Plant Antioxidants Affect Human and Gut Health, and Their Biosynthesis Is Influenced by Environment and Reactive Oxygen Species

Duroy A. Navarre 1,*, Meijun Zhu 2 and Hanjo Hellmann 3

1 Temperate Tree Fruit and Vegetable Research Unit, United States Department of Agriculture-Agricultural Research Service, Prosser, WA 99350, USA
2 School of Food Science, Washington State University, Pullman, WA 99164, USA
3 School of Biological Sciences, Washington State University, Pullman, WA 99164, USA
* Correspondence: roy.navarre@usda.gov

Abstract: Many environmental stresses cause an increase in reactive oxygen species in plants and alter their nutritional value. Plants respond to many stresses by producing increased amounts of compounds with antioxidant properties including vitamins, phenylpropanoids and carotenoids. Such compounds have wide-ranging health-promoting effects in humans that are partly due to their antioxidant function because oxidative stress underlies many human diseases. Some of these compounds have complex interactions with the gut, promoting gut health and changing the gut microbiome, whereas the gut influences the bioavailability of the ingested compounds and may metabolize them into products with different effects on health than the original compound. Substantial efforts have been made to increase the nutritional value of crops through breeding or transgenic approaches, but comparatively little effort has been directed towards increasing nutritional value through crop management and environment, which may present another approach to enhance the nutritional quality.

Keywords: plants; crops; health; nutrition; inflammation; vitamins; phenylpropanoids; carotenoids

1. Introduction

Plants are vulnerable to high light intensity and oxidative stress because they lack the option to adapt to environmental stress by changing location. Consequently, plants have evolved complex mechanisms to cope with adverse environmental conditions, including the synthesis of small molecules that protect them from oxidative stress and that can have similar protective properties for humans when ingested in the diet.

Abiotic stress results from any environmental condition that has a negative impact on plants and is one of the major factors that reduces agricultural output worldwide. Estimates of worldwide yield losses due to abiotic stresses range from 30–70% (https://www.seedquest.com/News/releases/2008/october/23973.htm accessed on 15 May 2022). Such losses may become even more severe given predicted global climate changes that are expected to cause fluctuations in precipitation patterns and extreme temperature shifts [1]. Abiotic stressors include water, salt, light, heat, and cold [2,3]. In addition, plants often face not just one but several stress conditions simultaneously. For example, reduced availability of water induces stomatal closure, which results in heat stress due to reduced transpiration and cooling efficiency, but also in light stress if CO2 becomes a limiting factor for photosynthesis [2,4]. Plants must respond to a wide range of light conditions, and excess light can lead to photoinhibition, photooxidative damage and reactive oxygen species (ROS) production [5,6]. A typical consequence abiotic stresses is increased oxidative stress in the plant (Figure 1) [7]. Alternatively, plants may produce ROS as a defense mechanism against biotic stress, for example, to increase disease resistance. Among the most common ROS...
that are generated in a plant cell under stress are superoxide ($O_2^-$), hydrogen peroxide ($H_2O_2$), singlet oxygen ($^1O_2$), and hydroxyl (OH-) radicals [2,8].

**ABBIOTIC STRESS**

Salt  
Drought  
Light  
Temperature  
Heavy Metals

**ROS DEFENSE**

1. Detoxifying enzymes  
   e.g., catalases, peroxidases  
2. Antioxidants e.g.,  
   - carotenoids (vitamin A)  
   - Riboflavin (vitamin B$_2$)  
   - pyridoxine (vitamin B$_6$)  
   - ascorbate (vitamin C)  
   - tocopherol (vitamin E)  
   - phenylpropanoids

**CELLULAR DAMAGE**

- lipid peroxidation  
- DNA mutations  
- protein modifications

![Figure 1. Reactive Oxygen Species Generation and Cellular Defense. Reactive oxygen species (ROS) production in cells increase under any prolonged abiotic stress condition such as salt, drought, or temperature stress. ROS increase can be detrimental for the cellular integrity as it may cause membrane damage (lipid peroxidation) or DNA and protein modifications. To prevent this, cells have developed sophisticated defense mechanisms that are either based on enzymatic activities or on secondary metabolites that act as antioxidants, and which can quench and detoxify ROS. These compounds can have similar health-promoting effects when consumed in the diet.](image)

Accumulation of ROS represents a threat for the vitality of a cell because they promote uncontrolled chemical reactions if in close vicinity to other molecules. As such they can cause peroxidation chain reactions in membranes as well as in densely packed oil bodies that can critically harm membrane integrity and render storage oils useless [9,10]. ROS can cause point mutations in DNA, render enzymes non-functional, or react and non-specifically modify many of the organic molecules present in a cell [11]. If not quickly removed, this modification of DNA, proteins, or lipids poses a hazard to the cell [8,9,11–14]. Consequently, organisms must quickly remove these aggressive molecules to reduce damage.

ROS detoxification is mainly accomplished in two complementary ways: cells utilize enzymes such as catalases or peroxidases that react with ROS and convert them into non-aggressive forms such as molecular oxygen ($O_2$) or water ($H_2O$) and/or a range of metabolites with antioxidant capabilities are synthesized that detoxify ROS either as enzymatic cofactors or through direct interaction with ROS [15]. These antioxidants are essential to broadly protect plants from long term impact from various stress situations.

A plant’s response to abiotic stress impacts human nutrition because many of the compounds synthesized by the plant in response to stress are beneficial in the human diet. Many compounds synthesized by plants to protect against oxidative stress function ubiquitously as protective agents in living organisms and are equally capable of providing similar protection to human cells. Oxidative stress and inflammation contribute to many human diseases, including cancer and diabetes [16,17]. Plant antioxidants reduce risk of diabetes and cancer, promote cardiovascular and gut health, and have anti-aging function [18–22].

This review will discuss some vitamins and phytonutrients whose amounts increase in response to oxidative stress and that are provided to the diet by plants. Their effect on human health will be examined, emphasizing their role in the gut, because of the cross talk between the gut and phytonutrients, where the gut influences the efficacy of the ingested phytonutrients, and the phytonutrients mediate gut health and microbiota in turn [23]. A common theme among these molecules, is that a major way they promote health once ingested by humans functionally mimics how they promote health in plants—namely, by reducing damage from oxidative stress. An in-depth understanding of the nature and function of these compounds may help to develop crops with increased amounts of
antioxidants that not only increase the plant’s nutritional value but result in more robust crops that are better able to handle abiotic stress.

2. Vitamins

2.1. Vitamin C

Unlike most animals, humans cannot synthesize vitamin C, so plants are the primary dietary source [24]. Vitamin C has a wide range of health-promoting effects, including stimulating immune function and decreasing risk of strokes, hypertension, coronary heart disease, diabetes, and metabolic disorder [25–27]. Vitamin C deficiency is a worldwide issue, including in the US where up to 13% of young adults were found to have suboptimal levels [28]. Severe vitamin C deficiency can lead to scurvy, which includes bleeding, liver spots and tooth loss. Men with marginal deficient serum amounts had a 57% higher all-cause mortality risk after 12–16 years than men with the highest serum concentrations [29]. The recommended daily allowance in the U.S. for vitamin C is 90 mg for men and 75 mg for women [30].

Vitamin C is a hydrophilic molecule with six carbons and functions as a cofactor for several enzymes. It exists in two primary forms, ascorbic and dehydroascorbic acids, with the different redox state between the two forms being the basis for much of its biological function [29]. The ascorbic form is a potent antioxidant that protects the cell from free radicals and ROS, but also provides reducing power for carotenoid biosynthesis and can regenerate vitamin E [31–33]. The loss of two electrons from ascorbic acid yields the oxidized dehydroascorbic acid form that is stable for several minutes and can be reduced back to ascorbic acid or is irreversibly metabolized. In plants, ascorbate has key roles in coping with the stress from excessive light and in detoxifying \( H_2O_2 \) produced in the chloroplast, with the resulting oxidized monodehydroascorbate regenerated via the Foyer-Halliwell-Asada cycle [34,35].

The major pathway for vitamin C synthesis in plants is through the L-galactose pathway, but other pathways are known and have a role [36,37]. Not surprisingly given its key role in photosynthesis, leaves tend to have high concentrations of vitamin C, up to 50 mM in spinach chloroplasts and 1–5 mM in leaves and can be especially high in alpine plants [38,39]. Amounts in leafy green vegetables such as kale, spinach and mustard greens range from 30–130 mg/100 g fresh weight (FW) [40]. Non-leafy vegetables can contain high amounts, with peppers having up to 242 mg/100 g FW and broccoli 91 mg/100 g FW. More modest amounts occur in beets, carrots, peas, corn, and onions (3–10 mg/100 g FW). Notably, non-green vegetables not exposed to sun can contain significant amounts. Vitamin C content in over 75 potato breeding lines grown in the Pacific Northwest ranged from 11 to 40 mg/100 g FW, with both location and year affecting concentrations [41,42]. Amounts of up to 139 mg/100 g FW were reported in Russet Burbank somaclones [43]. The wide range reported in potato is similar to what is observed in other crops, where the amounts of a given vitamin can vary widely by cultivar [44], and thus it is unlikely any one reported concentration accurately captures the range in a crop.

Perhaps the highest known concentrations of vitamin C occur in camu-camu, a fruit from the Amazon that can have up to 5000 mg/100 g FW [45]. Other fruits with high amounts include the West Indian Cherry (1600 mg/100 g FW), guava (228 mg/100 g FW) and litchis (183 mg/100 g FW) [40]. Amounts are lower in more widely consumed fruits such as oranges (59 mg/100 g FW), apples (4 mg/100 g FW), pears (4 mg/100 g FW), apricots (3 mg/100 g FW) and strawberries (41 mg/100 g FW).

Environmental conditions heavily influence on vitamin C metabolism. Light is the most important signal, and ascorbate amounts increase with light duration and intensity, and decrease in the dark [46]. Lettuce grown under continuous illumination for 48 h had over a 4-fold increase in vitamin C with the amount of the increase dependent on the light intensity [47]. Arabidopsis plants placed in darkness for 72 h had a 91% decrease in leaf ascorbate levels [48]. Levels decreased up to 50% in apples grown under shade cloth, which is often used to prevent sun scalding [49]. Green tomatoes exposed to light
accumulated vitamin C, but mature red fruit did not, suggesting a role for chlorophyll [50]. The wavelength of light influences the effect on vitamin C, with exposure to blue LEDs inducing larger vitamin C increases in citrus and leafy vegetables [51,52]. The higher amounts of vitamin C resulting from high light intensity could be due to several factors, including being a response by the plant to mitigate damage from free radicals and ROS, but also because vitamin C is synthesized from sugars generated during photosynthesis. Several genes involved in ascorbate synthesis in rice have light-responsive cis-elements in their promoters [53] and multiple transcription factors that regulate the pathway are known [54–56].

Ozone and cadmium induce oxidative stress and both increased ascorbate pools in sunflower [57]. Ethylene and jasmonic acid are plant hormones well-known to be responsive to numerous environmental stimuli, including disease and salt stress and both phytohormones are implicated in regulating vitamin C [58,59]. Cherry tomatoes grown with higher amounts of NaCl had higher amounts of vitamin C and tocopherol but gave lower yields [60]. Temperature during the growing season can alter vitamin C amounts, with colder temperatures often resulting in higher amounts, and higher temperatures in decreased amounts, including in broccoli and other Brassicas [44,61]. Temperature during storage may alter levels, with vitamin C losses up to 60% occurring in potatoes after weeks of cold storage [62,63]. Application of higher amounts of nitrogen fertilization resulted in lower vitamin C amounts in fresh-cut potatoes and in a more rapid loss during storage of the cut product [64]. These illustrate the complexity of managing or breeding a crop to maximize its nutritional value, because in addition to field-season effects, post-harvest factors also mediate amounts. Not all potato cultivars lose vitamin C at the same rate in storage, as seen in a study showing some lines had no loss after 2 months of cold storage [65]. Thus, when pursuing breeding approaches to enhance phytonutrient content there are numerous independent mechanisms that could result in higher levels, from plants with higher constitutive expression of the pathway, to a genotype that responds to an environmental signal by synthesizing more of a vitamin than other cultivars, or a line that maintains higher amounts during storage and transport.

2.2. Vitamin E

Vitamin E (vitE) comprises a group of eight related compounds that all contain a chromanol ring and belong either to tocopherols or tocotrienols [66,67]. While tocopherols have a saturated phytol side chain, this chain is unsaturated in tocotrienols. Tocopherols and tocotrienols can be further separated into α-, β-, γ-, and δ-derivatives, which differ in the numbers and location of methyl groups added to their chromanol ring [66]. VitE is a lipophilic compound that provides protection against 1O2 and lipid peroxidation [68,69]. For example, the vitamin is critical in plants for the protection of thylakoid membranes, but it is also needed to reduce peroxidation chain reactions in seed storage oils [68–70]. Leaves primarily synthesize α-tocopherol, which is more efficient in quenching 1O2 [71]. This ROS can easily be generated in chloroplasts via triplet chlorophyll that dissipates its excessive energy to oxygen rather than to photosystem II [68]. In contrast, oil storing seeds (e.g., palm tree fruits, soybean, sunflower, or rapeseed) normally contain either higher amounts of γ-tocopherol or γ-tocotrienol that better protect the stored fatty acids against lipid peroxidation than α-tocopherol, thereby improving long-term viability of the seeds [69,70,72]. Plants with altered vitE levels better tolerate water, osmotic and oxidative stress, and show reduced lipid peroxidation rates [71,73,74].

VitE is only synthesized in photosynthetically active organisms, such as cyanobacteria, algae, and plants, and is essential in the human diet [66,75,76]. Severe vitE deficiencies contribute to cardiovascular diseases and spinocerebellar ataxia, which can manifest in symptoms such as problems with balance and movement coordination, or damage to the retina and vision problems, as well as muscle weakness [77–79]. However, severe deficiencies in the vitamin are uncommon in humans, and are either connected with malnutrition or genetic defects that impact tocopherol uptake [80,81]. Nevertheless, phytofortification in
plants may have general human health benefits by providing greater protection against ROS. Transgenic approaches to increase vitE were successful in wheat, rapeseed, and potato [82–86]. In addition, quantitative trait loci analysis can help to identify traits connected with increased tocopherol contents and enable targeted breeding approaches, as successfully accomplished in rice [87]. Overall, these examples underscore the potential for generation of crops with increased vitE content. The benefit of such approaches may not only be reflected in increased nutritional values but may also generate plants that are more resilient against, e.g., drought or heat stress.

