90) and anthocyanins (health risk 0.24, 95%CI 0.15, 0.39).	The Framingham Heart Study Offspring cohort, including more than 2800 participants who were followed for an average of 19.7 y.	[147]
Soy iso-flavonoids	Type 2 Diabetes. Women, but not men, in the upper third of soy-based food and isoflavone intake had a significantly lower risk of developing type 2 diabetes (HR 0.45, 95%CI 0.30, 0.68), as compared with women in the lowest third of intake.	Prospective cohort study of 13,521 Japanese subjects (5883 men, 7638 women; 35–69 y old). Subjects completed questionnaires regarding diet and lifestyle during a 10-year follow-up period.	[148]
Isoflavone intake	Coronary Heart Disease. Isoflavone intake was inversely associated with CHD when comparing the upper and lower quintiles. Isoflavone intake (HR 0.87, 95%CI 0.81, 0.94; $p = 0.008$), and tofu (HR 0.82, 95%CI 0.70, 0.95; $p = 0.005$) were significantly associated with decreased CHD, but this significance was mostly driven by pre-menopausal women and postmenopausal women who were not using hormone therapy. Soy milk was not significantly associated with decreased CHD risk.	Analysis of three cohort studies Nurses' Health study ($n = 74,241$ women, data from 1984–2012), Nurses' Health Study II ($n = 94,233$ women, data from 1991–2013), and Health Professionals Follow-up Study ($n = 42,226$ men, data from 1986–2012). Subjects were free of cardiovascular disease and cancer at baseline.	[149]
Soy intake	Breast Cancer. Soy intake lowered breast cancer risk in Asian women, both pre- and post-menopause (pre-menopause OR 0.59, 95%CI 0.48, 0.69; post-menopause OR 0.59, 95%CI 0.44, 0.74); in Western countries, this association was marginal, and only in post-menopausal women (OR 0.92, 95%CI 0.83, 1.00).	Meta-analysis of 35 epidemiological studies.	[150]

Several prospective cohort studies also indicate flavonoids, cumulatively and individually, have a protective nature against a variety of chronic diseases. Several meta-analyses

examining the impacts of specific dietary flavonoids found significantly reduced CVD risk when comparing groups with highest and lowest intakes of anthocyanins, proanthocyanidins, flavones, flavanones, flavan-3-ols, flavonols, and catechins. Although studies varied in the extent of reduced risk, there was generally a 10–15% reduction in CVD risk for all compounds [151,152], with catechins offering the greatest protection at 25% reduced risk [152]. For other measures of cardiovascular health, a meta-analysis [145] found dietary anthocyanins were associated with a reduced risk of CHD and CVD mortality; this reduced risk was more pronounced for anthocyanidin intake, as opposed to intake of anthocyanin or berries (Table 5).

Flavonoids are also associated with a reduced risk of Type 2 diabetes. When individual flavonoid subclasses were analyzed, this inverse correlation was significant for anthocyanidin, flavan-3-ol, flavonol, and isoflavone intake (Table 5) [146]. Another study indicated a protective nature of several flavonoids against Alzheimer's disease. Analysis of The Framingham Heart Study Offspring cohort indicated participants with the greatest intakes of flavonols and anthocyanins had a significantly lower health risk of Alzheimer's Disease and related dementias, relative to those with the lowest intakes (Table 5) [147].

5.3.4. Flavonoids as Therapeutic Agents

Flavonoids, in general, have been shown to act synergistically with a variety of partners. For example, the combined effects of the flavonoids rutin and silibinin had a greater impact on colon cancer cells than either alone [153]. Other research found that when the flavonoids luteolin and silibinin were given in combination, they prevented glioblastoma cell migration and invasion, and induced apoptosis in glioblastoma stem cells [154]. However, despite their potential as a source of therapeutic drugs, only a few isolated flavonoids have, thus far, shown promise, since many of them have significant drawbacks due to their poor bioavailability, low water solubility, rapid metabolism and excretion, or possible adverse effects. Although silymarin, a flavonoid from *Silybum marianum* known for protecting the liver of people who ingested *Amanita phalloides* has been approved in an injectable form, other phenolics such as resveratrol and curcumin have shown clinically inconsistent results [155]. Epigallocatechin gallate (EGCG), for example, exhibits many anti-cancer capabilities, such as: acting as an antioxidant and an anti-inflammatory; attenuating the NF κ B pathway and, thus, its target genes that are involved in tumorigenesis; inhibiting angiogenesis and metastasis; and inducing apoptosis [156]. On the negative side, in addition to its low bioavailability, EGCG also exhibits liver toxicity at high concentrations [157].

