Antioxidants in Photosynthesis and Human Nutrition

Barbara Demmig-Adams* and William W. Adams, III

The harnessing of solar energy by photosynthesis depends on a safety valve that effectively eliminates hazardous excess energy and prevents oxidative damage to the plant cells. Many of the compounds that protect plant cells also protect human cells. Improving plant resistance to stress may thus have the beneficial side effect of also improving the nutritional quality of plants in the human diet. The pathways that synthesize these compounds are becoming amenable to genetic manipulation, which may yield benefits as widespread as improved plant stress tolerance and improved human physical and mental health.

Photosynthesis Fuels and Protects Life on Earth

By converting solar energy into usable energy and building material, photosynthesis supports much of the life on this planet (Fig. 1). Photosynthesis' role as a carbon sink is also important in view of the role of atmospheric CO_2 in global warming. Yet photosynthetic productivity is threatened when the global environment turns more extreme. The mechanisms responsible for productivity and survival of photosynthetic organisms (plants, algae, and photosynthetic bacteria) in stressful environments are far from being fully understood. Understanding these is necessary to engineer photosynthetic organisms with enhanced stress tolerance.

Enhancing the photosynthesizers' own protective systems may also improve the nutritional quality of foods, because fundamental cellular signaling processes and protective mechanisms are highly conserved. Hence, many plant and algal products (often collectively termed "phytochemicals") are able to manipulate human cellular signaling and gene expression. For example, "phytoestrogens" (a group of plant flavonoids) mimic the human hormone estrogen. Plants produce these flavonoids as messengers in plant-microbe communication. It is less widely known that the tables can be turned by adding estrogen to soil, thereby fooling soil bacteria into "concluding" that they are receiving a signal from a plant inviting them to form a symbiosis (*1*). Human cells contain steroid hormone receptors derived from bacterial receptors; the human steroid hormones binding to these receptors are structurally reminiscent of flavonoids but evolved much later (*2*).

Carotenoid pigments such as zeaxanthin and lutein (Fig. 2) protect photosynthesis under benign conditions as well as under a plethora of environmental stresses (*3*). These same pigments have been identified as possible protective agents in human vision and immune function and in the prevention of cancer and heart disease (*4*). Improvements in amounts or functions of these and other phytochemicals may well aid both plant productivity and human health.

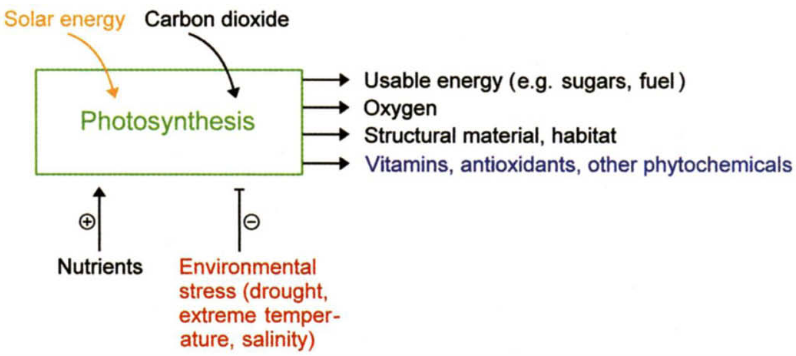

Fig. 1. Interactions of photosynthesis with the environment and humans. The features emphasized in this review are highlighted in color. The terms vitamins, antioxidants, and phytochemicals are not mutually exclusive. Major groups of phytochemicals (produced by photosynthetic organisms) include isoprenoids, phenolic compounds, sulfur compounds, and essential fatty acids. Marine algae produce the omega-3 fatty acids that accumulate in fish. +, factors that increase photosynthesis; –, factors that decrease photosynthesis.

Photosynthesis and Global Change

Environmental stresses such as extreme temperatures or drought can decrease the productivity and survival of plants. Crop plants can be particularly affected because they are often grown in environments to which they are already less than well adapted. Drought, increased salinity, and extreme temperatures thus threaten crop productivity. It is hoped that crop resistance to these environmental stresses can be enhanced by genetic engineering.

Gene therapy in humans as currently implemented seeks to rectify mutations in single genes. Engineering of plants with improved nutrient quality and quantity similarly targets individual genes or pathways. The engineering of plants with enhanced stress resistance may require manipulation of complex traits and thus takes on the challenge of improving evolution's product—a far taller order. Therefore, the identification of any individual genes conferring an important part of stress resistance is highly desirable. Key protective mechanisms and the genes involved are beginning to be identified, as is the case for protection against oxidative damage resulting from an excess absorption of solar energy, discussed in this review.