2.3. Vitamin B₂

Vitamin B₂ (vitB₂) or riboflavin is the precursor for flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), two compounds that function in various enzymatic reactions as co-factors, and as such participate in fatty acid oxidation, electron transport, or the biosynthesis of other vitamins [88]. FMN is also the chromophore in the photosensory region of the phototropin blue-light receptors that control plant movements, as well as F-box proteins that are involved in the circadian rhythm [89,90]. Critical for these diverse functions of FAD and FMN is an isoalloxazine ring that is already present in riboflavin. Because of that ring system, riboflavin is a double-sided sword with respect to ROS. The ring system can easily be excited by blue light and thereby may function as a photosensitizer with the potential to generate $^{1}\text{O}_2$ and $\text{O}_2^{-}$; but riboflavin has also been found to act as an antioxidant and participates in the regeneration of reduced glutathione, a key metabolite to quench ROS [91–96]. Humans can utilize riboflavin as a precursor for FAD and FMN biosynthesis, but they lack the enzymatic machinery to make riboflavin [88]. The vitamin is therefore essential to the human diet, and deficiencies have been related to neurological and developmental disorders, cardiovascular disease, anemia, diabetes, and even cancer [97]. Riboflavin deficiencies are fortunately rare, and mostly occur in context with endocrine abnormalities, chronic diarrhea, alcoholism, or liver disorders [98–100]. The biosynthesis of riboflavin is comparably well understood in plants [101]; however, there is no research available that convincingly demonstrate increasing the amount of the vitamin in plants is currently feasible.

2.4. Vitamin B₆

Vitamin B₆ (vitB₆) comprises a group of six related compounds that contain a pyridine ring as their core. They mainly differ in their 4’ substituent that can be an aldehyde group (pyridoxal), an amino methyl group (pyridoxamine), or a hydroxy methyl group) [102]. In addition, these three derivatives can be phosphorylated, which is a requirement for the vitamin to function as cofactor in enzymatic reactions [102]. In plants, two enzymes are involved in vitB₆ de novo biosynthesis called Pyridoxal Synthase (PDX) 1 and 2 that are expressed throughout the plant body [103]. The main biologically active form is pyridoxal-5-phosphate, which is involved in more than 140 biochemical reactions in the cell, mainly related to amino acid metabolism [102]. Besides being a central cofactor for the cellular metabolism, it has also been demonstrated that the vitamin is capable of quenching ROS, such as $^{1}\text{O}_2$ [104], a ROS that can accumulate under light stress in chloroplasts [105]. Consequently, plants deficient in vitB₆ biosynthesis accumulate $^{1}\text{O}_2$ under high light conditions and have increased lipid peroxidation [105]. VitB₆ likely protects more broadly against ROS since vitB₆ mutants are widely sensitive to osmotic and oxidative stress situations as well as UV-B exposure [106–109]. A role in stress protection is further supported by the notion that in Arabidopsis expression of some genes involved in vitB₆ biosynthesis is increased under stress (e.g., paraquat, UV, heat) [110,111]. VitB₆ is an essential nutrient in the human diet as we are unable to synthesize it [102]. Given the broad involvement in cellular metabolism and its potential as an antioxidant, it is not surprising that the vitamin has human health benefits including reduced risk of mental disorders, cardiovascular diseases or diabetes [112]. Although vitB₆ malnutrition is not a general
problem in humans, phytofortification in crops may be beneficial, and the feasibility has been demonstrated by overexpressing PDX genes [113,114].

3. Phytonutrients

Unlike the vitamins above, phytonutrients such as phenylpropanoids and carotenoids do not have recommended daily allowances, yet are highly beneficial in the diet and have numerous health-promoting properties [115].

3.1. Phenylpropanoids

Phenylpropanoids are a diverse group of compounds, of which thousands of types are synthesized by plants (Figure 2). The three largest dietary sources of phenylpropanoids in the U.S. are apples, oranges and potatoes in a study of 34 fruits and vegetables [116]. Not only are phenylpropanoids are the most abundant antioxidants in the human diet, but they also act synergistically with other antioxidants, including vitamin C and tocopherols [117,118]. Moreover, phenylpropanoids are metabolized upon ingestion, and the resulting metabolites may have different health-promoting properties from the ingested compound [119]. Further complicating analysis of phenylpropanoid efficacy is that gut microbiota influence their bioefficacy but because people do not necessarily have the same microbiota, the efficacy of dietary phenylpropanoids can vary among individuals [120–122]. Phenylpropanoids are the most abundant dietary antioxidants, and a great deal has been learned about their effect on gut health over the last decade. Interactions between dietary antioxidants and the gut will be discussed in Section 4.

Figure 2. Three types of phenylpropanoid classes in plants. Plants contain tens of thousands of different phenylpropanoids. Examples are shown of some common phenolic acids, flavonols and anthocyanins found in many fruits and vegetables.

Major dietary phenylpropanoids from plants include hydroxycinnamic acids, anthocyanins and flavonols, most of which are stronger antioxidants than vitamin C and tocopherols [123]. Like vitamin C and carotenoids, phenylpropanoids are critical for plants to cope with light stress and mitigate damage from the resulting $^1$O$_2$ and O$_2^-$, the hydroxyl radical and hydrogen peroxide [124]. Phenylpropanoids contain an aromatic ring with at least one hydroxyl group and function both as reducing agents and hydrogen donors. Their antioxidant strength has been characterized in structure-activity relationships studies that show numerous factors influence their antioxidant activity, including the number and posi-
tion of the hydroxyl groups, C2=C3 conjugation, number and types of ring structure, and whether they are conjugated to other molecules such as sugars or proteins [118,125,126]. Not all phenylpropanoids are equally bioavailable, and some of the factors including structure that influence their antioxidant strength also influence bioavailability.

Phenylpropanoids have numerous roles in plants, not just in abiotic and biotic stress resistance, but in plant growth and development, flowering, fertility, signal transduction and mitigation of damage from ozone [127–129]. Despite the lack of a daily intake reference, they are highly desirable in the diet, conferring various health-promoting properties too numerous to describe in full here, but including anti-obesity, anti-inflammatory and anti-cancer effects, improved concentration, eye, and gut health [120,130–133]. Some, such as the polyphenol, resveratrol, found in grapes and other plants, may extend lifespan through anti-aging mechanisms including modulating telomere attrition and cell senescence, and conferring some of the benefits seen from caloric restriction [134,135].

Phenylpropanoid metabolism begins with the deamination of phenylalanine into cinnamate by phenylalanine ammonia lyase (PAL), which is encoded by a multi-gene family [136–138]. Individual members of the PAL gene family can respond differentially to environmental stress, such as in potato and mushroom where expression of some PAL isogenes, but not others, increases in response to heat stress [139,140]. PAL essentially functions as a gatekeeper, playing a key role in regulating overall phenylpropanoid metabolism, which can assimilate up to 40% of biospheric organic carbon [138]. Phenylpropanoid metabolism can be considered a central component of how plants adapt to and survive environmental stress. Not only PAL, but biosynthetic and regulatory genes downstream in the pathway are highly responsive to environmental stimuli including light, pathogens, cold and heat stress [141–144].

Anthocyanin biosynthesis is mediated by environmental conditions including light, temperature and water stress [145]. Anthocyanins function as light attenuators and biosynthesis increases in high-light conditions [146]. In apple, anthocyanin biosynthesis is increased by colder temperatures and repressed by higher temperatures via various MYB transcription factors [147,148]. Drought stress can increase respiration and reduce photosynthesis, creating conditions of excess light energy. Anthocyanin amounts increased in grapes subjected to drought stress, whereas only small changes were seen in flavonols [149,150]. Tomato cultivars that were more resistant to drought had higher amounts of chlorogenic acid and flavonols, and reduced amounts of H2O2 and lipid peroxidation [151]. Low temperatures more than doubled anthocyanin amounts in blood orange and the authors suggested post-harvest cold storage could be used to increase the nutritional value of oranges grown in warm locations [152]. Higher temperatures increased amounts of chlorogenic acid in potato but decreased anthocyanin amounts and reduced expression of a MYB transcription factor that positively regulates the anthocyanin pathway [153,154]. Plants grown in higher light intensity, such as occurs at high elevation, typically have higher amounts of phenylpropanoids [155]. UV-C irradiation increased anthocyanin in cherries up to 77% [156]. Studies have shown radioprotective effects of phenylpropanoids, and also vitamin C and carotenoids in humans, and they have been proposed for use in mitigating effects from cancer radiotherapy, space travel and nuclear accidents [157].

Soil with higher metal content is another environmental stressor that causes oxidative damage in plants, including formation of OH· radicals. Metals can induce plant polyphenols that mitigate oxidative damage via their antioxidant ability, but also reduce generation of OH· radicals by chelating metals [158]. Salt stress causes a metabolic imbalance and leads to a rapid increase in ROS in plant organelles and induces ROS signal transduction [159]. Plants can respond by synthesizing phenolic acids, flavonols and anthocyanins that ameliorate the oxidative damage [160]. In tomato, salinity led to the preferential accumulation of chlorogenic acids, whereas heat stress led to preferential accumulation of flavonols [161].

Types and amounts of phenylpropanoids vary widely among plants. Hydroxycinnamic acids such as chlorogenic, caffeic and ferulic acids are much more abundant than hydroxybenzoic acids. A 200 mL cup of coffee can contain up to 350 mg of chlorogenic...
acids [162]. Chlorogenic acid can comprise up to 90% of the total soluble phenylpropanoids in potatoes and can rival the amounts found in coffee [163,164]. Blueberries, cherries, apples and plums contain from 50–200 mg per 100 g serving [131] and eggplant, endive and lettuce from 5–60 mg/100 g [162]. Anthocyanins tend to be found in high amounts in foods with the most intense red, blue, or purple pigmentation. Raspberries, blackberries, strawberries and blueberries contain from 20–690 mg/100 g serving, while even higher amounts are in elderberry and chokeberry (410–1800 mg/100 g serving [165,166]. Amounts in a 100 g serving of other fruits and vegetables include red cabbage (322 mg), red onion (49 mg), red grape (27 mg), apple (12 mg), peach (5 mg) and red bean (7 mg) [167]. Purple potato contains up to 16 mg per gram dry weight [168].

Flavonol content also varies widely among plants. Amounts reported in some fruits per 100 g serving range from 1.4–18 mg among blueberry, blackberry, strawberry, apple and cherry [169]. Among onions, kale, broccoli, green beans, and green peppers, that range was 1.4–63.4 mg, with onions having the highest amounts [170,171]. Flavanols in tomato fruit from 20 varieties varied from 0.13–2.2 mg/100 g, with 98% of the amount present in the skin and higher amounts found in those from sunnier environments [172]. Flavonol amounts ranged from 0.1–8 mg/100 g among 91 grape varieties, and an even greater range for anthocyanins of 2.5–628 mg/100 g was found in 64 red-skinned grape varieties [173]. Collectively, these data make it clear that both cultivar and environment have a substantial effect on phenylpropanoid amounts and this should be considered by consumers seeking to increase their dietary intake of phenylpropanoids.

3.2. Carotenoids

Humans cannot synthesize carotenoids, so fruits and vegetables are the major dietary source for carotenoids, but egg yolks, diary and seafood also contribute [174]. Carotenoids are lipophilic terpenoids with phytoene backbones that are derived from C5 isoprenoid precursors and synthesized in chloroplasts [174]. Plant carotenoids are typically C40 molecules and classified as either carotenes or xanthophylls based on their structure and oxygen content. They are pigments responsible for the color of yellow potatoes (lutein), orange carrots (β-carotene) and red tomato (lycopene). While over 1100 carotenoids occur in nature, only around 40 have been found in human blood samples, with six the most abundant in blood: lutein, lycopene, zeaxanthin, β-cryptoxanthin, β-carotene and α-carotene [175–177]. The primary role of carotenoids in plants is light harvesting in photosynthesis and protection from excess light [174]. Carotenoids are antioxidants that have been particularly studied for their role in quenching $^{1}\text{O}_2$, which is produced in chloroplasts under conditions of excess light energy [178]. Additionally, volatile carotenoid oxidation products such as β-cyclocitrinal are generated by $^{1}\text{O}_2$ attack on β-carotene and act as signal molecules that induce changes in large sets of genes that overlap with genes induced by $^{1}\text{O}_2$ oxygen but not H$_2$O$_2$ [179]. These are thought to reprogram the cell from active growth to defense against photooxidative stress. Oxidized carotenoids resulting from scavenging radicals can be regenerated by vitamin C and tocopherols, which prevents their transformation into radical-propagating pro-oxidants [180].

Carotenoids are anti-inflammatory, can improve cognitive performance and decrease the risk of cancer, cardiovascular disease, and diabetes [181–187]. A unique property of dietary carotenoids that functionally mimics their role in plants, is in reducing the risk of age-related macular degeneration [181,182,188], which is an increasing problem with the growing global elderly population [189]. Zeaxanthin and lutein are concentrated in the macula and protect the retina from light, reducing damage from $^{1}\text{O}_2$ oxygen, ROS, and UV-induced peroxidation [186]. Studies suggest supplements of these two carotenoids are beneficial for eye health, even in healthy people [186]. The United States does not have a dietary reference intake, but the China Nutrition Society recommends a daily intake of 10 mg lutein and 2 mg zeaxanthin [186].

A wide range of lutein and zeaxanthin amounts are found in various fruits and vegetables per 100 g serving including spinach (16 mg), turnip greens (13 mg), chard
(11 mg), collards (11 mg), peas (2.5 mg), corn (0.64 mg), and orange (0.13 mg) [40]. \(\beta\)-carotene amounts reported per 100 g serving include sweet potato (12.5 mg), carrots (8.2 mg), and spinach (6.3 mg) [40]. However, the range for a given crop likely varies widely as seen in potato, where white potatoes contain 27–74 \(\mu\)g/100 g FW of carotenoids [190], and cultivated diploid potatoes up to 2 mg of zeaxanthin per 100 g FW [191–193], indicating that breeding can likely greatly increase amounts in crops. Transgenic approaches have increased potato carotenoids over 3000-fold [194,195].

