*Review*

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

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**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 $CO_2$ 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 ($OH\cdot$) radicals [2,8].

**ABIOTIC STRESS**

Salt
Drought
Light
Temperature
Heavy Metals

**ROS**
$H_2O_2$, $O_2^-$, $OH\cdot$ , $^1O_2$

**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
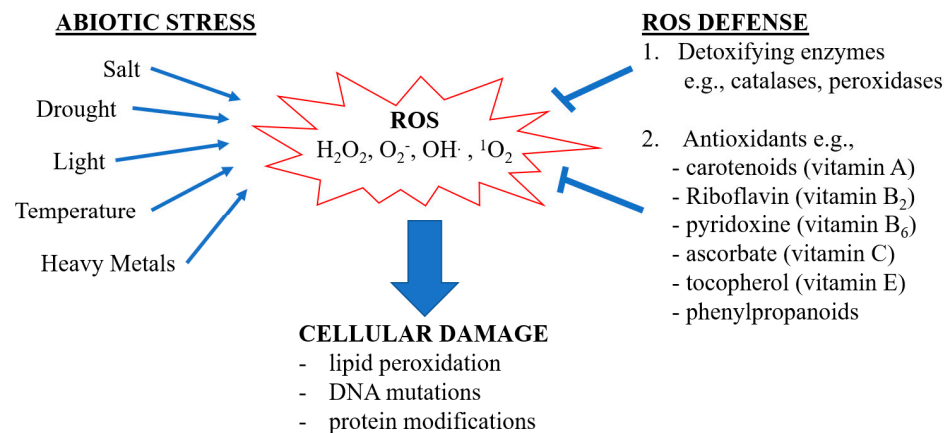   - DNA mutations
   - protein modifications

**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.

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 phytyl 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 $^1O_2$ 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 $^1O_2$ [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 B$_2$*

Vitamin B$_2$ (vitB$_2$) 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 $^1O_2$ and $O_2^-$; 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 B$_6$*

Vitamin B$_6$ (vitB$_6$) 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 vitB$_6$ 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 $^1O_2$ [104], a ROS that can accumulate under light stress in chloroplasts [105]. Consequently, plants deficient in vitB$_6$ biosynthesis accumulate $^1O_2$ under high light conditions and have increased lipid peroxidation [105]. VitB$_6$ likely protects more broadly against ROS since vitB$_6$ 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 vitB$_6$ biosynthesis is increased under stress (e.g., paraquat, UV, heat) [110,111]. VitB$_6$ 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 vitB$_6$ 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.
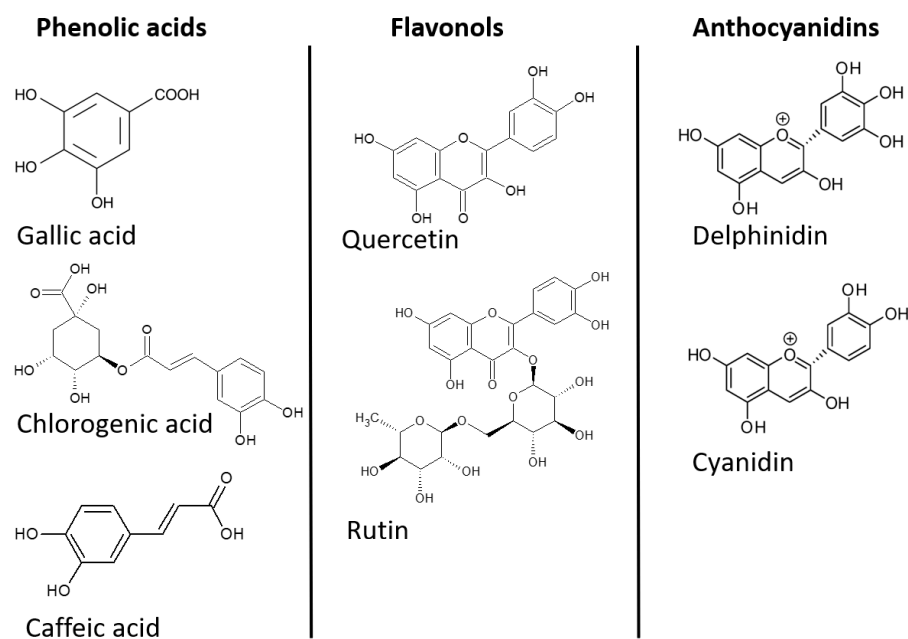
**Phenolic acids**      **Flavonols**      **Anthocyanidins**

Gallic acid      Quercetin      Delphinidin

Chlorogenic acid      Cyanidin

Rutin

Caffeic acid

**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 anthocyandins 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 $^1O_2$ 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 $H_2O_2$ 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]. Flavonols 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 $^1O_2$, which is produced in chloroplasts under conditions of excess light energy [178]. Additionally, volatile carotenoid oxidation products such as β-cyclocitral are generated by $^1O_2$ attack on β-carotene and act as signal molecules that induce changes in large sets of genes that overlap with genes induced by $^1O_2$ oxygen but not $H_2O_2$ [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 $^1O_2$ 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]. β-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 μg/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. prazusnitzii*, 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.

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