Protection of Photosynthesis Against Oxidative Damage

Photosynthesis is all about the collection of solar energy and its efficient conversion into chemical energy. Yet by their very nature, the processes accomplishing this are susceptible to damage by any excess solar energy. (Similar considerations apply to other light processors, such as the human eye.) Photosynthesis as it exists today would not be possible

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Department of Environmental, Population, and Organismic Biology, University of Colorado, Boulder, CO 80309–0334, USA.

*To whom correspondence may be addressed. E-mail: barbara.demmig-adams@colorado.edu

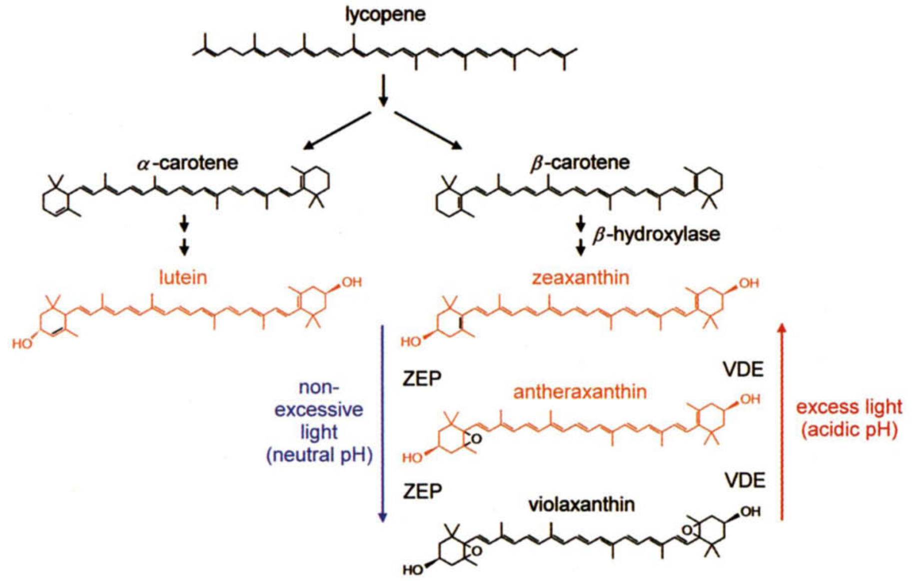

Fig. 2. Biosynthetic pathway of the synthesis of cyclic carotenoids and xanthophyll cycle in plants. The xanthophylls participating in thermal energy dissipation are shown in orange. The key structural differences between lutein, zeaxanthin, and antheraxanthin are shown in black. The enzymes of the xanthophyll cycle, zeaxanthin epoxidase (ZEP) and violaxanthin de-epoxidase (VDE), are both members of the lipocalin protein family. VDE is stimulated under excess light (shown in red) and ZEP under nonexcessive light (shown in blue).

without a safety valve, something akin to a lightning rod, that dissipates excitation energy in a harmless way (as thermal energy) whenever more energy is absorbed than can be used in photosynthesis. Photo synthesis in nature thus operates in a constantly shifting balance between efficient capture of solar energy and quick loss of that energy when it is in excess. The need to dissipate excess energy is ever-present. Even forest-floor plants, shielded from the sun by an overstory of trees, must dissipate excess energy during the fleeting moments when rays of sunlight penetrate the canopy (Fig. 3). In a sun-exposed site, on the other hand, the need for thermal dissipation of excess light energy continues for much of the day (Fig. 3). These two situations illustrate the importance of thermal energy dissipation, where the majority of absorbed sunlight is dissipated as heat, even in situations that are by no means extremely stressful. Under extreme environmental conditions (for example, during icy winters or scorching, dry summers), many native evergreens, while maintaining their light-absorbing chlorophyll, suspend growth and photosynthesis and dissipate virtually all of the light they absorb (*5*, *6*)! Thus, a whole host of environmental stresses, all of which slow down or arrest growth and photosynthesis (Fig. 1), enhance the need for photoprotective thermal energy dissipation.