Another approach to improve bioavailability has been to create complexes of flavonoids bound to cyclodextrins. These are cyclic oligosaccharides composed of five or more glucose units that possess a hydrophilic exterior; this adds stability and increases the solubility of hydrophobic molecules such as flavonoids [158]. It is also possible to increase bioavailability by creating emulsions of nano-particles that control compound release. As compared to aqueous tea polyphenol-fed rat controls, rats that were fed tea polyphenols in a nano-emulsion attained lower maximal plasma EGCG concentrations, but the concentration–time curve indicated a higher total amount of EGCG was absorbed [159]. Depending on the system used, carrier molecules have been shown to enhance EGCG's intestinal stability, prolong its retention time in the intestine, and promote intestinal absorption [157].

5.3.5. Health Impacts of Dietary Isoflavonoids

Isoflavonoids, an important subclass of the flavonoids, also function as antioxidants, with aglycones having greater antioxidant ability than various glucosides [160]. They are also recognized for their ability to bind to estrogen receptors. In cellular environments with a high estrogen concentration, isoflavonoids and their metabolites act as estrogen antagonists; however, in cellular environments with low estrogen, they can act as estrogen agonists [161]. Thus, they are effective in reducing the low estrogen symptoms of menopause (e.g., soy isoflavones lower the risk of a myocardial infarction in early post-

menopausal women by 37%) [162], while decreasing the likelihood of developing certain cancers such as colorectal and endometrial cancer [163]. Other isoflavonoid activity includes their anti-inflammatory action [164], and their ability to inhibit angiogenesis, thus lowering the metastatic potential of some tumors. Decreased angiogenesis appears to be related to several mechanisms, such as inducing apoptosis, decreased cellular proliferation, and decreased migration of endothelial cells [165]. These occur due to blocking tyrosine phosphorylation and modulating gene expression of VEGF, MMPs, and EGFR [166].

5.3.6. Impacts of Gender, Age, Population, and Hormone Status

Increased consumption of soy isoflavonoids has been linked to decreases in several chronic illnesses, including diabetes, CHD, dementia, and cancer. Results appear to be modified by factors such as gender, age, and population-based effects. For example, a prospective cohort study that followed Japanese men and women over 10 years found women, but not men, in the upper third of soy-based food and isoflavone consumption had a significantly lower risk of developing type 2 diabetes, as compared to the group with the lowest consumption (Table 5) [148]. Age and estrogen status also impact results. Data analysis of three U.S. prospective cohort studies indicates that greater isoflavone intake and tofu consumption (but not soymilk) were inversely related to a moderately lower CHD risk. This significance was mostly driven by pre-menopausal women and postmenopausal women who were not using hormone therapy (Table 5) [149].

In addition to age and gender, population-based differences are also evident. Observational studies examining soy's impact on CHD found that in Asian cohorts, dietary soy isoflavones were inversely associated with CHD, but similar findings were not evident in a trial investigating the impact of soy isoflavones in a US population of postmenopausal women [167]. This population-based difference was also seen in soy's association with breast cancer. Soy intake significantly lowered breast cancer risk in Asian women, both pre- and post-menopause, but in Western countries, this association was marginal, and only in post-menopausal women (Table 5) [150]. Potential reasons for population differences could be related to cultural dietary patterns causing a high exposure to estrogenic isoflavonoids before puberty in Asian cultures [168] or perhaps other genetic polymorphisms. Population-based differences might also result from differences in gut microflora. S-equol, for example, is a powerful antioxidant created by gut microbes from the isoflavone daidzein. While 50–70% of northeast Asians produce equol, only 20–30% of Westerners do. Equol appears to improve arterial stiffness, thus helping prevent CHD and cognitive impairment [169]. Likewise, urinary equol, but not other isoflavonoids such as daidzein or genistein, is associated with significantly lower rates of type 2 diabetes in Chinese adults [170].