Various environmental stresses increase amounts of carotenoids in plants and Orange (OR) genes help the plant adapt to stress [196]. OR genes were first discovered in cauliflower and activate chromoplast biogenesis creating a sink for stable storage of carotenoids [196]. Increased expression of the OR and the resulting increase in carotenoids conferred additional protection against salt, heat, drought and oxidative stress in sweet potato, alfalfa and tobacco [197–199]. Light generally increases the amounts of carotenoids in plants, although light treatment decreased carotenoids in carrots [200]. Low temperatures can increase carotenoid amounts in plants [200]. A study examining carotenoid content in potatoes grown in multiple locations from the Arctic Circle to Texas and Florida found modest differences in total carotenoids but dramatic changes in carotenoid composition, with violaxanthin predominant in all Alaska locations, but zeaxanthin predominant in Florida and lutein in Texas [201]. Like phenylpropanoids, cultivar and environment strongly influence carotenoid amounts in plants, impacting dietary intake. Moreover, transgenic approaches to increase carotenoids have been very successful, at least in the lab, if not the marketplace.

4. Effect of Plant Foods on Gut Health from an Antioxidant Perspective

It is now realized that many of the compounds discussed above mediate human health through their effect on gut health and the gut microbiome, which has extensive influence on overall health. This is a two-way street, with the gut, in-turn, acting on the ingested compounds, influencing their bioavailability and even metabolizing them into compounds with different bioactivity. As discussed below, data suggest that polyphenols and other antioxidants exert beneficial effects on gut epithelium through improving gut microbiota and their metabolites, which are closely associated with their anti-oxidative and anti-inflammatory functions.

4.1. Oxidative Stress, Inflammation, and Gut Health

The gut epithelium is a large, highly selective barrier [202] that contains a single layer of epithelial cells, which undergo constant self-renewal. This process requires the proliferation and differentiation of epithelial stem cells located at the bottom of the crypts [203,204]. Proliferating cells migrate upwards while differentiating into enterocytes, goblet cells, and enteroendocrine cells [205]. Enterocytes are responsible for nutrient absorption [206], goblet cells secrete mucin to form a protective mucus barrier, and enteroendocrine cells produce hormones that regulate food intake and other physiological responses [207]. On the surface of the epithelial layer, a mucus layer is formed through the mucin secretion by goblet cells and is the frontline in defending against pathogenic bacteria and their translocation into host tissue [208,209]. An impaired mucus layer increases the adhesion of bacteria and delays the elimination of pathogens that can trigger inflammation [210,211]. Therefore, this layer is critical for maintaining epithelial integrity and barrier function [212,213]. Disturbances of gut epithelial barrier function account for the etiologies of many diseases, including inflammatory bowel disease (IBD), colorectal cancer, and other diseases originating from the gut [214–219].

The gut is also an immune organ [220], with immune cells densely populated in intestinal lymphoid follicles or Peyer’s patches [221]. When microorganisms breach the intestinal epithelial cell barrier, they are phagocytized and eliminated by lamina propria macrophages [222], during which macrophages and other cells secrete inflammatory cytokines to elicit local inflammation.
Inflammation is a major factor leading to epithelial dysfunction. The epithelial barrier is disrupted, or the passage of harmful antigens across the epithelial barrier fuels local inflammation, which attracts macrophages and other immune cells to produce ROS and elicit oxidative stress [223]. Thus, gut inflammation and oxidative stress are integrated processes [224]. In addition, inflammatory cytokines impair epithelial barrier function by weakening tight junctions among epithelial cells [225–230]. These changes may result in gut chronic inflammation, as observed in patients with inflammatory bowel diseases (IBD), leading to mucosal erosion and ulceration [231]. Therefore, oxidative stress, inflammation, and impaired gut epithelial barrier create a worsening spiral. Dietary antioxidants from plants can suppress oxidative stress and inflammation in the gut mucosal layer, which improves overall gut health [232–235].

4.2. Plant Antioxidants in Alleviating Gut Epithelial Barrier Disruption, Inflammation, and Oxidative Stress

Dietary phenylpropanoids suppress inflammation and improve gut epithelial barrier function. Naringenin, a major polyphenol in citrus fruits, enhances intestinal barrier integrity [236] and alleviates the dextran sulfate sodium (DSS)-induced colitis in BALB/c mice [237]. Similarly, the green tea flavonoid, epigallocatechin gallate, improves the intestinal barrier of pigs [238]. Polyphenol rich grape seed extract reduces the severity of DSS-induced colitis, alleviates the inflammatory response in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats, and interleukin-10-deficient mice [239–241]. Resveratrol from grape promotes the expression of tight junction proteins to improve epithelial barrier function [242]. Anthocyanins attenuated lipopolysaccharide (LPS)-induced inflammatory response in macrophages, attenuated inflammation, and improved colonic histological architecture in DSS-induced colitis mice [243]. Polyphenol-rich purple potato extract enhanced intestinal epithelial differentiation and improved intestinal barrier functions [219]. Pigmented potato consumption resulted in reduced inflammation and DNA oxidative damage in healthy adult males [244]. Finally, vitamin C suppresses oxidative stress and inflammation in the gut [27].

Carotenoid rich fruit and vegetables are beneficial for gut health. β-carotene fed to mice enhances the expression of antioxidant enzymes, reduces oxidative products, and improves gut epithelial barrier function [245]. Vitamin A, derived from β-carotene, facilitates epithelial differentiation and barrier function [246]. Capsicum extract, which is rich in both polyphenolics and lycopene, prevents oxidative stress and inflammation of gut epithelium and other tissues [247]. Dietary lycopene protects intestinal epithelium from deoxynivalenol-induced oxidative damage [248]. In addition, tocopherols, including vitamin E, mitigate colitis and protect intestinal barrier function [249]. Antioxidant enzyme GSH-Px and plasma antioxidant capacity were significantly increased in the colon of colitis mice supplemented with antioxidant rich Lacto-wolfberry [250]. These benefits are mainly due to the anti-oxidative and anti-inflammatory effects of the ingested compounds [227].

4.3. Plant Antioxidants Shape Gut Microbiota

4.3.1. Gut Microbiota and Gut Health

The human intestine is inhabited by over 100 trillion microorganisms, accounting for ~35,000 different species that are dominated by *Bacteroidetes*, *Firmicutes*, and *Actinobacteria* [251]. The microbial ecosystem in the gut is dynamic and determined by numerous factors. The microbiota colonization begins immediately following birth and is shaped by the host genetics and the environment, including diet and lifestyle.

The gut microbiota has been recognized as a “separate organ” inside our body with vital roles in host physiology, metabolism, and health [252]. The gut epithelial structure is compromised in germ-free mice; colonization of germ-free mice with *Bacteroides thetaiotaomicron*, a prominent constituent of mouse/humane gut normal flora, improves host nutrient absorption and strengthens epithelial barrier function [253,254]. Gut microbiota is an important player in the incidence of chronic diseases, including gastrointestinal dis-
orders and metabolic diseases. The imbalanced gut microbiota, also known as dysbiosis, is closely associated with chronic gut inflammation, and is recognized as an important etiological factor of inflammatory bowel disease (IBD) [255,256]. IBD subjects are characterized by reduced alpha diversity [257], a lower Firmicutes to Bacteroidetes ratio [258], decreased total bacterial load [256], depletion of the butyrate-producing bacteria family Lachnospiraceae [256], Clostridium cluster XIVa [259], Clostridium leptum [258,260], Butyricimonas [257], and Faecalibacterium prausnitzii [258]. On the other hand, IBD patients are associated with the enrichment of the Proteobacteria [256,261].

Gut microbiota also deliver beneficial effects by producing metabolites, including short-chain fatty acids (SCFAs), that have a crucial role in maintaining intestinal epithelial homeostasis, and intestinal barrier function [262]. Butyrate, a major SCFA, inhibits cell proliferation and promotes cell differentiation, induces immune cell differentiation into an anti-inflammatory state, alleviates the inflammatory responses, strengthens the intestinal barrier function [263–269], and ameliorates TNBS-induced colitis in C57BL/6 mice [263]. Alterations in SCFAs, bile acid metabolites, and tryptophan metabolites associated with dysbiosis are implicated in the development of IBD [270,271]. Oral microencapsulated butyrate supplementation increased SCFA-producing bacteria, Lachnospiraceae spp. and Butyricicoccus, in IBD patients [272]. Therefore, the dietary approach to restoring dysbiosis and associated gut metabolites is a viable intervention strategy in IBD management.

4.3.2. Plant Antioxidants and Gut Microbiota

Dietary factors have a predominant role in controlling the composition of gut microbiota. Besides impacting the composition of gut microbes, diet influence the function of gut microbiota through microbial metabolism. Besides the well-known antioxidative benefits of phytonutrients, they also have prebiotic effects and modulate gut microbiota. Phenylpropanoid-rich grape seed extract increased the abundance of beneficial bacteria, specifically Lactobacilli and Bacteroides, in the gut microbiota of mice [240]. Consumption of a high-flavonol cocoa drink or polyphenols from red wine increased Bifidobacteria abundance in feces [273]. Flavanol-enriched cocoa powder supplementation augments Bifidobacteria and Lactobacilli in pig gut microbiota [274]. Quercetin improved the gut microbiota diversity and fecal butyrate level in antibiotic-treated mice, reduced Phascolarctobacterium and Anaerovibrio levels in high cholesterol diet-fed atherosclerotic mice, and increased Bacteroidetes/Firmicutes ratio, Akkermansia muciniphila and Bacteroides vulgatus abundance associated with metabolic improvements in diet-induced obese rats [242,275,276]. Likewise, chlorogenic acid supplementation decreased Blautia, Sutterella, and Akkermansia and increased bacterial diversity and butyrate levels in rats, augmented SCFA-producing bacteria in weaned piglets and in mice induced with hyperuricemia [277–279]. Microbially derived metabolites of quercetin and chlorogenic acid down-regulated the expression of the inflammatory enzyme, cyclooxygenase-2, in human colon adenoma cells [280].

Purple sweet potato anthocyanins increase Bifidobacteria and Lactobacilli abundance and SCFA production in vitro culture of human intestinal microbiota [281]. Phenylpropanoid-rich purple-flesh potato intake results in an increase in the gut microbiota Bacteroidetes/Firmicutes ratio associated with suppressed systemic oxidative stress and gut inflammation in pigs fed a high-fat diet [282]. Similarly, antioxidant rich Goji berry extracts promoted the growth of probiotic Bifidobacterium and Lactobacillus casei in simulated gastric and intestinal juices [283]. Anthocyanin-rich extracts from black goji berry supplementation augmented SCFA-producing bacteria, Coprobacter, and the cecal and fecal acetate and butyrate contents associated with increased antioxidant status in liver and anti-inflammatory status in the colon of C57BL/6 mice [284]. Furthermore, anthocyanin extracts from black goji berry prevented high-fat diet-induced obesity, alleviated intestinal barrier dysfunction and inflammation in mice fed a high-fat diet, and was linked to the increased colonic SCFA level and enriched SCFA producing bacteria, including Roseburia, Bacteroides, and Akkermansia [285]. Goji berry intake in IL-10-deficient mice enriched Bifidobacteria and SCFA-producing bacteria, including Lachnospiraceae-Ruminococcaceae family and Roseburia spp. under Clostridium
cluster XIV, butyrate-producers *C. leptum* and *F. prausnitzii*, and augmented fecal SCFA levels linked to the improved colitis symptom and colonic pathobiological status [286].

Other phytonutrients besides phenylpropanoids modulate gut microbiota. Lycopene increases the abundance of *Bifidobacterium adolescentis* and *Bifidobacterium longum* associated with improvement of gut, blood, and liver lipid metabolism in subjects with moderate obesity [287]. Lycopene supplementation attenuates DSS-induced colitis and gut inflammation and increases *Bifidobacterium* and *Lactobacillus* abundance and fecal SCFA level in colitis mice [288]. β-carotene ameliorates the severity of colitis, suppresses inflammation, and increases the relative abundance of *Faecalibacterium* in DSS-induced colitis rat [289], prevents weaning-induced intestinal inflammation in piglets and alters gut microbiota composition, particularly decreased *Prevotella* abundance [290]. Capsicum extract rich in polyphenols, β-carotene, and lycopene promotes weight loss, improves metabolic markers, and alleviates obesity-associated inflammation and intestinal barrier dysfunction in mice fed with a high-fat diet, likely due to its antioxidant properties and associated gut microbiota modulation [247].

Recently, Otten et al. [291] reported that a two-week supplementation of vitamin C at 1000 mg in healthy individuals resulted in a shift in gut microbiota composition, especially increased relative abundance of *Lachnospiraceae* and decreased *Bacteroidetes*, *Enterococci*, and *Gemmiger formicilis*. Supplementation of 2-O-β-D-glucopyranosyl-L-ascorbic acid (AA-2βG), a natural ascorbic acid derivative isolated from goji berry, alleviates colitis symptoms, inflammatory response, and intestinal barrier impairment in DSS-treated mice accompanied by increased SCFA levels and altered gut microbiota composition [292]. Dietary vitamin E improve intestinal epithelial barrier and suppress oxidative stress in heat-stressed pigs [293]. Consistently, γ-tocopherol-rich tocopherols vitamin E supplementation mitigates colitis, colitis-induced tight junction protein loss, and attenuated DSS-induced depletion of *Roseburia* in DSS-induced colitis mice [249].

5. Conclusions

The findings summarized in this review illustrate the complex role environment can have on human health by altering the nutritional composition of fruits and vegetables. Environmental signals that cause oxidative stress in plants can markedly change the nutritional profile of a crop by triggering the plant to make more of the compounds that counter the stress. This can benefit human health by increasing dietary intake of health-promoting compounds such as phenylpropanoids that mitigate oxidative stress in humans as they do in plants. To be efficacious in humans, such compounds must be bioavailable, which is not just a function of the molecule’s structure, but is also influenced by gut microbiota composition, which can vary among individuals. These illustrate the complex role environment has on human health, including by altering the composition of our foods and our gut microbiome. Substantial effort has taken place to increase the nutritional value of food by breeding or transgenic approaches, but very little attention has been paid to increasing nutritional value by managing crops to maximize their nutritional value, despite numerous studies showing that environment can markedly alter phytonutrient content in crops. Perhaps the lack of such strategies stem from the complexity of the question, which would likely require years of field trials for each crop across multiple locations and with multiple cultivars. Then, there is the challenge of controlling for environmental variables and assessing compounds that are naturally variable in amounts anyway. Positive effects on nutrition from deliberate management would have to be balanced with potentially negative effects on the crop, such as yield reduction. To date, viticulture may have been the most active studying the environment-crop quality interaction, where the concept of terroir is now well-established [150]. Terroir is a concept that the land and climate where a grape is grown imparts unique characteristics, so one region might produce a better quality of wine than another region. Of course, efforts to maximize terroir are largely due to interest in sensory qualities, not nutritional value, although some of the compounds that influence flavor also have nutritional value. At least one kind of abiotic stress has been
deliberately used to alter a crop’s phytonutrient content, with water stress used to improve flavor, anthocyanin content and quality in grapes [150]. Perhaps in the future more crops will be similarly managed to maximize their nutritional value using more sophisticated agronomic approaches. As with grapes, additional incentive for such approaches may come from the fact that taste and appearance (such as more intense coloration) may also be enhanced, further increasing the appeal to consumers.