Among the genes required for thermal energy dissipation (*6*, *7*), one encodes a protein related to the family of light-harvesting proteins, the PsbS protein (*8*) (Fig. 4). Although the precise mechanism of its function remains to be clarified, the most attractive hypothesis is that PsbS senses the presence of excess light and then triggers the switch from efficient conversion of absorbed light by photosynthesis to thermal dissipation. Solar energy is converted to chemical energy (through photosynthesis) via the build-up of a proton gradient across the photosynthetic membrane; when more energy is absorbed than can be used, the pH gradient increases. This pH signal is apparently perceived by the PsbS protein (*9*) and translated into a structural change (*8*) in the light-collecting antenna, thus triggering thermal energy dissipation. The ecological importance of PsbS-dependent energy dissipation was addressed by Jansson and co-workers (*10*), who showed that, in a fluctuating light situation (Fig. 3, left panels), the PsbS protein is vital for plant fitness. PsbS-deficient mutants had a limited seed yield as compared to that of wild-type plants, indicating that a gene involved in stress resistance has an impact on plant fitness. In an environment with fluctuating light levels, the PsbS-controlled rapid alternation between efficient energy capture and effective thermal dissipation is thus crucial to a plant's success. Future studies are needed to determine (i) whether overexpression of the PsbS gene further enhances plant fitness under fluctuating light and (ii) whether the PsbS protein is also essential under long-term extreme stress where absorbed light remains continuously excessive.

Also required for thermal energy dissipation are the xanthophylls, particularly zeaxanthin (synthesized from β-carotene via hydroxylation) and, to a lesser extent, lutein (synthesized from α-carotene via hydroxylation) (*11*–*13*) (Figs. 2 and 4). Plants overexpressing the gene for an enzyme (β-hydroxylase) in the biosynthetic pathway of zeaxanthin formation and showing elevated levels of zeaxanthin also exhibit enhanced heat tolerance (*14*). Furthermore, plants overexpressing an enzyme involved in lutein formation (lycopene ε-cyclase, which converts lycopene to α-carotene) and showing elevated lutein levels also exhibited some enhancement of thermal energy dissipation (*15*).

Plants and algae possess an additional set of reactions (a xanthophyll cycle as shown in Fig. 2) that rapidly optimizes the concentra-

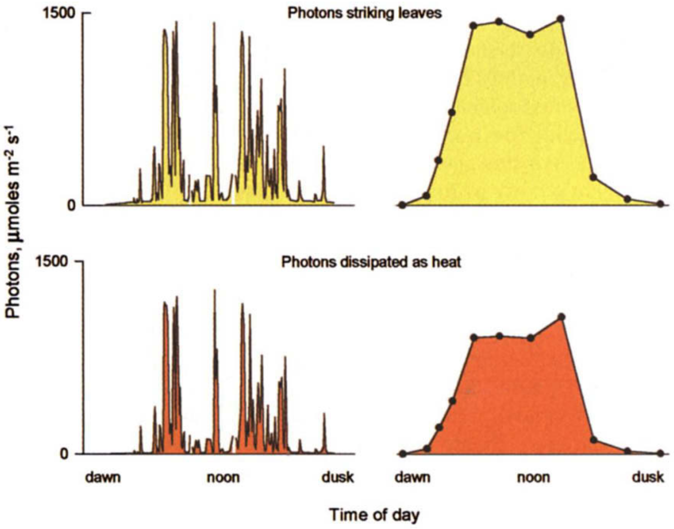

Fig. 3. Changes in light intensity (photons striking leaves, yellow) and in the level of thermal energy dissipation (expressed as photons dissipated as heat, orange) over the course of a day in the vine *Stephania japonica* growing either under a tree canopy (left) or exposed to full sunlight [right; recalculated from (*50*)]. Thermal energy dissipation was estimated from non-photochemical quenching of chlorophyll fluorescence and from the degree decreased efficiency of the conversion of absorbed photons into photochemistry in photosystem II. Of the photons striking a green leaf, typically 85 to 90% are absorbed, and this percentage of the photons striking leaves (shown in yellow) can thus be assumed to be absorbed. In this vine as well as in most species, a large fraction of this absorbed light is dissipated as heat when irradiance is high. Only some weeds and crop plants use a greater fraction (typically half) of the sunlight absorbed under full-sun exposure.

tion of zeaxanthin. When light needs to be used efficiently for photosynthesis, the dissipator zeaxanthin is converted (via the intermediate antheraxanthin) to a nondissipating pigment, violaxanthin, and this process is rapidly reversed under excess light (*13*). Zeaxanthin and antheraxanthin are required not only for rapidly modulated thermal dissipation but also for persistent thermal energy dissipation in plants under long-term environmental stress, during which the xanthophyll cycle is arrested in the form of zeaxanthin and antheraxanthin (*3*, *5*).