5.3.7. Isoflavonoid Use as Chemotherapeutic Agents

Soy isoflavones are showing promise as a potential therapeutic agent in a variety of cancer treatments, especially prostate and breast cancer. There is evidence they can increase the efficacy of cancer treatments while lessening adverse reactions in healthy cells [171]. Other cancers respond favorably to treatments utilizing isoflavonoids. Ferrari et al. [172] found that treating thyroid tissues with the isoflavone genistein decreased papillary thyroid cancer cell proliferation. This effect was enhanced by cotreatment with sorafenib, an antineoplastic drug, suggesting the potential use of genistein as an adjuvant in cancer therapy. The study also found genistein pre-treatment did not cause any primary DNA damage, and reduced hydrogen-peroxide-induced DNA damage to thyrocytes. Another isoflavone, daidzein, also shows promise as an adjuvant treatment. Daidzein's ability to help control human breast cancer cells was examined singly, and in combination with Centchroman, an oral contraceptive with potential use as an anti-cancer. When combined, daidzein and Centchroman caused elevated toxicity in cancerous cells (inducing apoptosis), without affecting non-tumorigenic Human Mammary Epithelial Cells. In cancerous cells, the synergistic combination was effective by down-regulating the expression of several proteins essential for cell survival [173].

5.4. Alkaloids

Within the organisms that ingest them, alkaloids have a wide array of targets [174,175]. Due to structural similarities between alkaloids and neurotransmitters, neuroreceptors are common alkaloid targets, where they act as agonists or antagonists. For example, indole alkaloids have structural similarities to serotonin, so they are potential sources of anti-depressant drugs [176]. Alkaloids can also impact signal transduction in neurons, and can reduce pain by altering the activity of voltage-gated sodium channels [177]. Other alkaloids intercalate or alkylate DNA, or interfere with protein synthesis or the cytoskeleton, actions that often trigger apoptosis [174]. Alkaloids can also act as antioxidants through a variety of mechanisms. In addition to the upregulation of endogenous antioxidants or detoxifying enzymes, alkaloids are being examined for their ability to scavenge free radicals. Berberine and morphine (both exhibiting 1,1-Diphenyl-2-picryl-hydrazyl scavenging activity) and piperine (inhibiting lipid peroxidation), among many other alkaloids, can act as antioxidants [40].

5.4.1. Dietary Alkaloids

The typical human diet contains a wide array of alkaloids. Solanaceae is often viewed as a major alkaloid contributor to the diet (e.g., potatoes contain solanine and nicotine; tomatoes contain solanine, tomatine, and nicotine; peppers/capsicum contain nicotine; and eggplant contains nicotine) [178]. However, other common foods and beverages also contribute significant amounts of dietary alkaloids, including coffee (caffeine), cacao/chocolate (theobromine), tea (theophylline, nicotine), cauliflower (nicotine), and black pepper (piperine) [179,180]. Poppy seeds can also be contaminated with morphine and other opium alkaloids during processing, or as a result of insect damage during growth [181]. While alkaloid production is genetically determined, endogenous production may not be the only source. Nicotine, for example, was found in peppermint plants, at least partially due to its absorption from environmental nicotine sources [182]. Foods can also be contaminated with alkaloids via fungal-produced mycotoxins, as is the case of the ergot alkaloids, or from certain toxic nectars gathered by bees while foraging on plants [180]. Toxic nectars contaminating honey could contain, for example, pyrrolizidine alkaloids gathered from *Senecio* sp. that cause liver damage with chronic consumption [180], or 14-(R)-hydroxy-gelsenicine from *Gelsmium elegans* that acts as a neurotoxin [183].

5.4.2. Health Impacts of Dietary Alkaloids—Parkinson’s Disease

A population-based study of patients newly diagnosed with Parkinson’s Disease, compared to healthy controls, investigated how consuming nicotine-containing foods (peppers, potatoes, and tomatoes) was associated with the risk of developing Parkinson’s Disease. After adjusting for age, sex, ethnicity, other vegetable consumption, tobacco use, and caffeine, Parkinson’s Disease was found to be inversely associated with consumption of all edible Solanaceae combined, especially when weighted for nicotine concentration. This apparent protection was most obvious in men and women who never smoked tobacco, or smoked for fewer than ten years (Table 6) [184]. The association between nicotine-containing foods and developing Parkinson’s Disease was also examined in non-smokers from two prospective cohorts (Table 6). For those cohorts, dietary nicotine was determined based on consumption of tea in addition to peppers, potatoes, tomatoes, and tomato products. When the highest and lowest quintiles were compared, there was a significant 36% decreased chance of developing Parkinson’s Disease for women; although, the association was not significant in men. Further, when individual foods were examined, greater pepper consumption lowered the risk of developing Parkinson’s disease in women, but again, this was not significant in men [185].