**Author Contributions:** Conceptualization, D.A.N., M.Z. and H.H.; All authors participated in writing and editing the manuscript. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Thornton, P.K.; Ericksen, P.; Herrero, M.; Challinor, A. Climate variability and vulnerability to climate change: A review. *Glob. Chang. Biol.* 2014, 20, 3313–3328. [CrossRef] [PubMed]
2. He, M.; He, C.-Q.; Ding, N.-Z. Abiotic Stresses: General Defenses of Land Plants and Chances for Engineering Multistress Tolerance. *Front. Plant Sci.* 2018, 9, 1771. [CrossRef] [PubMed]
3. Mahajan, S.; Tuteja, N. Cold, salinity and drought stresses: An overview. *Arch. Biochem. Biophys.* 2005, 444, 139–158. [CrossRef] [PubMed]
4. Jiang, W.; Tong, T.; Chen, X.; Deng, F.; Zeng, F.; Pan, R.; Zhang, W.; Chen, G.; Chen, Z.-H. Molecular response and evolution of plant anion transport systems to abiotic stress. *Plant Mol. Biol.* 2021, 1–16. [CrossRef]
5. Bassi, R.; Dall’Osto, L. Dissipation of Light Energy Absorbed in Excess: The Molecular Mechanisms. *Annu. Rev. Plant Biol.* 2020, 72, 47–76. [CrossRef]
6. Pascual, J.; Rahikainen, M.; Kangasjärvi, S. *Plant Light Stress*; Wiley Online Library: Hoboken, NJ, USA, 2017; pp. 1–6.
7. Demidchik, V. Mechanisms of oxidative stress in plants: From classical chemistry to cell biology. *Environ. Exp. Bot.* 2015, 109, 212–228. [CrossRef]
8. Zandi, P.; Schnug, E. Reactive Oxygen Species, Antioxidant Responses and Implications from a Microbial Modulation Perspective. *Biology* 2022, 11, 155. [CrossRef]
9. Auten, R.L.; Davis, J.M. Oxygen Toxicity and Reactive Oxygen Species: The Devil Is in the Details. *Pediatr. Res.* 2009, 66, 121–127. [CrossRef]
10. Apel, K.; Hirt, H. Reactive oxygen species: Metabolism, oxidative stress, and signal transduction. *Annu. Rev. Plant Biol.* 2004, 55, 373–399. [CrossRef]
11. Singh, A.; Mehta, S.; Yadav, S.; Nagar, G.; Ghosh, R.; Roy, A.; Chakraborty, A.; Singh, I.K. How to Cope with the Challenges of Environmental Stresses in the Era of Global Climate Change: An Update on ROS Stave off in Plants. *Int. J. Mol. Sci.* 2022, 23, 1995. [CrossRef]
12. Al Hassan, M.; Chaura, J.; Donat-Torres, M.P.; Boscaiu, M.; Vicente, O. Antioxidant responses under salinity and drought in three closely related wild monocots with different ecological optima. *AoB Plants* 2017, 9, plx009. [CrossRef] [PubMed]
13. Ray, P.D.; Huang, B.-W.; Tsuji, Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cell. Signal.* 2012, 24, 981–990. [CrossRef] [PubMed]
14. Hayes, J.D.; Dinkova-Kostova, A.T.; Tew, K.D. Oxidative Stress in Cancer. *Cancer Cell* 2020, 38, 167–197. [CrossRef] [PubMed]
15. Halim, M.; Halim, A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). *Diabetes Metab. Syndr. Clin. Res. Rev.* 2019, 13, 1165–1172. [CrossRef]
16. Black, H.S.; Boehm, F.; Edge, R.; Truscott, T.G. The Benefits and Risks of Certain Dietary Carotenoids that Exhibit both Anti- and Pro-Oxidative Mechanisms—A Comprehensive Review. *Antioxidants* 2020, 9, 264. [CrossRef]
17. Favela-González, K.M.; Hernández-Almanza, A.Y.; De la Fuente-Salcido, N.M. The value of bioactive compounds of cruciferous vegetables (*Brassica*) as antimicrobials and antioxidants: A review. *J. Food Biochem.* 2020, 44, e13414. [CrossRef]
18. Pathan, S.; Siddiqui, R.A. Nutritional Composition and Bioactive Components in Quinoa (*Chenopodium quinoa* Willd.) Greens: A Review. *Nutrients* 2022, 14, 558. [CrossRef]
19. Naidu, K.A. Vitamin C in human health and disease is still a mystery? An overview. *Nutr. J.* 2003, 2, 7. [CrossRef]
20. Gruber, J.; Schaffer, S.; Halliwell, B. The mitochondrial free radical theory of ageing—Where do we stand? *Front Biosci.* 2008, 13, 6554–6579. [CrossRef]
23. Bresciani, L.; Martini, D.; Mená, P.; Tassotti, M.; Calani, L.; Brigati, G.; Briganti, F.; Holasek, S.; Malliga, D.-E.; Lamprecht, M.; et al. Absorption Profile of (Poly)Phenolic Compounds after Consumption of Three Food Supplements Containing 36 Different Fruits, Vegetables, and Berries. *Nutrients* **2017**, *9*, 194. [CrossRef]

24. Vicente, A.R.; Manganaris, G.A.; Darre, M.; Ortiz, C.M.; Sozzi, G.O.; Crisostomo, C.H. Chapter 19—Composition of fruit and vegetable quality and nutritional value. In *Postharvest Handling*, 4th ed.; Florkowski, W.J., Banks, N.H., Shewfelt, R.L., Prussia, S.E., Eds.; Academic Press: San Diego, CA, USA, 2022; pp. 565–619.

25. Moser, M.A.; Chun, O.K. Vitamin C and Heart Health: A Review Based on Findings from Epidemiologic Studies. *Int. J. Mol. Sci.* **2016**, *17*, 1328. [CrossRef]

26. Pearson, J.F.; Pullar, J.M.; Wilson, R.; Spittlehouse, J.K.; Vissers, M.C.M.; Skidmore, P.M.L.; Willis, J.; Cameron, V.A.; Carr, A.C. Vitamin C Status Correlates with Markers of Metabolic and Cognitive Health in 50-Year-Olds: Findings of the CHALICE Cohort Study. *Nutrients* **2017**, *9*, 831. [CrossRef]

27. Carr, A.C.; Maggini, S. Vitamin C and Immune Function. *Nutrients* **2017**, *9*, 1211. [CrossRef]

28. Hamp, J.S.; Taylor, C.A.; Johnston, C.S. Vitamin C Deficiency and Depletion in the United States: The Third National Health and Nutrition Examination Survey, 1988 to 1994. *Am. J. Public Health* **2004**, *94*, 870–875. [CrossRef]

29. Granger, M.; Eck, P. Chapter Seven—Dietary Vitamin C in Human Health. In *Advances in Food and Nutrition Research*; Eskin, N.A.M., Ed.; Academic Press: San Diego, CA, USA, 2018; Volume 83, pp. 281–310.

30. National Institutes of Health. Vitamin C. Office of Dietary Supplements. 2022. Available online: <https://ods.od.nih.gov/factsheets/VitaminCHealthprofessional/> (accessed on 20 June 2022).

31. Carità, A.C.; Fonseca-Santos, B.; Shultz, J.D.; Michniak-Kohn, B.; Chorilli, M.; Leonardi, G.R. Vitamin C: One compound, several uses. Advances for delivery, efficiency and stability. *Nanomed. Nanotechnol. Biol. Med.* **2020**, *24*, 102117. [CrossRef]

32. Njus, D.; Kelley, P.M.; Tu, Y.-J.; Schlegel, H.B. Ascorbic acid: The chemistry underlying its antioxidant properties. *Free Radic. Biol. Med.* **2020**, *159*, 37–43. [CrossRef]

33. Saga, G.; Giorgetti, A.; Fufezan, C.; Giacometti, G.M.; Bassi, R.; Morosinotto, T. Mutation Analysis of Violaxanthin De-epoxidase Identifies Substrate-binding Sites and Residues Involved in Catalysis. *J. Biol. Chem.* **2010**, *285*, 23763–23770. [CrossRef]

34. Foyer, C.H.; Noctor, G. Ascorbate and Glutathione: The heart of the redox hub. *Plant Physiol.* **2011**, *155*, 2–18. [CrossRef]

35. Miyaji, T.; Morosinotto, T.; Takeuchi, Y.; Yamaji, N.; Yokosho, K.; Shimazawa, A.; Sugimoto, E.; Omote, H.; Ma, J.F.; Shinozaki, K.; et al. AtPHT4.4 is a chloroplast-localized ascorbate transporter in Arabidopsis. *Nat. Commun.* **2015**, *6*, 5928. [CrossRef]

36. Wheeler, G.L.; Jones, M.A.; Smirnoff, N. The biosynthetic pathway of vitamin C in higher plants. *Nature* **1998**, *393*, 365–369. [CrossRef]

37. Laing, W.A.; Wright, M.A.; Cooney, J.; Bulley, S.M. The missing step of the L-galactose pathway of ascorbate biosynthesis is dependent on the photosynthetic electron transport chain but independent of sugars in Arabidopsis. *J. Exp. Bot.* **2007**, *58*, 2661–2671. [CrossRef]

38. Shigeoka, S.; Maruta, T. Cellular redox regulation, signaling, and stress response in plants. *Environ. Exp. Bot.* **2002**, *49*, 156–160. [CrossRef]

39. Nassar, A.M.K.; Kubow, S.; Leclerc, Y.; Donnelly, D.J. Somatic mining for phytonutrient improvement of ‘Russet Burbank’ potato. *Ann. Bot.* **1999**, *84*, 661–669. [CrossRef]

40. McVaugh, D. Identification of the light of different intensities. *J. Hortic. Sci. Biotechnol.* **2012**, *87*, 429–434. [CrossRef]

41. Love, S.L.; Salaiz, T.; Shafii, B.; Price, W.J.; Mosley, A.R.; Thornton, R.E. Stability of Expression and Concentration of Ascorbic Acid in North American Potato Germplasm. *HortScience* **2004**, *39*, 1328. [CrossRef]

42. Love, S.L.; Neves, D.A.; Martinez, J.; Neves, D.A.; Martínez, J.; Godoy, H.T. Vitamin C in camu-camu [Myrciaria dubia (H.B.K.) McVaugh]: Evaluation of extraction and analytical methods. *Food Res. Int.* **2019**, *115*, 160–166. [CrossRef]

43. Ishikawa, T.; Shigeoka, S. Light regulation of vitamin C in tomato fruit is mediated [CrossRef]

44. Lee, S.K.; Kader, A.A. Preharvest and postharvest factors influencing vitamin C content of horticultural crops. *Postharvest Biol. Technol.* **2000**, *20*, 207–220. [CrossRef]

45. Cunha-Santos, E.C.E.; Viganó, J.; Neves, D.A.; Martinez, J.; Godoy, H.T. Vitamin C in camu-camu [Myrciaria dubia (H.B.K.) McVaugh]: Evaluation of extraction and analytical methods. *Food Res. Int.* **2019**, *115*, 160–166. [CrossRef]

46. Shigeoka, S.; Maruta, T. Cellular redox regulation, signaling, and stress response in plants. *Biosci. Biotechnol. Biochem.* **2014**, *78*, 1457–1470. [CrossRef]

47. Zhou, W.L.; Liu, W.K.; Yang, Q.C. Quality changes in hydroponic lettuce grown under pre-harvest short-duration continuous light of different intensities. *J. Hortic. Sci. Biotechnol.* **2012**, *87*, 429–434. [CrossRef]

48. Shigeoka, S.; Naka, M.; Moroiki, S.; Motoki, T.; Maruta, T.; Yoshimura, K.; Ishikawa, T.; Shigeoka, S. Light regulation of ascorbate biosynthesis is dependent on the photosynthetic electron transport chain but independent of sugars in Arabidopsis. *J. Exp. Bot.* **2007**, *58*, 2661–2671. [CrossRef]

49. Li, M.; Ma, F.; Wang, P.; Zhang, M.; Hou, C.; Liang, D. Influence of light on ascorbate formation and metabolism in apple fruits. *Planta* **2009**, *230*, 39–51. [CrossRef]

50. Ngkas, N.; Witting, E.; Nicole, C.; Labrie, C.; Marcellis, L.F.M. Light regulation of vitamin C in tomato fruit is mediated through photosynthesis. *Environ. Exp. Bot.* **2019**, *158*, 180–188. [CrossRef]
Oxygen 2022, 2

52. Ohashi-Kaneko, K.; Takase, M.; Kon, N.; Fujiwara, K.; Kurata, K. Effect of light quality on growth and vegetable quality in leaf lettuce, spinach and komatsuna. *Environ. Control Biol.* 2007, 45, 189–198. [CrossRef]

53. Fukunaga, K.; Fujikawa, Y.; Esaka, M. Light regulation of ascorbic acid biosynthesis in rice via light responsive cis-elements in genes encoding ascorbic acid biosynthetic enzymes. *Biosci. Biotechnol. Biochem.* 2010, 74, 888–891. [CrossRef]

54. Hu, T.; Ye, J.; Tao, P.; Li, H.; Zhang, J.; Zhang, Y.; Ye, Z. The tomato HD-Zip I transcription factor SI HZ 24 modulates ascorbate accumulation through positive regulation of the d-mannose/l-galactose pathway. *Plant J.* 2016, 85, 16–29. [CrossRef]

55. Zhang, W.; Lorence, A.; Gruszewski, H.A.; Chevone, B.I.; Nessler, C.L. AMR1, an Arabidopsis gene that coordinately and negatively regulates the mannose/l-galactose ascorbic acid biosynthetic pathway. *Plant Physiol.* 2009, 150, 942–950. [CrossRef]

56. Wang, J.; Yu, Y.; Zhang, Z.; Quan, R.; Zhang, H.; Ma, L.; Deng, X.W.; Huang, R. *Arabidopsis* CSN5B Interacts with VTC1 and Modulates Ascorbic Acid Synthesis. *Plant Cell* 2015, 25, 625–636. [CrossRef]

57. Di Cagno, R.; Guidi, L.; De Gara, L.; Soldatini, G.F. Combined cadmium and ozone treatments affect photosynthesis and ascorbate-deficient defences in sunflower. *New Phytol.* 2001, 151, 627–636. [CrossRef]