Although *Arabidopsis* is an excellent model to study rapidly modulated thermal dissipation, this species does not exhibit any appreciable levels of persistent thermal dissipation. As is the case for most crop species, *Arabidopsis* may be considered an escapist, evading the effects of environmental stresses by maintaining growth and metabolic activity at any cost and by continuing to use solar energy in photosynthesis. However, these plants do not survive extreme environmental stress. Those plants that do possess a high stress tolerance (commonly long-lived native plants) are more difficult to target with molecular approaches. These plants frequently persist through seasonal stress periods in a state of suspended metabolism with persistent high levels of thermal energy dissipation. Comparative studies of plant stress tolerance should prove useful for a potential transfer of stress tolerance traits from native to crop plants.

The precise mechanism of xanthophyll action in thermal energy dissipation is unknown. An attractive hypothesis is that these xanthophylls (zeaxanthin, antheraxanthin, and lutein) accept excess excitation energy from chlorophyll (*16*) and subsequently readily lose this energy as heat. Irrespective of the precise mode of action, xanthophylls facilitate the de-excitation of singlet excited chlorophyll, thus preventing a transfer of this excitation energy (via triplet chlorophyll) to oxygen that would otherwise form reactive singlet oxygen (Fig. 4). The dissipation of excess excitation furthermore counteracts the formation of reactive superoxide (resulting from a transfer of unused electrons to oxygen; Fig. 4). Both of these reactive oxygen species readily oxidize macromolecules and are also part of signal transduction pathways that modulate leaf gene expression (Fig. 4). Synthesis of key proteins in photosynthesis is controlled by lipid messengers, collectively termed oxylipins, and redox events (Fig. 4) (*17*, *18*). In general, an overproduction of reactive oxygen species leads to a net degradation of key photosynthetic proteins. Furthermore, lipid messengers derived from oxidized membrane lipids can even trigger programmed cell death (Fig. 4) (*19*).

In addition to de-excitation of singlet chlorophyll, carotenoids can also facilitate several back-up defense processes, including the scavenging of triplet chlorophyll and of singlet oxygen. Furthermore, zeaxanthin inhibits the oxidation of membrane lipids by an unknown mechanism. This additional role was demonstrated in a study showing that double mutants deficient in both zeaxanthin and the PsbS protein were highly susceptible to lipid oxidation at low temperatures (*20*). In contrast, mutants deficient in the PsbS protein (and deficient in thermal energy dissipation) but with normal levels of zeaxanthin were able to keep the levels of lipid oxidation low. Mutants deficient in thermal energy dissipation had elevated levels of vitamin E (α- and γ-tocopherol), which also has the ability to scavenge singlet oxygen and inhibit lipid oxidation (*21*). We conclude that thermal energy dissipation is the preferred defense mechanism under excess light stress. When this route is not available, tocopherols act as a back-up to allow survival under moderate levels of excess light. However, the decreased fitness in PsbS-deficient plants (*10*) indicates that a hefty price is attached to using only this back-up route. Under extremely excessive light, this up-regulation of tocopherol content is not sufficient for survival, and only the presence of zeaxanthin can prevent massive lipid oxidation (*20*). Synergistic effects between carotenoids and vitamin E (typically α-tocopherol, although there is a whole group of tocopherols) have also been noted in human physiology, and novel mechanisms of action—with an emphasis on signal transduction—are being sought for antioxidants in this area as well.