Table 6. Parameters and pertinent results from cited studies examining health outcomes associated with dietary alkaloids. RR = Relative risk, HR = Hazard risk.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
Nicotine containing foods	Parkinson's Disease was inversely associated with consumption of all edible Solanaceae combined (RR 0.81, 95%CI 0.65, 1.01 per time per day), but not consumption of all other vegetables combined (RR 1.00, 95%CI 0.92, 1.10). The trend was strengthened by weighting the edible Solanaceae by their nicotine concentration ($p = 0.004$). Individually, peppers were also inversely associated with developing Parkinson's Disease ($p = 0.005$). This protective effect of edible Solanaceae largely occurred in those who had never used tobacco or had smoked cigarettes for less than 10 years.	Population-based study of 490 newly diagnosed with Parkinson's Disease compared with 644 unrelated, neurologically normal controls.	[184]
Nicotine containing foods	Parkinson's Disease. Participants who had never smoked were followed for 26 years. HR for the highest compared with the lowest quintile of dietary nicotine intake was 0.70 (95%CI 0.51, 0.94). A significant inverse association was only observed in women (adjusted HR 0.64, 95%CI 0.42, 0.96), not in men (adjusted HR 0.77, 95%CI 0.50, 1.20). Greater pepper consumption was associated with lower Parkinson's Disease risk in women (adjusted HR for consuming peppers ≥ 5 times/w compared with ≤ 3 times/mo: 0.49, 95%CI 0.25, 0.94), but not in men (adjusted HR: 1.04, 95%CI 0.57, 1.90).	Dietary nicotine intake was calculated (based on consumption of peppers, tomatoes, processed tomatoes, potatoes, and tea) for two large prospective cohorts: The Nurses' Health Study ($n = 31,615$) and the Health Professionals Follow-up Study ($n = 19,523$) who completed dietary questionnaires.	[185]
Caffeine	Markers of oxidative stress, including total antioxidant capacity, glutathione, oxidized glutathione, the ratio of glutathione to oxidized glutathione, lipid hydroperoxide, and malondialdehyde were measured. All measures changed significantly, and favorably after caffeine administration. Oxidized glutathione levels decreased 41% while lipid hydroperoxides levels decreased 70%. Glutathione levels increased 106%, while the ratio of glutathione to oxidized glutathione rose 249%. Changes were uniform across subjects. Caffeine appears to have consistent antioxidant properties.	Fifteen male volunteers (18–25 y with normal body mass index) who regularly consumed coffee were tested. Plasma oxidative stress markers were analyzed before and after caffeine consumption. A room temperature caffeine solution was consumed, at a rate of 5 mg/kg body weight/day, that was given in two daily doses (2.5 mg/kg mornings, 2.5 mg/kg after lunch) for seven days. Blood was drawn in the morning prior to the first dose of caffeine, and the final sample was drawn in the morning of the eighth day.	[186]

Caffeine also reduces elevated levels of oxidative stress, as well as reducing neuroinflammation, thus helping relieve symptoms of both Parkinson's disease and Alzheimer's disease. Ikram et al. [187] suggest caffeine's anti-neuroinflammatory effects are due to caffeine's antagonistic impacts on the adenosine A2A microglial receptor, while its antioxidant effects are due to agonistic effects causing the upregulation of Nrf2 [187,188]. In an assessment of pure caffeine's ability to act as an antioxidant, Metro et al. [186] examined

several plasma antioxidants after subjects ingested pure caffeine and found all measures changed significantly, and in a favorable manner; at the extremes, there was a 70% decline in lipid hydroperoxides, and a 249% increase in the glutathione/oxidized glutathione ratio (Table 6) [186]. The products of caffeine metabolism also appear to function as effective antioxidants. In a test of oxidative stress caused by hydroxyl radicals towards adenine, the oxidation products of caffeine were found to be capable of regenerating/repairing oxidized adenine [189]. While coffee provides caffeine, it also provides polyphenolic compounds that, when ingested, become bound to LDL-cholesterol, and protect LDL against oxidation, even after a single dose of coffee [190]. Coffee ingestion also appears protective against some cancers. An umbrella review of 28 meta-analyses indicated an inverse relationship exists between coffee intake and the risk of both liver cancer and endometrial cancer, with greater levels of intake associated with greater protection [191]. When interpreting the health impacts of coffee on CVD, its benefits go beyond its caffeine.