58. Zhang, Z.; Wang, J.; Zhang, R.; Huang, R. The ethylene response factor AtERF98 enhances tolerance to salt through the transcriptional activation of ascorbic acid synthesis in Arabidopsis. *Plant J.* 2012, 71, 273–287. [CrossRef]

59. Sasaki-Sekimoto, Y.; Taki, N.; Obayashi, T.; Aono, M.; Matsumoto, F.; Sakurai, N.; Suzuki, H.; Hirai, M.Y.; Noji, M.; Saito, K.; et al. Coordinated activation of metabolic pathways for antioxidants and defence compounds by jasmonates and their roles in stress tolerance in Arabidopsis. *Plant J.* 2005, 44, 653–668. [CrossRef]

60. Serio, F.; De Gara, L.; Caretto, S.; Leo, L.; Santamaria, P. Influence of an increased NaCl concentration on yield and quality of cherry tomato grown in posidonia (*Posidonia oceanica* (L) Delile). *J. Sci. Food Agric.* 2004, 84, 1885–1890. [CrossRef]

61. Dominguez-Perles, R.; Mená, P.; García-Vigüera, C.; Moreno, D.A. *Brassica* Foods as a Dietary Source of Vitamin C. A Review. *Crit. Rev. Food Sci. Nutr.* 2014, 54, 1076–1091. [CrossRef]

62. Dale, M.F.B.; Griffiths, D.W.; Todd, D.T. Effects of genotype, environment, and postharvest storage on the total ascorbate content of potato (*Solanum tuberosum*) tubers. *J. Agric. Food Chem.* 2003, 51, 244–248. [CrossRef]

63. Keijbets, M.J.H.; Ebbenhorst-Seller, G. Loss of vitamin C (L-ascorbic acid) during long-term cold storage of Dutch table potatoes. *Crit. Rev. Food Sci. Nutr.* 1999, 39, 125–130. [CrossRef]

64. Licciardello, F.; Lombardo, S.; Rizzo, V.; Pittino, I.; Pandino, G.; Strano, M.G.; Muratore, G.; Restuccia, C.; Mauronicale, G. Integrated agronomical and technological approach for the quality maintenance of ready-to-fry potato sticks during refrigerated storage. *Postharvest Biol. Technol.* 2012, 65, 13–20. [CrossRef]

65. Külen, O.; Stushnoff, C.; Holm, D.G. Effect of cold storage on total phenolics content, antioxidant activity and vitamin C level of selected potato clones. *J. Sci. Food Agric.* 2013, 93, 2437–2444. [CrossRef]

66. Lushchak, V.I.; Semchuk, N.M. Tocopherol biosynthesis: Chemistry, regulation and effects of environmental factors. *Acta Physiol. Plant.* 2012, 34, 1607–1628. [CrossRef]

67. Fritsche, S.; Wang, X.; Jung, C. Recent Advances in our Understanding of Tocopherol Biosynthesis in Plants: An Overview of Key Genes, Functions, and Breeding of Vitamin E Improved Crops. *Antioxidants* 2017, 6, 99. [CrossRef]

68. Krieger-Liszka, A.; Trebst, A. Tocopherol is the scavenger of singlet oxygen produced by the triplet states of chlorophyll in the PSII reaction centre. *J. Exp. Bot.* 2005, 57, 1677–1684. [CrossRef]

69. Salimath, S.S.; Romsdahl, T.B.; Konda, A.R.; Zhang, W.; Cahoon, E.B.; Dowd, M.K.; Wedegaertner, T.C.; Hake, K.D.; Chapman, K.D. Production of Tocotrienols in Seeds of Cotton (*Gossypium hirsutum*) Enhances Oxidative Stability and Offers Nutraceutical Potential. *Plant Biotechnol. J.* 2019, 17, 1268–1282. [CrossRef]

70. Konda, A.R.; Nazarenus, T.J.; Nguyen, H.; Yang, J.; Gelli, M.; Swenson, S.; Shipp, J.M.; Schmidt, M.A.; Cahoon, R.E.; Ciftci, O.N.; et al. Metabolic engineering of soybean seeds for enhanced vitamin E tocochromanol content and effects on oil antioxidant properties in polyunsaturated fatty acid-rich germplasm. *Metab. Eng.* 2020, 57, 63–73. [CrossRef]

71. Abbasi, A.R.; Hajirezaei, M.; Hofius, D.; Sonnewald, U.; Voll, L.M. Specific roles of alpha- and gamma-tocopherol in abiotic stress responses of transgenic tobacco. *Plant Physiol.* 2007, 143, 1720–1738. [CrossRef]

72. Mangold, H.K. *The Lipid Handbook*, 2nd ed.; Gunstone, F.D., Harwood, J.L., Padley, F.B., Eds.; Chapman & Hall: London, UK, 1994; Volume 39, pp. 315–316, ISBN 0412433206.

73. Liu, X.; Hua, X.; Guo, J.; Qi, D.; Wang, L.; Liu, Z.; Jin, Z.; Chen, S.; Liu, G. Enhanced tolerance to drought stress in transgenic tobacco plants overexpressing VTE1 for increased tocopherol production from Arabidopsis thaliana. *Biotechnol. Lett.* 2008, 30, 1275–1280. [CrossRef]

74. Ouyang, S.; He, S.; Liu, P.; Zhang, W.; Zhang, J.; Chen, S. The role of tocopherol cyclase in salt stress tolerance of rice (*Oryza sativa*). *Sci. China Life Sci.* 2011, 54, 181–188. [CrossRef]

75. Cheng, Z.; Sattler, S.; Maeda, H.; Sakuragi, Y.; Bryant, D.A.; DellaPenna, D. Highly Divergent Methyltransferases Catalyze a Conserved Reaction in Tocopherol and Plastoquinone Synthesis in Cyanobacteria and Photosynthetic Eukaryotes. *Plant Cell* 2003, 15, 2343–2356. [CrossRef]

76. Grusak, M.A.; DellaPenna, D. Improving the nutrient composition of plants to enhance human nutrition and health. *Annu. Rev. Plant Biol.* 1999, 50, 133–161. [CrossRef]

77. Traber, M.G.; Leonard, S.W.; Ebenuwa, I.; Violet, P.C.; Wang, Y.; Niyyati, M.; Padayatty, S.; Tu, H.; Courville, A.; Bernstein, S.; et al. Vitamin E absorption and kinetics in healthy women, as modulated by food and by fat, studied using 2 deuterium-labeled alpha-tocopherols in a 3-phase crossover design. *An. J. Clin. Nutr.* 2019, 110, 1148–1167. [CrossRef] [PubMed]
86. Chaudhary, N.; Khurana, F. Cloning, functional characterisation and transgenic manipulation of vitamin E biosynthesis genes of wheat. *Funct. Plant Biol.* 2013, 40, 1129–136. [CrossRef] PubMed

87. Wang, X.Q.; Yoon, M.Y.; He, Q.; Kim, T.S.; Tong, W.; Choi, B.W.; Lee, Y.S.; Park, Y.J. Natural variations in OsgammaTMT contribute to diversity of the alpha-tocopherol content in rice. *Mol. Genet. Genom.* 2015, 290, 2121–2135. [CrossRef] PubMed

88. Wolak, N.; Zawrotniak, M.; Gogol, M.; Kozik, A.; Rapala-Kozik, M. Vitamins B1, B2, B3 and B9—Occurrence, Biosynthesis Pathways and Functions in Human Nutrition. *Mini-Rev. Med. Chem.* 2017, 17, 1075–1111. [CrossRef] PubMed

89. Ito, S.; Song, Y.H.; Imazumi, T. LOV Domain-Containing F-Box Proteins: Light-Dependent Protein Degradation Modules in Arabidopsis. *Mol. Plant* 2012, 5, 573–582. [CrossRef]

90. Roberts, D.; Pedmale, U.V.; Morrow, J.; Sachdev, S.; Lechner, E.; Tang, X.; Zheng, N.; Hannink, M.; Genschik, P.; Liscum, E. Modulation of Phototropic Responsiveness in Arabidopsis through Ubiquitination of Phototropin 1 by the CUL3-Ring E3 Ubiquitin Ligase CRL3NPB3. *Plant Cell* 2011, 23, 3627–3640. [CrossRef] PubMed

91. Ashoori, M.; Saedisomeilia, A. Riboflavin (vitamin B2) and oxidative stress: A review. *Br. J. Nutr.* 2014, 111, 185–199. [CrossRef] PubMed

92. De Gara, L.; de Pinto, M.C.; Tommasi, F. The antioxidant systems vis-à-vis reactive oxygen species during plant–pathogen interaction. *Plant Physiol. Biochem.* 2003, 41, 863–870. [CrossRef]

93. Liang, J.-Y.; Yuann, J.-M.P.; Cheng, C.-W.; Jian, H.-L.; Lin, C.-C.; Chen, L.-Y. Blue light induced free radicals from riboflavin on E. coli DNA damage. *J. Photochem. Photobiol. B Biol.* 2013, 119, 60–64. [CrossRef]

94. Olfat, N.; Ashoori, M.; Saedisomeilia, A. Riboflavin is an antioxidant: A review update. *Br. J. Nutr.* 2022, 1–27. [CrossRef]

95. Silva, R.; Aguiar, T.Q.; Oliveira, R.; Domingues, L. Light exposure during growth increases riboflavin production, reactive oxygen species accumulation and DNA damage in Ashbya gossypii riboflavin-overproducing strains. *FEMS Yeast Res.* 2019, 19, foy114.

96. Toyosaki, T. Antioxidant Effect of Riboflavin in Enzymatic Lipid-Peroxidation. *J. Agric. Food Chem.* 1992, 40, 1727–1730. [CrossRef]

97. Suwannasom, N.; Kao, I.; Pruß, A.; Georgieva, R.; Bäumler, H. Riboflavin: The Health Benefits of a Forgotten Natural Vitamin. *Int. J. Mol. Sci.* 2020, 21, 950. [CrossRef] PubMed

98. Balasubramaniam, S.; Christodoulou, J.; Rahman, S. Disorders of riboflavin metabolism. *J. Inherit. Metab. Dis.* 2019, 42, 608–619. [CrossRef] PubMed

99. Finnsterer, J. An update on diagnosis and therapy of metabolic myopathies. *Expert Rev. Neurother.* 2018, 18, 933–943. [CrossRef] PubMed

100. Pechakara, B.V.; Gupta, M. Vitamin B2 (Riboflavin); StatPearls: Treasure Island, FL, USA, 2022.

101. Sandoval, F.J.; Zhang, Y.; Roje, S. Flavin Nucleotide Metabolism in Plants: Monofunctional enzymes synthesize fad in plastids. *J. Biol. Chem.* 2008, 283, 30890–30900. [CrossRef]

102. Parra, M.; Stahl, S.; Hellmann, H. Vitamin B6 and Its Role in Cell Metabolism and Physiology. *Cells* 2018, 7, 84. [CrossRef]

103. Tambasco-Studart, M.; Titiz, O.; Raschle, T.; Forster, G.; Amrhein, N.; Fitzpatrick, T.B. Vitamin B6 biosynthesis in higher plants. *Proc. Natl. Acad. Sci. USA* 2005, 102, 13687–13692. [CrossRef] PubMed

104. Bilski, P.; Li, M.Y.; Ehrenshaft, M.; Daub, M.E.; Chignell, C.F. Symposium-in-Print Vitamin B6 (Pyridoxine) and Its Derivatives Are Efficient Single Oxygen Quenchers and Potential Fungal Antioxidants. *Photochem. Photobiol.* 2000, 71, 129–134. [CrossRef]

105. Havaux, M.; Kas, B.; Szewczyk, A.; Rumeau, D.; Franck, F.; Caffarri, S.; Triantaphylides, C. Vitamin B6 deficient plants display increased sensitivity to high light and photo-oxidative stress. *BMC Plant Biol.* 2009, 9, 130. [CrossRef]

106. Titiz, O.; Tambasco-Studart, M.; Warzyh, E.; Apel, K.; Amrhein, N.; Laloï, C.; Fitzpatrick, T.B. PXD1 is essential for vitamin B6 biosynthesis, development and stress tolerance in Arabidopsis. *Plant J.* 2006, 48, 933–946. [CrossRef]

107. Chen, H.; Xiong, L. Pyridoxine is required for post-embryonic root development and tolerance to osmotic and oxidative stresses. *Plant J.* 2005, 44, 396–408. [CrossRef]
108. Czégény, G.; Körösi, L.; Strid, Á.; Hideg, É. Multiple roles for Vitamin B6 in plant acclimation to UV-B. Sci. Rep. 2019, 9, 1259. [CrossRef]

109. Raschke, M.; Boycheva, S.; Crèvecœur, M.; Nunes-Nesi, A.; Witt, S.; Fernie, A.R.; Amrhein, N.; Fitzpatrick, T.B. Enhanced levels of vitamin B6 increase aerial organ size and positively affect stress tolerance in Arabidopsis. Plant J. 2011, 66, 414–432. [CrossRef] [PubMed]

110. Leutendorf, J.E.; Mooney, S.L.; Chen, L.; Hellmann, H.A. Arabidopsis thaliana PDX1.2 is critical for embryo development and heat shock tolerance. Planta 2014, 240, 137–146. [CrossRef] [PubMed]

111. Denslow, S.A.; Rueeschhoff, E.E.; Daub, M.E. Regulation of the Arabidopsis thaliana vitamin B6 biosynthesis genes by abiotic stress. Plant Physiol. Biochem. 2007, 45, 152–161. [CrossRef] [PubMed]

112. Hellmann, H.; Mooney, S. Vitamin B6: A molecule for human health? Molecules 2010, 15, 442–459. [CrossRef]

113. Fudge, J.B.; Mangel, N.; Gruissem, W.; Vanderschuren, H.; Fitzpatrick, T.B. Rationalising vitamin B6 biofortification in crop plants. Curr. Opin. Biotechnol. 2017, 44, 130–137. [CrossRef]

114. Vanderschuren, H.; Boycheva, S.; Li, K.-T.; Szydlowski, N.; Gruissem, W.; Fitzpatrick, T.B. Strategies for vitamin B6 biofortification of plants: A dual role as a micronutrient and a stress protectant. Front. Plant Sci. 2013, 4, 143. [CrossRef]

115. Nasri, H.; Baradaran, A.; Shirzad, H.; Rafieian-Kopaei, M. New Concepts in Nutraceuticals as Alternative for Pharmaceuticals.