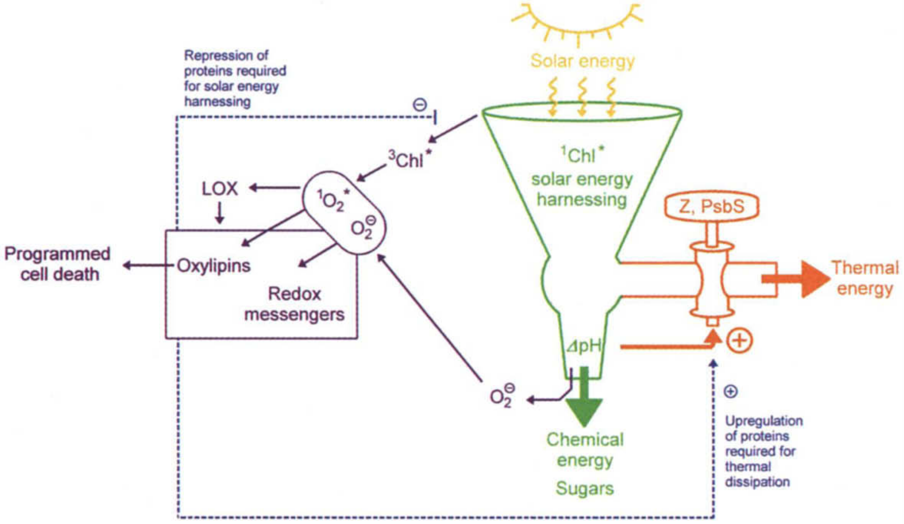

Fig. 4. Scheme showing the different possible fates of sunlight absorbed in the light-collecting antenna. Light energy absorbed by chlorophyll, and resulting in the formation of singlet excited chlorophyll (^{1}Chl*), can be used (green arrow) in photosynthetic electron transport and carbon fixation or, if in excess of what can be used, is dissipated as heat (orange arrow). Dissipation of excess light as heat suppresses the formation of singlet excited oxygen ($^1O_2$*, formed via conversion of ^{1}Chl* to triplet excited Chl, ^{3}Chl*, and subsequent transfer of energy to oxygen) as well as superoxide (O_2^-). Singlet oxygen and superoxide are part of lipid and redox signaling pathways (shown in purple) that are stimulated when ^{1}Chl* is insufficiently removed by the combined action of photosynthesis and thermal dissipation. There is direct evidence for the repression of proteins involved in light collection and photochemistry by reactive oxygen and lipid messengers (*17*, *18*), but evidence for up-regulation of proteins involved photoprotection by similar signals is indirect (feedback loops shown in blue). Carotenoids and vitamin E counteract the stimulation of these pathways via multiple mechanisms. Factors required for thermal dissipation are zeaxanthin (Z), antheraxanthin, and possibly lutein (not shown here), as well as the PsbS protein and a sufficiently large proton gradient (ΔpH) across the photosynthetic membrane. These factors facilitate the switch from an efficient conversion of solar energy to electron transport when all of the absorbed light can be used in photosynthesis to an efficient conversion of solar energy into thermal energy under excess light. Augmentation of the transmembrane pH gradient under excess light simultaneously induces the conversion of violaxanthin to zaxanthin (Z) and antheraxin and is sensed by the PsbS protein that triggers the thermal dissipation process.

The genetic engineering of plants with an enhanced antioxidant capacity can be expected to have a dual effect on stress response. For one, onsite protection against oxidative damage should increase. In addition, messages resulting in degradative processes, and possibly cell death, may be dampened (Fig. 4). Moreover, it may turn out that the contrasting adaptive strategies employed by species with different life spans relate to differences in this signaling network. It will be important to test these possibilities through molecular approaches.

Moreover, enhanced carotenoid or vitamin E content improves the nutrient quality of plant-based foods. Classic breeding created the attractive, bright red tomato with its high content of (intensely red) lycopene (Fig. 2) that turned out to possess cancer-fighting properties (*22*). Zeaxanthin and lutein have roles in protecting human vision and other aspects of human health. Green parts of wild-type plants after harvest typically contain high levels of lutein but, due to the continuing action of the xanthophyll cycle (Fig. 2), retain mere traces of zeaxanthin. Yet zeaxanthin is highly desirable, because it is preferentially accumulated and incorporated into the parts of the mammalian retina exposed to high irradiance (*23*) and may thus be more useful in human diets than the readily available lutein. Arrest of the xanthophyll cycle to allow accumulation of zeaxanthin would thus be a desirable trait to incorporate into crops that provide leafy foods. Early progress in this direction is apparent in *Arabidopsis*, algae, and tomato. Xanthophyll cycle mutants that accumulate zeaxanthin have already been produced in model plants and algae (*7*), and these traits can be transferred to crop plants. Tomato fruit with an increased zeaxanthin content has recently been engineered [by overexpression of lycopene β-cyclase and β-carotene hydroxylase (*24*)]. One might ask: Why not simply grow existing food crops in the presence of environmental stress to enhance antioxidant content? Environmental stress can severely diminish crop productivity. Furthermore, additional plant defense compounds with adverse effects on human health are likely to be formed under the influence of environmental stress. Selective engineering of plants with enhanced antioxidant content should be the safer route.