5.5. Glucosinolates and Isothiocyanates

Glucosinolates, compounds typically found within members of the Brassicaceae (i.e., cruciferous vegetables), also exhibit antioxidant properties. These compounds contain sulfur and nitrogen, as well as a sugar moiety to increase their stability and solubility in water. When plant cells of this family are damaged (e.g., chewed), the wall-bound enzyme myrosinase comes in contact with the cell's vacuole contents, interacting with glucosinolates stored there. Myrosinase cleaves their sugar molecules, and the resulting unstable molecule converts to one of several different chemicals, often isothiocyanates, nitriles, or thiocyanates, compounds that give Cruciferous vegetables their spicy, hot flavors [192]. Myrosinase is also produced by some gut bacteria, especially after a prolonged period of exposure to glucosinolates [193]; long-term ingestion of cooked broccoli (i.e., inactivated myrosinase and lowered isothiocyanate production) could potentially lead to isothiocyanate release and absorption from the large intestine. Ingestion of cruciferous vegetables also impacts diversity in the gut microbiome. Participants in a randomized cross-over study showed significant reductions in Firmicutes, concomitant with increases in Bacteroidetes and Bacteroides relative to controls. These dietary and microbiota changes were also associated with increased endocrine function and energy metabolism [194].

5.5.1. Health Impacts of Cruciferous Vegetables

While meta-analyses comparing high vs. low intake of cruciferous vegetables indicated they were inversely associated with both total cancer and all-cause mortality, cruciferous vegetable intake was not significantly associated with decreased levels of CHD, cardiovascular disease, or total stroke (Table 7) [6]. Other analyses indicate that glucosinolates were actually associated with increased CHD risk. When three prospective longitudinal studies were examined, comparison of the top and bottom quintiles of glucosinolate-containing vegetables indicate a weak but significant increased CHD risk; those who consumed one or more servings of Brussels sprouts and cabbage per week had a higher CHD risk than those who consumed them less than once a month (Table 7) [195].

Table 7. Parameters and pertinent results from cited studies examining health outcomes associated with dietary glucosinolates. RR = Relative risk, HR = Hazard risk, CHD = coronary heart disease.

Antioxidant/Food	Biological Impacts Observed	Type of Study	Reference
Cruciferous vegetables (glucosinolates)	Comparison of high vs. low intake of cruciferous vegetables indicated they were inversely associated with both total cancer (RR 0.84, 95%CI 0.72,0.97) and all-cause mortality (RR 0.88, 95%CI 0.80, 0.97).	Meta-analyses examining coronary heart disease (seven studies), total stroke (four studies), cardiovascular disease (eight studies), total cancer (five studies), all-cause mortality (six studies).	[6]
Glucosinolate-containing foods (Brussels sprouts and cabbage)	After adjusting for risk factors, comparison of the top and bottom quintiles found a weak but significant association with increased CHD risk (HR 1.09, 95%CI 1.01, 1.17); those who consumed one or more servings of Brussels sprouts and cabbage per week had a higher CHD risk than those who consumed them less than once a month.	Participants from three prospective longitudinal cohort studies (Nurses' Health Study, Nurses' Health Study II, Health Professionals Follow-up Study) who were free of cardiovascular diseases and cancer at baseline completed food-frequency questionnaires.	[195]