116. Wang, T.-Y.; Li, Q.; Bi, K.-S. Bioactive flavonoids in medicinal plants: Structure, activity and biological fate.

117. Croft, K.D. The chemistry and biological effects of flavonoids and phenolic acids: A colorful model for the regulation and evolution of biochemical pathways. Ann. Agric. Sci. 2018, 73, 17–23. [CrossRef]

118. Espín, J.C.; González-Sarrias, A.; Tomás-Barberán, F.A. The gut microbiota: A key factor in the therapeutic effects of (poly)phenols. Biochem. Pharmacol. 2017, 139, 82–93. [CrossRef] [PubMed]

119. Hernández, I.; Alegría, L.; Van Breusegem, F.; Munné-Bosch, S. How relevant are flavonoids as antioxidants in plants? Trends Plant Sci. 2009, 14, 125–132. [CrossRef] [PubMed]

120. Cardona, F.; Andrés-Lacueva, C.; Tulipani, S.; Tínahones, F.J.; Queipo-Ortuño, M.I. Benefits of polyphenols on gut microbiota and implications in human health. J. Nutr. Biochem. 2013, 24, 1415–1422. [CrossRef] [PubMed]

121. Bolca, S.; Van de Wiele, T.; Possemiers, S. Gut metabolotypes govern health effects of dietary polyphenols. Curr. Opin. Biotechnol. 2013, 24, 220–225. [CrossRef]

122. Manach, C.; Scalbert, A.; Morand, C.; Růžička, M. Phenols in the plant and in man. The potential for possible nutritional enhancement of the diet by modifying the phenols content or profile. J. Sci. Food Agric. 2000, 80, 985–1012. [CrossRef]

123. Andrade, L. Dietary Polyphenols and the Prevention of Diseases. Mini-Rev. Med. Chem. 2017, 17, 1013–1027. [CrossRef]

124. Cotrozzoli, L.; Campanella, A.; Pellegrini, E.; Lorenzini, G.; Nali, C.; Paoletti, E. Phenylpropanoids are key components of the antioxidant defense system of plants facing severe excess light stress. Environ. Exp. Bot. 2015, 119, 54–62. [CrossRef]

125. Bendary, E.; Francis, R.R.; Ali, H.M.G.; Sarwat, M.I.; El Hady, S. Antioxidant and structure–activity relationships (SARs) of some phenolic and anilines compounds. Ann. Agric. Sci. 2013, 58, 173–181. [CrossRef]

126. Wang, T.-Y.; Li, Q.; Bi, K.-S. Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. Asian J. Pharm. Sci. 2018, 13, 12–23. [CrossRef]

127. Rogers, R.; Verweij, W.; Quattrocchio, F. Flavonoids: A colorful model for the regulation and evolution of biochemical pathways. Trends Plant Sci. 2005, 10, 236–242. [CrossRef]

128. Vogt, T. Phenylpropanoid biosynthesis. Mol. Plant 2010, 3, 2–20. [CrossRef]

129. Cotrozzoli, L.; Campanella, A.; Pellegrini, E.; Lorenzini, G.; Nali, C.; Paoletti, E. Phenylpropanoids are key players in the antioxidant defense system of plants facing severe excess light stress. Environ. Sci. Pollut. Res. 2015, 22, 8137–8147. [CrossRef] [PubMed]

130. Scalbert, A.; Manach, C.; Morand, C.; Rémyès, C.; Jiménez, L. Dietary Polyphenols and the Prevention of Diseases. Crit. Rev. Food Sci. Nutr. 2005, 45, 287–306. [CrossRef]

131. Manach, C.; Scalbert, A.; Morand, C.; Rémyès, C.; Jiménez, L. Polyphenols: Food sources and bioavailability. An. J. Clin. Nutr. 2004, 79, 727–747. [CrossRef]

132. Parr, A.J.; Bolwell, G.P. Phenols in the plant and in man. The potential for possible nutritional enhancement of the diet by modifying the phenols content or profile. J. Sci. Food Agric. 2000, 80, 985–1012. [CrossRef]

133. Tohge, T.; Fernie, A.R. An Overview of Compounds Derived from the Shikimate and Phenylpropanoid Pathways and Their Medicinal Importance. Mini-Rev. Med. Chem. 2017, 17, 1013–1027. [CrossRef]

134. Longo, V.D.; Antebi, A.; Bartke, A.; Barzilai, N.; Brown-Borg, H.M.; Caruso, C.; Curiel, T.J.; de Cabo, R.; Franceschi, C.; Gems, D.; et al. Interventions to Slow Aging in Humans: Are We Ready? Aging Cell 2015, 14, 497–510. [CrossRef]

135. Bhuflar, K.S.; Hubbard, B.P. Lifespan and healthspan extension by resveratrol. Plant J. 2011, 66, 414–432. [CrossRef] [PubMed]

136. Deng, Y.; Li, S. Biosynthesis and Regulation of Phenylpropanoid in Plants. Crit. Rev. Plant Sci. 2017, 36, 257–290. [CrossRef]

137. Barros, J.; Dixon, R.A. Plant Phenylalanine/Tyrosine Ammonia-lyases. Trends Plant Sci. 2019, 25, 66–79. [CrossRef]

138. Zhang, X.; Liu, C.-J. Multifaceted Regulations of Gateway Enzyme Phenylalanine Ammonia-Lyase in the Biosynthesis of Phenylpropanoids. Mol. Plant 2015, 8, 17–27. [CrossRef]
139. Hou, L.; Wang, L.; Wu, X.; Gao, W.; Zhang, J.; Huang, C. Expression patterns of two pal genes of Pleurotus ostreatus across developmental stages and under heat stress. BMC Microbiol. 2019, 19, 231. [CrossRef] [PubMed]

140. Mo, F.; Li, L.; Zhang, C.; Yang, C.; Chen, G.; Niu, Y.; Si, J.; Liu, T.; Sun, X.; Wang, S.; et al. Genome-Wide Analysis and Expression Profiling of the Phenylalanine Ammonia-Lyase Gene Family in Solanum tuberosum. Int. J. Mol. Sci. 2022, 23, 6833. [CrossRef] [PubMed]

141. Christie, P.J.; Alfenito, M.R.; Walbot, V. Impact of low-temperature stress on general phenylpropanoid and anthocyanin pathways: Enhancement of transcript abundance and anthocyanin pigmentation in maize seedlings. Planta 1994, 194, 541–549. [CrossRef]

142. Lamb, C.J.; Rubery, P.H. Photocontrol of chlorogenic acid biosynthesis in potato tuber discs. Phytochemistry 1976, 15, 665–668. [CrossRef]

143. Rivero, R.M.; Ruiz, J.M.; Garcia, P.C.; López-Lefebre, L.R.; Sánchez, E.; Romero, L. Resistance to cold and heat stress: Accumulation of phenolic compounds in tomato and watermelon plants. Plant Sci. 2001, 160, 315–321. [CrossRef]

144. Yoshioka, H.; Miyabe, M.; Hayakawa, Y.; Doke, N. Expression of Genes for Phenylalanine Ammonia-Lyase and 3-Hydroxy-3-Methylglutaryl-CoA Reductase in Aged Potato Tubers Infected with Phytophthora infestans. Plant Cell Physiol. 1996, 37, 81–90.

145. Chalker-Scott, L. Environmental Significance of Anthocyanins in Plant Stress Responses. Photochem. Photobiol. 1999, 70, 1–9. [CrossRef]

146. Hughes, N.M.; Neufeld, H.S.; Burkey, K.O. Functional role of anthocyanins in high-light winter leaves of the evergreen herb Galax urceolata. New Phytol. 2003, 168, 575–587. [CrossRef]

147. An, J.-P.; Wang, X.-F.; Zhang, X.-W.; Xu, H.-F.; Bi, S.-Q.; You, C.-X.; Hao, Y.-J. An apple MYB transcription factor regulates cold tolerance and anthocyanin accumulation and undergoes MIEL1-mediated degradation. Plant Biotechnol. J. 2020, 18, 337–353. [CrossRef]

148. Lin-Wang, K.; Micheletti, D.; Palmer, J.; Volz, R.; Lozano, L.; Espley, R.; Hellens, R.P.; Chagné, D.; Rowan, D.D.; Troggio, M.; et al. High temperature reduces apple fruit colour via modulation of the anthocyanin regulatory complex. Plant Cell Environ. 2011, 34, 1176–1190. [CrossRef]

149. Castellarin, S.D.; Matthews, M.A.; di Gaspero, G.; Gambetta, G.A. Water deficits accelerate ripening and induce changes in gene expression regulating flavanoid biosynthesis in grape berries. Planta 2007, 227, 101–112. [CrossRef] [PubMed]

150. Berdeja, M.; Nicolas, P.; Kappel, C.; Dai, Z.W.; Hilbert, G.; Peccoux, A.; Lafontaine, M.; Ollat, N.; Gomès, E.; Delrot, S. Water limitation and rootstock genotype interact to alter grape berry metabolism through transcriptome reprogramming. Hortic. Res. 2015, 2, 15012. [CrossRef]

151. Sánchez-Rodríguez, E.; Moreno, D.A.; Ferreres, F.; Rubio-Wilhelmi, M.D.M.; Ruiz, J.M. Differential responses of five cherry tomato varieties to water stress: Changes on phenolic metabolites and related enzymes. Phytochemistry 2011, 72, 723–729. [CrossRef]

152. Carmona, L.; Alquézar, B.; Marques, V.V.; Peña, L. Anthocyanin biosynthesis and accumulation in blood oranges during postharvest storage at different low temperatures. Food Chem. 2017, 237, 7–14. [CrossRef] [PubMed]

153. Liu, Y.; Lin-Wang, K.; Espley, R.; Wang, L.; Li, Y.; Liu, Z.; Zhou, P.; Zeng, L.; Zhang, X.; Zhang, J.; et al. StMYB44 negatively regulates anthocyanin biosynthesis at high temperatures in tuber flesh of potato. J. Exp. Bot. 2019, 70, 3809–3824. [CrossRef] [PubMed]

154. Fogelman, E.; Oren-Shamir, M.; Hirschberg, J.; Mandolino, G.; Gambetta, G.A. Nutritional value of potato (Solanum tuberosum) in hot climates: Anthocyanins, carotenoids, and steroidal glycoalkaloids. Planta 2019, 249, 1143–1155. [CrossRef]

155. Kasote, D.M.; Katyare, S.S.; Hegde, M.V.; Bae, H. Significance of Antioxidant Potential of Plants and its Relevance to Therapeutic Applications. Int. J. Biol. Sci. 2015, 11, 982–991. [CrossRef]

156. Zhang, Q.; Yang, W.; Liu, J.; Liu, H.; Lv, Z.; Zhang, C.; Chen, D.; Jiao, Z. Postharvest UV-C irradiation increased the flavonoids and anthocyanins accumulation, phenylpropanoid pathway gene expression, and antioxidant activity in sweet cherries (Prunus avium L.). Postharvest Biol. Technol. 2021, 175, 111490. [CrossRef]

157. Fischer, N.; Seo, E.-J.; Effrth, T. Prevention from radiation damage by natural products. Phytomedicine 2018, 47, 192–200. [CrossRef]

158. Williams, R.J.; Spencer, J.P.; Rice-Evans, C. Flavonoids: Antioxidants or signalling molecules? Free Radic. Biol. Med. 2004, 36, 838–849. [CrossRef]

159. Yang, Y.; Guo, Y. Unraveling salt stress signaling in plants. J. Integr. Plant Biol. 2018, 60, 796–804. [CrossRef]

160. Sarker, U.; Oba, S. Augmentation of leaf color parameters, pigments, vitamins, phenolic acids, flavonoids and antioxidant activity in selected Amaranthus tricolor under salinity stress. Sci. Rep. 2018, 8, 12349. [CrossRef] [PubMed]

161. Martinez, V.; Mestre, T.C.; Rubio, F.; Girone-Valaplana, A.; Moreno, D.A.; Mittler, R.; Rivero, R.M. Accumulation of Flavonols over Hydroxycinnamic Acids Favors Oxidative Damage Protection under Abiotic Stress. Front. Plant Sci. 2016, 7, 838. [CrossRef] [PubMed]

162. Clifford, M.N. Chlorogenic acids and other cinnamates–nature, occurrence and dietary burden. J. Sci. Food Agric. 1999, 79, 362–372. [CrossRef]

163. Malmberg, A.G.; Theander, O. Determination of chlorogenic acid in potato tubers. J. Agric. Food Chem. 1985, 33, 549–551. [CrossRef]
164. Navarre, D.A.; Pillai, S.S.; Shakya, R.; Holden, M.J. HPLC profiling of phenolics in diverse potato genotypes. *Food Chem.* 2011, 127, 34–41. [CrossRef]

165. de Pascual-Teresa, S.; Sanchez-Ballesta, M.T. Anthocyanins: From plant to health. *Phytochem. Rev.* 2008, 7, 281–299. [CrossRef]

166. Koga, I.; Milenkovic, D. Anthocyanins: From Sources and Bioavailability to Cardiovascular-Health Benefits and Molecular Mechanisms of Action. *J. Agric. Food Chem.* 2019, 67, 1771–1783. [CrossRef]

167. Wu, X.; Beecher, G.R.; Holden, J.M.; Haytowitz, D.B.; Gebhardt, S.E.; Prior, R.L. Concentrations of Anthocyanins in Common Foods in the United States and Estimation of Normal Consumption. *J. Agric. Food Chem.* 2006, 54, 4069–4073. [CrossRef]

168. Andre, C.M.; Ouifir, M.; Guignard, C.; Hoffmann, L.; Hausman, J.-F.; Evers, D.; Larondelle, Y. Antioxidant profiling of native Andean potato tubers (*Solanum tuberosum* L.) reveals cultivars with high levels of β-carotene, α-tocopherol, chlorogenic acid, and petanin. *J. Agric. Food Chem.* 2007, 55, 10839–10849. [CrossRef]

169. Jakobek, L.; Seruga, M.; Novak, I.; Medvidovic-Kosanovic, M. Flavanols, phenolic acids and antioxidant activity of some red fruits. *Disch. Lebensm. Rundsch.* 2007, 103, 369–377.