Protection Against Oxidative Damage in Humans

Oxidative stress and/or disturbances in cellular redox balance have been identified as key elements underlying a plethora of human diseases (Fig. 5) (*25–28*). A shift toward more oxidizing conditions generally promotes cell proliferation [(*29*), as in cancer] and inflammation [(*30*, *31*), as in heart disease, diabetes, autoimmune diseases, and neurodegenerative diseases] and even affects neurotransmitter levels [and processes underlying various mental disorders (*32*, *33*)]. Mechanisms involved include reactive oxygen species in (i) modulation of gene expression via key signal transduction processes that turn out to be redox-regulated (Fig. 5) and in (ii) DNA damage–causing mutations (not depicted in Fig. 5) in genes for key regulatory proteins. Furthermore, singlet and triplet excited molecular species are formed in many physiological reactions in humans as well. An early response to an increase in reactive oxygen species is an up-regulation of endogenous antioxidants (as is depicted for plants in Fig. 4). However, unlike plants, humans are unable to synthesize the full complement of required antioxidants and are dependent on antioxidants obtained from their diet. Dietary antioxidants and phytochemicals with related functions are thus potential protective agents that can counteract oxidizing species and potentially reestablish a healthy cellular redox balance (Fig. 5). Antioxidants and omega-3 fatty acids act synergistically in the modulation of signal transduction (Fig. 5) (*34*, *35*) and in the protection of human vision (*4*, *36*) and many other functions (*37*). Key antioxidants as well as the essential omega-3 fatty acids are synthesized by plants and algae. The switch of affluent nations away from plant-based food lowered the dietary intake of antioxidants and other phytochemicals and is thought to be a major factor in promoting these "redox imbalance diseases" (Fig. 5) (*38*).

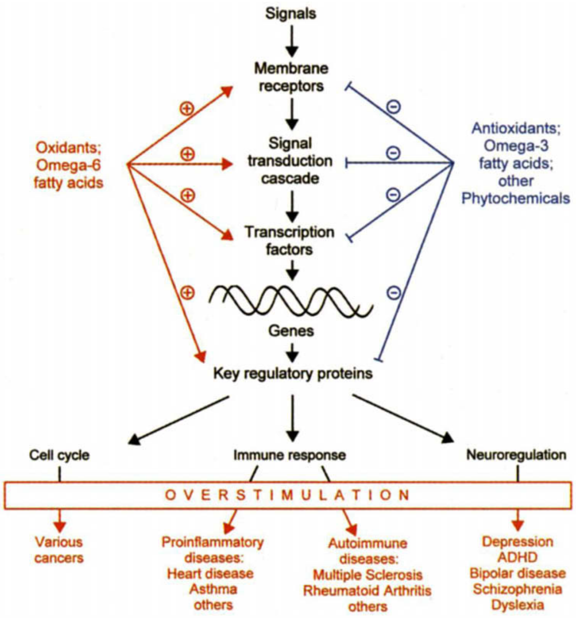

Fig. 5. Scheme showing key redox-modulated pathways of signal transduction, their relationships to human diseases and disorders (ADHD, attention deficit hyperactivity disorder), and their generalized patterns of modulation by oxidants and antioxidants as well as omega-6 fatty acids (particularly arachidonic acid) and omega-3 fatty acids (particularly eicosapentaenoic acid and docasahexaenoic acid). Neurodegenerative diseases, age-related macular degeneration, and the aging process itself are modulated similarly but are not shown because they fall into more than one of the depicted categories (cell cycle, immune system, and neurotransmitter dysregulation). Major groups of dietary antioxidants-phytochemicals are vitamin C (ascorbic acid), isoprenoids (vitamin E tocopherols, terpenes such as limonene, and carotenoids), phenolic compounds [phenolic acids such as cinnamic acid and polyphenols such as flavonoids (*51*)], and organosulfur compounds (*52*). It should be noted that antioxidants can promote oxidative stress at excessive concentrations. One mechanism involved is an induction of cytochrome P450 (that generates reactive oxygen species during oxidative breakdown of "foreign" substances) by high concentrations of β-carotene or flavonoids (*53*, *54*).