5.5.2. Molecular and Cellular Impacts of Isothiocyanates

As an antioxidant, Sulforaphane, an isothiocyanate produced from the breakdown of glucoraphanin, does not directly inactivate free radicals. Instead, it raises glutathione levels by inhibiting phase I (e.g., cytochrome P450) detoxification enzymes and inducing phase II enzymes that catalyze conjugation reactions. Sulforaphane is known to induce several enzymes that help animal cells deal with oxidative stress, including glutathione transferases, NAD(P)H quinone reductase, and heme oxygenase via the Keap1/Nrf2/ARE pathway [196–198]. Similarly, isothiocyanates such as phenethyl isothiocyanate, indole-3-carbinol, and 3,3'-diindolylmethane have potent chemopreventive activities against hormone-responsive cancers including breast, prostate, and ovarian cancer [197]. These phytochemicals are also associated with several epigenetic mechanisms, including histone modifications, changes in expression of microRNAs, and modification of CpG methylation of cancer-related genes [199]. These molecular-level effects are at least partially responsible for observations that isothiocyanates such as sulforaphane act as a chemopreventive by causing apoptosis or arresting cell growth in cell lines such as breast cancer, colon cancer, ovarian cancer, prostatic cancer, and skin cancer.

Their usefulness in cancer therapy may, however, be impeded by toxicities at high concentrations. Phenethyl isothiocyanate, for example, causes ROS accumulation, leading to cytotoxic effects; this is thought to be due to the reactivity of its sulfhydryl with cysteine residues in its protein targets [200]. Other potential toxicities have been observed in foraging animals, including goiters due to interference with iodine uptake [201], and damage to the gastrointestinal tract, thyroid, kidneys, and liver [202]. Another factor that might interfere with using glucosinolates as a cancer therapy is a human genetic polymorphism in glutathione-S-transferases (GSTs), enzymes that function to protect organisms from oxidative stress triggered by xenobiotics. Individuals with homozygous glutathione transferase mu 1 (GSTM1) or glutathione transferase theta 1 (GSTT1) deletions would experience prolonged exposure to glucosinolate products, possibly causing greater damage if they were being treated with chemotherapeutic doses. While data are still inconclusive, many studies have found the GSTM1 deletion protects against breast cancer development [203].

6. Synergism

Many phytochemicals are known to interact synergistically with other phytochemicals [204], or enhance the effectiveness of conventional therapies [205], possibly due, at least partially, to impacts on the gut microbiome [9]. While an in-depth coverage of the known interactions is beyond the scope of this paper, several authors have reviewed the extensive range of synergistic impacts resulting from mixtures of phytochemicals [204,206]. Understanding and utilizing these synergisms between phytochemicals and other therapeutics may lead to greater effectiveness at lower doses, as well as less injurious treatments and better quality of life. While this certainly rings true for cancer treatment, utilizing synergistic effects of phytochemicals, either within the diet or concomitant with drug therapy, seems to be a treatment option we should consider for other chronic diseases, such as heart disease and type 2 diabetes [207,208].

One of the reasons that phytochemical synergism is of great interest in cancer treatment is because many cancers develop multidrug resistance. Multidrug resistance in cancer cells is often due to increased activity and overexpression of the transmembrane ATP-binding cassette (ABC) transporter [209]. While the original function of these ABC transporters appears to be cellular protection against toxic dietary plant compounds (e.g., phytochemicals), they can also be used to transport lipophilic anticancer drugs out of a cell [210]. A wide range of phytochemicals have reversal effects on multidrug resistance, either due to direct targeting of ABC transporters (e.g., many quinoline and indole alkaloids, epigallocatechin gallate, quercetin, and curcumin), or their ability to regulate expression of ABC transporters (e.g., epigallocatechin gallate, and quercetin) [209]. These reversals or changes in expression when phytochemicals are present allow for greater effectiveness of chemotherapeutic agents.

Perhaps more importantly, basic ideas about dietary synergism are an easily implemented form of health insurance that can be quickly and clearly passed on to patients. As an example of dietary synergism, Thompson et al. [211] developed two diets, one low in plant diversity but containing antioxidant-rich foods, the other high in plant diversity chosen for their ability to reduce oxidative damage to lipids or DNA (Table 8). While both diets were beneficial, the diet providing lesser amounts of a wider array of phytochemicals (high diversity diet) had a greater benefit than consuming higher amounts of fewer phytochemicals, even when those phytochemicals were known for their antioxidant capabilities. Specifically, while lipid peroxidation was significantly lowered in both diets, women consuming the high diversity diet showed a greater benefit. More importantly, measures of DNA oxidation indicated that only those consuming the high diversity diet experienced a significant reduction in DNA oxidation [211]. While the cellular mechanisms may be complex, the take-home message of “darkly colored, strongly flavored, eat a rainbow, add some spice” can help guide food choices and help reduce the incidence of chronic diseases.