170. Crozier, A.; Lean, M.E.J.; McDonald, M.S.; Black, C. Quantitative Analysis of the Flavonoid Content of Commercial Tomatoes, Onions, Lettuce, and Celery. *J. Agric. Food Chem.* 1997, 45, 590–595. [CrossRef]

171. Sampson, L.; Rimm, E.; Hollman, P.C.; de Vries, J.H.; Katan, M.B. Flavonol and Flavone Intakes in US Health Professionals. *J. Am. Diet. Assoc.* 2002, 102, 1414–1420. [CrossRef]

172. Stewart, A.J.; Bozornte, S.; Mullen, W.; Jenkins, G.I.; Lean, M.E.J.; Crozier, A. Occurrence of Flavonols in Tomatoes and Tomato-Based Products. *J. Agric. Food Chem.* 2000, 48, 2663–2669. [CrossRef]

173. Mattivi, F.; Guzzon, R.; Vrhovsek, U.; Stefanini, A.M.; Velasco, R. Metabolite Profiling of Grape: Flavonols and Anthocyanins. *J. Agric. Food Chem.* 2006, 54, 7692–7702. [CrossRef]

174. Rodriguez-Concepcion, M.; Avalos, J.; Bonet, M.L.; Boronat, A.; Gomez-Gomez, L.; Hornero-Mendez, D.; Limon, M.C.; Melendez-Martinez, A.J.; Olmedilla-Alonso, B.; Palou, A.; et al. A global perspective on carotenoids: Metabolism, biotechnology, and benefits for nutrition and health. *Prog. Lipid Res.* 2018, 70, 62–93. [CrossRef]

175. Yabuzaki, J. Carotenoids Database: Structures, chemical fingerprints and distribution among organisms. *Database* 2017, 2017, ba004. [CrossRef]

176. Zimmer, J.P.; Hammond, B.R., Jr. Possible influences of lutein and zeaxanthin on the developing retina. *Clin. Ophthalmol.* 2007, 1, 25.

177. Al-Delaimy, W.K.; Van Kappel, A.L.; Ferrari, P.; Slimani, N.; Steghens, J.-P.; Bingham, S.; Johansson, I.; Wallström, P.; Overvad, K.; Tjønneland, A. Plasma levels of six carotenoids in nine European countries: Report from the European Prospective Investigation into Cancer and European nutrition (EPIC). *Public Health Nutr.* 2004, 7, 713–722. [CrossRef]

178. Edge, R.; Truscott, T.G. Singlet Oxygen and Free Radical Reactions of Retinoids and Carotenoids—A Review. *Antioxidants* 2018, 7, 5. [CrossRef]

179. Ramel, F.; Birtic, S.; Ginies, C.; Soubigou-Taconnat, L.; During, A.; Chew, E.Y.; Politi, L.E. Lutein and zeaxanthin protect photoreceptors from apoptosis induced by oxidative stress: Relation with docosahexaenoic acid. *Investig. Ophthalmol. Vis. Sci.* 2007, 48, 5168–5177. [PubMed]

180. Tan, J.S.; Wang, J.J.; Flood, V.; Rochtchina, E.; Smith, W.; Mitchell, P. Dietary antioxidants and the long-term incidence of age-related macular degeneration: The Blue Mountains Eye Study. *Ophthalmol. Physiol. Opt.* 2008, 115, 334–341. [CrossRef] [PubMed]

181. Desmarchelier, C.; Borel, P. Overview of carotenoid bioavailability determinants: From dietary factors to host genetic variations. *Trends Food Sci. Technol.* 2015, 2017, 69, 270–280. [CrossRef]

182. Fraser, P.D.; Bramley, P.M. The biosynthesis and nutritional uses of carotenoids. *Prog. Lipid Res.* 2004, 43, 228–265. [CrossRef]

183. Desmarchelier, C.; Borel, P. Overview of carotenoid bioavailability determinants: From dietary factors to host genetic variations. *Trends Food Sci. Technol.* 2017, 69, 270–280. [CrossRef]

184. Gammone, M.A.; Riccioni, G.; D’Orazio, N. Carotenoids: Potential allies of cardiovascular health? *Food Nutr. Res.* 2015, 59, 26762.

185. Eggersdorfer, M.; Wyss, A. Carotenoids in human nutrition and health. *Arch. Biochem. Biophys.* 2018, 652, 18–26. [CrossRef]

186. Saini, R.K.; Keum, Y.-S.; Daglia, M.; Rengasamy, K.R. Dietary carotenoids in cancer chemoprevention and chemotherapy: A review of emerging evidence. *Pharmacol. Res.* 2020, 157, 104830. [CrossRef]

187. Yabuzaki, J. Carotenoids Database: Structures, chemical fingerprints and distribution among organisms. *Database* 2017, 2017, ba004. [CrossRef]

188. Abdel-Aal, E.-S.M.; Akhtar, H.; Zaheer, K.; Ali, R. Dietary Sources of Lutein and Zeaxanthin Carotenoids and Their Role in Eye Health. *Nutrients* 2013, 5, 1169–1185. [CrossRef]

189. Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.G.; Klein, R.; Cheng, C.Y.; Wong, T.Y. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *Lancet Glob. Health.* 2014, 2, e106–e116. [CrossRef]

190. Iwanziki, W.; Tevini, M.; Stute, R.; Hilbert, R. Carotinoidegehalt und-zusammensetzung verschiedener deutscher Kartoffelsorten und deren Bedeutung für die Fleischfarbe der Knolle. *Potato Res.* 1983, 26, 149–162. [CrossRef]

191. Brown, C.; Edwards, C.; Yang, C.-P.; Dean, B. Orange Flesh Trait in Potato: Inheritance and Carotenoid Content. *J. Am. Soc. Hortic. Sci.* 1993, 118, 145–150. [CrossRef]
223. Meira, L.B.; Bugnì, J.M.; Green, S.L.; Lee, C.-W.; Pang, B.; Borenshtein, D.; Rickman, B.H.; Rogers, A.B.; Moroski-Erkul, C.A.; McFalone, J.L.; et al. DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. J. Clin. Investig. 2008, 118, 2516–2525. [CrossRef] [PubMed]
224. Yang, G.; Bibi, S.; Du, M.; Suzuki, T.; Zhu, M.-J. Regulation of the intestinal tight junction by natural polyphenols: A mechanistic perspective. Crit. Rev. Food Sci. Nutr. 2017, 57, 3830–3839. [CrossRef]
225. Kisseleva, T.; Song, L.; Vorontchikhina, M.; Feirt, N.; Kitajewski, J.; Schindler, C. NF-kappaB regulation of endothelial cell function during LPS-induced toxemia and cancer. J. Clin. Investig. 2006, 116, 2955–2963. [CrossRef]
226. Rotches-Ribalta, M.; Andres-Lacueva, C.; Estruch, R.; Escribano, E.; Urpi-Sarda, M. Pharmacokinetics of resveratrol metabolic profile in healthy humans after moderate consumption of red wine and grape extract tablets. Pharmacol. Res. 2012, 66, 375–382. [CrossRef]
227. Amasheh, M.; Fromm, A.; Krug, S.M.; Amasheh, S.; Andres, S.; Zeitz, M.; Fromm, M.; Schulze, J.D. TNFalpha-induced and berberine-agonized tight junction barrier impairment via tyrosine kinase, Akt and NFkappaB signaling. J. Cell Sci. 2010, 123, 4145–4155. [CrossRef]
228. Zhang, Y.; Li, J. Carbachol ameliorates lipopolysaccharide-induced intestinal epithelial tight junction damage by down-regulating NF-kappabeta and myosin light-chain kinase pathways. Biochem. Biophys. Res. Commun. 2012, 428, 321–326. [CrossRef]
229. Wang, H.; Zhao, J.X.; Hu, N.; Ren, J.; Du, M.; Zhu, M.J. Side-stream smoking reduces intestinal inflammation and increases expression of tight junction proteins. World J. Gastroenterol. 2012, 18, 2180–2187. [CrossRef] [PubMed]
230. Petecchia, L.; Sabatini, F.; Usai, C.; Caci, E.; Varesio, L.; Rossi, G.A. Cytokines induce tight junction disassembly in airway cells via an EGFR-dependent MAPK/ERK1/2-pathway. Lab. Investig. J. Tech. Methods Pathol. 2012, 92, 1140–1148. [CrossRef] [PubMed]
231. Laukoetter, M.G.; Nava, P.; Nusrat, A. Role of the intestinal barrier in inflammatory bowel disease. World J. Gastroenterol. 2008, 14, 401–407. [CrossRef]
232. Chen, J.S.; Long, L.N.; Jiang, Q.; Kang, B.J.; Li, Y.H.; Yin, J. Effects of dietary supplementation of Lycium barbarum polysaccharides on growth performance, immune status, antioxidant capacity and selected microbial populations of weaned piglets. J. Anim. Physiol. Anim. Nutr. 2020, 104, 1106–1115. [CrossRef] [PubMed]
233. Wang, N.; Wang, G.; Hao, J.; Ma, J.; Wang, Y.; Jiang, X.; Jiang, H. Curcumin Ameliorates Hydrogen Peroxide-Induced Epithelial Barrier Disruption by Upregulating Heme Oxygenase-1 Expression in Human Intestinal Epithelial Cells. Am. J. Dig. Dis. 2012, 57, 1792–1801. [CrossRef]
234. Watson, J.L.; Ansari, S.; Cameron, H.; Wang, A.; Akhtar, M.; McKay, D.M. Green tea polyphenol (-)-epigallocatechin gallate blocks epithelial barrier disruption provoked by IFN-gamma but not by IL-4. Am. J. Physiol. Gastrointest. Liver Physiol. 2004, 287, G954–G961. [CrossRef]
235. Yang, G.; Wang, H.; Kang, Y.; Zhu, M.-J. Grape seed extract improves epithelial structure and suppresses inflammation in ileum of IL-10-deficient mice. Food Funct. 2014, 5, 2558–2563. [CrossRef]
236. Noda, S.; Tanabe, S.; Suzuki, T. Differential Effects of Flavonoids on Barrier Integrity in Human Intestinal Caco-2 Cells. J. Agric. Food Chem. 2012, 60, 4628–4633. [CrossRef]
237. Azuma, T.; Shigeshiro, M.; Kodama, M.; Tanabe, S.; Suzuki, T. Supplemental Naringenin Prevents Intestinal Barrier Defects and Inflammation in Colitic Mice. J. Nutr. Biochem. 2013, 24, 837–843. [CrossRef]
238. Wan, M.L.Y.; Ling, K.H.; Wang, M.F.; El-Nezami, H. Green tea polyphenol epigallocatechin gallate blocks epithelial barrier dysfunction provoked by IFN-gamma but not by IL-4. Am. J. Physiol. Gastrointest. Liver Physiol. 2004, 287, G954–G961. [CrossRef]
239. Wang, H.; Xue, Y.; Zhang, H.; Huang, Y.; Yang, G.; Du, M.; Zhu, M.-J. Dietary grape seed extract ameliorates symptoms of inflammatory bowel disease in IL10-deficient mice. Mol. Nutr. Food Res. 2013, 57, 2253–2257. [CrossRef] [PubMed]
240. Cheah, K.Y.; Bastian, T.M.V.; Abimosleh, S.M.; Lymn, K.A.; Howarth, G.S. Grape Seed Extract Reduces the Severity of Selected Disease Markers in the Proximal Colon of Dextran Sulphate Sodium-Induced Colitis in Rats. Am. J. Physiol. Gastrointest. Liver Physiol. 2013, 58, 970–977. [CrossRef] [PubMed]
241. Etcheberry, U.; Arias, N.; Boqué, N.; Macarulla, M.; Portillo, M.; Martinez, J.; Milagro, F. Reshaping faecal gut microbiota composition by the intake of trans-resveratrol and quercetin in high-fat sucrose diet-fed rats. J. Nutr. Biochem. 2015, 26, 651–660. [CrossRef] [PubMed]
242. Li, L.; Wang, L.; Wu, Z.; Yao, L.; Wu, Y.; Huang, L.; Liu, K.; Zhou, X.; Gou, D. Anthocyanin-rich fractions from red raspberries attenuate inflammation in both RAW264.7 macrophages and a mouse model of colitis. Sci. Rep. 2014, 4, 506234. [CrossRef]
243. Kaspar, K.L.; Park, J.S.; Brown, C.R.; Mathison, B.D.; Navarre, D.A.; Chew, B.P. Pigmented Potato Consumption Alters Oxidative Stress and Inflammatory Damage in Men. J. Nutr. 2011, 141, 108–111. [CrossRef]
244. Grar, H.; Bibi, S.; Dong, W.; Gourine, H.; Négaoui, H.; Taleb, B.H.F.; Louaar, A.; Ouldhocine, S.; Kaddouri, H.; Kheroua, O.; Saidi, D. Beta-Carotene improves intestinal barrier function by modulating proinflammatory cytokines and improving antioxidant capacity in beta-lactoglobulin-sensitized mice. J. Biol. Regul. Homeost. Agents 2020, 34, 1689–1697. [CrossRef]
245. Abdelhamid, L.; Luo, X.M. Retinoic Acid, Leaky Gut, and Autoimmune Diseases. Nutrients 2018, 10, 1016. [CrossRef]
247. Sinisgalli, C.; Vezza, T.; Diez-Echave, P.; Ostuni, A.; Faraone, I.; Hidalgo-Garcia, L.; Russo, D.; Armentano, M.F.; Garrido-Mesa, J.; Rodriguez-Cabezás, M.E.; et al. The Beneficial Effects of Red Sun-Dried Capsicum annuum L. Cv Senise Extract with Antioxidant Properties in Experimental Obesity are Associated with Modulation of the Intestinal Microbiota. *Mol. Nutr. Food Res.* **2021**, *65*, e2000812. [CrossRef]

248. Rajput, S.A.; Liang, S.J.; Wang, X.Q.; Yan, H.C. Lycopene Protects Intestinal Epithelium from Deoxynivalenol-Induced Oxidative Damage via Regulating Keap1/Nrf2 Signaling. *Antioxidants* **2021**, *10*, 1493. [CrossRef]

249. Liu, K.Y.; Nakatsu, C.H.; Jones-Hall, Y.; Kozik, A.; Jiang, Q. Vitamin E alpha- and gamma-tocopherol mitigate colitis, protect intestinal barrier function and modulate the gut microbiota in mice. *Free Radic. Biol. Med.* **2021**, *163*, 180–189. [CrossRef] [PubMed]

250. Philippe, D.; Brahmbhatt, V.; Foata, F.; Saudan, Y.; Serrat, P.; Blum, S.; Benyacoub, J.; Vidal, K. Anti-inflammatory effects of Lacto-Wolfberry in a mouse model of experimental colitis. *World J. Gastroenterol.* **2012**, *18*, 5351–5359. [CrossRef] [PubMed]

251. Human Microbiome Project, C. Structure, function and diversity of the healthy human microbiome. *Nature* **2012**, *486*, 207–214. [CrossRef]

252. Bäckhed, F.; Ley, R.E.; Sonnenburg, J.L.; Peterson, D.A.; Gordon, J.I. Host-Bacterial Mutualism in the Human Intestine. *Science* **2005**, *307*, 1915–1920. [CrossRef]

253. Hooper, L.V.; Wong, M.H.; Thelin, A.; Hansson, L.; Falk, P.G.; Gordon, J.I. Molecular Analysis of Commensal Host-Microbial Relationships in the Intestine. *Science* **2001**, *291*, 881–884. [CrossRef] [PubMed]

254. Stappenbeck, T.S.; Hooper, L.V.; Gordon, J.I. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 15451–15455. [CrossRef]

255. Sekirov, I.; Russell, S.L.; Antunes, L.C.M.; Finlay, B.B. Gut Microbiota in Health and Disease. *Physiol. Rev.* **2010**, *90*, 859–904. [CrossRef]

256. Frank, D.N.; St Amand, A.L.; Boedeker, E.C.; Harpaz, N.; Pace, N.R. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 13780–13785. [CrossRef]

257. Hirano, A.; Umeno, J.; Okamoto, Y.; Shibata, H.; Ogura, Y.; Moriyama, T.; Torisu, T.; Fujioka, S.; Fuyuno, Y.; Kawarabayashi, Y.; et al. Comparison of the microbial community structure between inflamed and non-inflamed sites in patients with ulcerative colitis. *J. Gastroenterol. Hepatol.* **2018**, *33*, 1590–1597. [CrossRef]

258. Sokol, H.; Seksik, P.; Furet, J.P.; Firmesse, O.; Nion-Larmurier, I.; Beaugerie, L.; Cosnes, J.; Corthier, G.; Marteau, P.; Doré, J. Low counts of Faecalibacterium prausnitzii in colitis microbiota. *Inflamm. Bowel Dis.* **2009**, *15*, 1183–1189. [CrossRef]

259. Takeshita, K.; Mizuno, S.; Mikami, Y.; Sujino, T.; Saigusa, K.; Matsuoka, K.; Naganuma, M.; Sato, T.; Takada, T.; Tsuji, H.; et al. A Single Species of Clostridium Subcluster XIVa Decreased in Ulcerative Colitis Patients. *Inflamm. Bowel Dis.* **2016**, *22*, 2802–2810. [CrossRef] [PubMed]

260. Kaberdooss, J.; Sankaran, V.; Pugazhendhi, S.; Ramakrishna, B. Clostridium leptum group bacteria abundance and diversity in the fecal microbiota of patients with inflammatory bowel disease: A case–control study in India. *BMJ Gastroenterol.* **2013**, *13*, 20. [CrossRef] [PubMed]

261. Muhkopadhyay, I.; Hansen, R.; El-Omar, E.M.; Hold, G.L. IBD-what role do Proteobacteria play? *Nat. Rev. Gastroenterol. Hepatol.* **2012**, *9*, 219–230. [CrossRef]

262. Xu, Y.; Zhu, Y.; Li, X.; Sun, B. Dynamic balancing of intestinal short-chain fatty acids: The crucial role of bacterial metabolism. *Trends Food Sci. Technol.* **2020**, *100*, 118–130. [CrossRef]

263. Chen, G.; Ran, X.; Li, B.; Li, Y.; He, D.; Huang, B.; Fu, S.; Liu, J.; Wang, W. Sodium Butyrate Inhibits Inflammation and Maintains Epithelium Barrier Integrity in a TNBS-induced Inflammatory Bowel Disease Mice Model. *EBioMedicine* **2012**, *18*, 5351–5359. [CrossRef] [PubMed]

264. Furusawa, Y.; Obata, Y.; Fukuda, S.; Endo, T.A.; Nakato, G.; Takahashi, D.; Nakanihsi, Y.; Uetae, C.; Kato, K.; Kato, T.; et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **2013**, *504*, 446–450. [CrossRef]

265. Comalada, M.; Bailón, E.; De Haro, O.; Lara-Villoslada, F.; Xaus, J.; Zarruzelo, A.; Galvez, J. The effects of short-chain fatty acids on colon epithelial proliferation and survival depend on the cellular phenotype. *J. Cancer Res. Clin. Oncol.* **2006**, *132*, 487–497. [CrossRef]

266. Klepinina, I.; Klepinin, A.; Truu, L.; Chekulaev, V.; Vija, K.; Kuus, K.; Teino, I.; Poook, M.; Maimets, T.; Kaambre, T. Colon cancer cell differentiation by sodium butyrate modulates metabolic plasticity of Caco-2 cells via alteration of phosphotransfer network. *PLoS ONE* **2011**, *6*, e2045348. [CrossRef]

267. Zheng, L.; Kelly, C.J.; Battista, K.D.; Schaefer, R.; Lanis, J.M.; Alexeev, E.E.; Wang, R.X.; Ornyiah, J.C.; Kominsky, D.J.; Colgan, S.P. Microbial-Derived Butyrate Promotes Epithelial Barrier Function through IL-10 Receptor-Dependent Repression of Claudin-2. *J. Immunol.* **2017**, *199*, 2976–2984. [CrossRef]

268. Peng, L.; Li, Z.-R.; Green, R.S.; Holzman, I.R.; Lin, J. Butyrate Enhances the Intestinal Barrier by Facilitating Tight Junction Assembly via Activation of AMP-Activated Protein Kinase in Caco-2 Cell Monolayers. *J. Nutr.* **2009**, *139*, 1619–1625. [CrossRef]

269. Kelly, C.J.; Zheng, L.; Campbell, E.L.; Saeedi, B.; Schulz, C.C.; Bayless, A.J.; Wilson, K.E.; Glover, L.E.; Kominsky, D.J.; Magnuson, A.; et al. Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. *Cell Host Microbe* **2015**, *17*, 662–671. [CrossRef] [PubMed]
270. Lavelle, A.; Sokol, H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat. Rev. Gastroenterol. Hepatol. 2020, 17, 223–237. [CrossRef] [PubMed]

271. Zhuang, X.; Li, T.; Li, M.; Huang, S.; Qiu, Y.; Feng, R.; Zhang, S.; Chen, M.; Xiong, L.; Zeng, Z. Systematic Review and Meta-analysis: Short-Chain Fatty Acid Characterization in Patients With Inflammatory Bowel Disease. Inflamm. Bowel Dis. 2019, 25, 1751–1763. [CrossRef] [PubMed]

272. Facchin, S.; Vitulo, N.; Calgaro, M.; Buda, A.; Romualdi, C.; Pohl, D.; Perini, B.; Lorenzon, G.; Marinelli, C.; D’Incà, R.; et al. Microbiota changes induced by microencapsulated sodium butyrate in patients with inflammatory bowel disease. Neurogastroenterol. Motil. 2020, 32, e13914. [CrossRef]

273. Queipo-Ortuño, M.I.; Boto-Ordóñez, M.; Murri, M.; Gomez-Zumaquero, J.M.; Clemente-Postigo, M.; Estruch, R.; Cardona Diaz, F.; Andres-Lacueva, C.; Timahones, F. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. Am. J. Clin. Nutr. 2012, 95, 1323–1334. [CrossRef] [PubMed]

274. Jang, S.; Sun, J.; Chen, P.; Lakshman, S.; Molokin, A.; Harmily, J.M.; Vinyard, B.T.; Urban, J.F.; Davis, C.D.; Solano-Aguilar, G. Flavanoid-Enriched Cocoa Powder Alters the Intestinal Microbiota, Tissue and Fluid Metabolic Profiles, and Intestinal Gene Expression in Pigs. J. Nutr. 2016, 146, 673–680. [CrossRef] [PubMed]

275. Wu, D.-N.; Guan, L.; Jiang, Y.-X.; Ma, S.-H.; Sun, Y.-N.; Lei, H.-T.; Yang, W.-F.; Fang, Q.-F. Microbiome and metabonomics study of quercetin for the treatment of atherosclerosis. Cardiowasc. Diagn. Ther. 2019, 9, 545–560. [CrossRef]

276. Shi, T.; Bian, X.; Yao, Z.; Wang, Y.; Gao, W.; Guo, C. Quercetin improves gut dysbiosis in antibiotic-treated mice. Food Funct. 2020, 11, 8003–8013. [CrossRef]

277. Chen, J.; Yu, B.; Chen, D.; Zheng, P.; Luo, Y.; Huang, Z.; Luo, J.; Mao, X.; Yu, J.; He, J. Changes of porcine gut microbiota in response to dietary chlorogenic acid supplementation. Appl. Microbiol. Biotechnol. 2019, 103, 8157–8168. [CrossRef]

278. Xie, M.G.; Fei, Y.Q.; Wang, Y.; Wang, W.Y.; Wang, Z. Chlorogenic Acid Alleviates Colon Mucosal Damage Induced by a High-Fat Diet via Gut Microflora Adjustment to Increase Short-Chain Fatty Acid Accumulation in Rats. Oxidative Med. Cell. Longev. 2021, 2021, 18. [CrossRef]

279. Zhou, X.; Zhang, B.; Zhao, X.; Lin, Y.; Wang, J.; Wang, X.; Hu, N.; Wang, S. Chlorogenic acid supplementation ameliorates hyperuricemia, relieves renal inflammation, and modulates intestinal homeostasis. Food Funct. 2021, 12, 5637–5649. [CrossRef]

280. Miene, C.; Weise, A.; Glei, M. Impact of Polyphenol Metabolites Produced by Colonic Microbiota on Expression of COX-2 and GSTT2 in Human Colon Cells (LT97). Nutcr. Cancer 2011, 63, 653–662. [CrossRef] [PubMed]

281. Zhang, X.; Yang, Y.; Wu, Z.; Weng, P. The Modulatory Effect of Anthocyanins from Purple Sweet Potato on Human Intestinal Microbiota in Vitro. J. Agric. Food Chem. 2016, 64, 2582–2590. [CrossRef] [PubMed]

282. Reddivari, L.; Kim, S.W.; Radhakrishnan, S.; Yang, P.; Knight, R.; Vanamala, J. Purple-fleshed potatoes suppress colon-systemic oxidative stress/inflammatory markers via alternations in the gut bacterial signature. FASEB J. 2013, 27, 1056.9. [CrossRef]

283. Skenderidis, P.; Mitsagga, C.; Lampakis, D.; Petrotsos, K.; Giavasis, I. The Effect of Encapsulated Powder of Goji Berry (Lycium barbarum) on Growth and Survival of Probiotic Bacteria. Microorganisms 2020, 8, 57. [CrossRef]

284. Peng, Y.; Yan, Y.; Wan, M.; Dong, W.; Huang, K.; Ran, L.; Mi, J.; Lu, L.; Zeng, X.; Cao, Y. Effects of long-term intake of anthocyanins from Lycium ruthenicum Murray on the organism health and gut microbiota in vivo. Food Res. Int. 2020, 130, 108952. [CrossRef]

285. Tian, B.M.; Zhao, J.H.; Zhang, M.; Chen, Z.F.; Ma, Q.Y.; Liu, H.C.; Nie, C.X.; Zhang, Z.Q.; An, W.; Li, J.X. Lycium ruthenicum Anthocyanins Attenuate High-Fat Diet-Induced Colonic Barrier Dysfunction and Inflammation in Mice by Modulating the Gut Microbiota. Mol. Nutr. Food Res. 2021, 65, e2000745. [CrossRef]

286. Kang, Y.; Yang, G.; Zhang, S.; Ross, C.F.; Zhu, M.-J. Goji Berry Modulates Gut Microbiota and Alleviates Colitis in IL-10-Deficient Mice. Mol. Nutr. Food Res. 2018, 62, e1800535. [CrossRef]

287. Wiese, M.; Bashmakov, Y.; Chalyk, N.; Nielsen, D.S.; Krych, L.; Kot, W.; Klokchov, V.; Pritskensy, D.; Bandeltova, T.; Chernyshova, M.; et al. Prebiotic Effect of Lycopene and Dark Chocolate on Gut Microbiome with Systemic Changes in Liver Metabolism, Skeletal Muscles and Skin in Moderately Obese Persons. BioMed Res. Int. 2019, 2019, 4625279. [CrossRef]

288. Zhao, B.; Wu, J.; Li, J.; Bai, Y.; Luo, Y.; Ji, B.; Xia, B.; Liu, Z.; Tan, X.; Lv, J.; et al. Lycopene Alleviates DSS-Induced Colitis and Behavioral Disorders via Mediating Microbes-Gut–Brain Axis Balance. J. Agric. Food Chem. 2020, 68, 3963–3975. [CrossRef]

289. Zhu, L.; Song, Y.; Liu, H.; Wu, M.; Gong, H.; Lan, H.; Zheng, X. Gut microbiota regulation and anti-inflammatory effect of beta-carotene in dextran sulfate sodium-stimulated ulcerative colitis in rats. J. Food Sci. 2021, 86, 2118–2130. [CrossRef] [PubMed]

290. Li, R.; Li, L.; Hong, P.; Lang, W.; Hui, J.; Yang, Y.; Zheng, X. beta-Carotene prevents weaning-induced intestinal inflammation by modulating gut microbiota in piglets. Anim. Biosci. 2021, 34, 1221–1234. [CrossRef] [PubMed]

291. Otten, A.T.; Bourgonje, A.R.; Peters, V.; Alizadeh, B.Z.; Dijkstra, G.; Harmesen, H.J.M. Vitamin C supplementation in healthy individuals leads to shifts of bacterial populations in the gut-a pilot study. Antioxidants 2021, 10, 1278. [CrossRef] [PubMed]

292. Huang, K.; Dong, W.; Liu, W.; Yan, Y.; Wan, P.; Peng, Y.; Xu, Y.; Zeng, X.; Cao, Y. 2-O-β-d-Glucopyranosyl-l-ascorbic Acid, an Ascorbic Acid Derivative Isolated from the Fruits of Lycium Barbarum L., Modulates Gut Microbiota and Palliates Colitis in Dextran Sodium Sulfate-Induced Colitis in Mice. J. Agric. Food Chem. 2019, 67, 11408–11419. [CrossRef]

293. Liu, F.; Cottrell, J.J.; Furness, J.B.; Rivera, L.R.; Kelly, F.W.; Wijesiriwardana, U.; Pustovit, R.V.; Fothergill, L.J.; Bravo, D.M.; Celi, P.; et al. Selenium and vitamin E together improve intestinal epithelial barrier function and alleviate oxidative stress in heat-stressed pigs. Exp. Physiol. 2016, 101, 801. [CrossRef]