Table 8. Parameters and pertinent results from dietary trials examining health outcomes.

Biological Impacts Observed	Details of Study	Reference
Researchers found urinary 8-isoprostane F2 α levels, a measure of lipid peroxidation, were significantly lowered in both low and high diversity diets; although, women who consumed the high diversity diet showed a greater attenuation in lipid peroxidation. The more compelling evidence was a measure of DNA oxidation based on 8-hydroxy-2-deoxyguanosine concentration from the DNA of peripheral lymphocytes. This measure indicated that only those consuming the high diversity diet experienced a significant reduction in DNA oxidation.	Two diets were developed, both supplying 8–10 daily servings of fruits and vegetables; the number of servings was based on individual energy intakes; 106 women consumed these diets over the course of two weeks. One diet (low diversity, antioxidant-rich) utilized mostly plants from five botanical families noted to have high antioxidant activity (e.g., spinach and beet from Chenopodiaceae, broccoli, and cabbage from Brassicaceae, garlic, and onion from Liliaceae, grapefruit and orange from Rutaceae, tomato, and peppers from Solanaceae). These same families were represented, albeit in lower concentration, in the high diversity (18 plant families) diet; the additional plant families in the high diversity diet were chosen because they were associated with a reduction in oxidative damage to lipids or DNA.	[211]
Changes in plasma non-enzymatic antioxidant capacity (NEAC) were much greater, and more often significant, when studies examined humans with oxidative stress-related risk factors, as opposed to healthy subjects (Standardized mean NEAC difference for beverages: healthy subjects 0.177, $p = 0.296$; subjects with risk factors 0.765, $p < 0.001$; for food: healthy subjects 0.502, $p < 0.001$; subjects with risk factors 1.253, $p < 0.001$).	Meta-analyses were performed on studies that examined the effects of long-term dietary supplementation with either plant-based foods (chocolate, fruits, vegetables) and/or beverages (tea, fruit juice, red wine) on plasma non-enzymatic antioxidant capacity.	[46]

7. Impacts on Subject Health

Along with a person’s genetics and gut microbiome, their overall health status appears to be important in determining if and how they respond to different phytochemicals. Observing significant health impacts after dietary interventions are often seen only in those individuals experiencing high oxidative stress. Examples of this include cardiovascular improvements after vitamin C supplementation that were only observed in individuals with high BMI [56], or significant reductions in both systolic and diastolic blood pressures after supplementation with soy isoflavones that were only observed in hypertensive subjects [212].

Those same trends are also associated with dietary interventions. Lettieri-Barbato et al. [46] performed meta-analyses on trials that examined the long-term effects of dietary supplementation with either plant-based foods or beverages on plasma non-enzymatic antioxidant capacity (NEAC). Changes in plasma NEAC were much greater, and more

often significant, when those studies examined humans with oxidative stress-related risk factors, as opposed to healthy subjects (Table 8). Similarly, in a one-year intervention of a Mediterranean diet (PREDIMED study), only the participants who were at high risk for cardiovascular disease showed significant increases in plasma NEAC levels [213]. This recurring theme also suggests that studies investigating phytochemicals for their beneficial impacts should not just focus on responses in healthy individuals when determining their potential health benefits.

8. Concluding Thoughts

Regardless of their original purpose within a plant, it is clear that plant-produced chemicals—from chlorophyll and vitamins to those that primarily act as plant defensive compounds—often benefit human health, especially when they are consumed as a part of a healthy diet. These phytochemicals improve our health through a wide variety of biochemical and molecular mechanisms. When phytochemicals are combined, these mechanisms may sometimes oppose each other; although, many synergistic interactions have been identified. While food-based phytochemicals are viewed as a safer source of chemotherapeutics, it is important to remember that even though humans may benefit from these phytochemicals in their diet, high doses of these compounds still have the potential to trigger toxic reactions and disease states. Despite these drawbacks, food-based phytochemicals hold great promise in our search for effective but more easily tolerated treatments. As we continue studying phytochemical mechanisms and interactions, we will soon be able to predict what combinations will have the greatest impact, for example, against specific cancers or other chronic diseases. While the future discovery of a single phytochemical silver bullet is certainly possible, a shift towards a synergistic approach using phytochemicals that humans typically encounter in their food certainly holds promise for both prevention and treatment of disease.

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