The precise molecular mechanisms of action through which many of these phytochemicals act remain poorly understood, and a number of clinical trials with high-dose, single-component supplements (such as β-carotene) have had disappointing results. However, other carotenoids may be more promising, particularly lycopene as well as zeaxanthin and lutein. There is evidence supporting a protective role for lutein and zeaxanthin in delaying chronic diseases, including age-related vision loss via macular degeneration and cataract formation, cancer, and heart disease [reviewed in (*4*)]. The classic antioxidant function of scavenging oxidants and re-reducing oxidized macromolecules is often assumed for these carotenoids, but other functions are waiting to be identified and are likely to involve direct interactions with signaling molecules. Future studies should examine whether the roles of lutein and zeaxanthin may parallel those of the vitamin E tocopherols. Vitamin E was initially recognized for its antioxidant properties, scavenging of reactive oxygen, and reduction of oxidized membrane lipids. However, much more specific and selective effects of tocopherols are now recognized. Tocopherols interact directly with key signaling proteins, for example, inhibiting lipoxygenases [LOXs (*19*)] and interacting in multiple ways with protein kinase C (*33*). LOXs oxidize specific membrane lipids to precursors of lipid messengers (oxylipins in Fig. 4), such as the plant stress hormone jasmonic acid and leukotrienes and similar messengers that trigger inflammation and cell death in humans. Vitamin E thus also has "nonantioxidant" functions, and similar notions exist concerning lutein and zeaxanthin in human health. Suggested functions for lutein include roles in the up-regulation of proteins (connexins) involved in cell-to-cell communication (*39*) as well as a role in the selective promotion of programmed cell death in cancer cells (*40*, *41*).

Closer inspection reveals that the inhibition of signal transduction can involve the same principal antioxidant effects, only focused directly on a signal transduction protein. In the example of LOX, Vitamin E reduces LOX's catalytic iron (that must be in oxidized form to allow LOX activity). In fact, although not widely noted, there are several studies showing that β-carotene also inhibits LOX activity (*42*, *43*). At higher concentrations, however, β-carotene can stimulate LOX activity (*42*). This may be one of the reasons why high-dose β-carotene supplements produced adverse effects in clinical trials. Future study should examine the effect of zeaxanthin on LOX activity in animals and plants and the possibility that zeaxanthin may afford inhibition without stimulation at higher concentrations.

Another avenue for future research into health-promoting effects of these xanthophylls are specific zeaxanthin- or lutein-binding proteins that may participate in signal transduction. In plants, xanthophyll-binding proteins include, in addition to light-harvesting proteins, the (lipocalin) proteins of the xanthophyll cycle (Fig. 2) (*44*). In animals, several lipocalin proteins are involved in immune function (*45*). Because immune function is stimulated by lutein, investigating a possible binding of lutein and zeaxanthin by lipocalins in the human immune response may prove rewarding.

Lastly, and in addition to the antioxidant and signal transduction functions of carotenoids, these versatile molecules also have profound effects on the structure of their environment. Carotenoids engage in structural interactions with lipid membranes and proteins [critically reviewed in (*46*)] and bind to the protein tubulin in the retina (*47*), enhancing visual acuity (*48*). Structural roles of carotenoids may have been the first to evolve (*49*). As evolution proceeded, many more of the properties of these molecules fit new functions that research is now venturing to study. We have much to learn about these colorful molecules.

Conclusions

Efforts to enhance plant antioxidant content may serve a dual purpose. We may be able to manipulate plant response to environmental stress (and hopefully enhance stress tolerance in certain scenarios) while simultaneously enhancing the nutritional quality of food plants. Furthermore, in light of the complex yet parallel functions of antioxidants in plants and humans, new mechanistic hypotheses should incorporate information from both plant physiology and human physiology. In the carotenoid field, this is already beginning. Carotenoid functions as antioxidants must be reconciled with carotenoid functions in signal transduction and redox-modulation of key signaling proteins. Protecting photosynthesis in the face of environmental stress as well as protecting human health against environmental or pathological stress requires improved understanding of molecular functions and the intersection between stress, disease, and physiology for both plants and humans.

References and Notes

1. Z. Gyorgypal, A. Kondorosi, *Mol. Gen. Genet.* **226**, 337 (1991).
2. J. W. Thornton, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 5671 (2001).
3. B. Demmig-Adams, W. W. Adams III, V. Ebbert, B. A. Logan, in *The Photochemistry of Carotenoids*, H. A. Frank, A. J. Young, G. Britton, R. J. Cogdell, Eds. (Kluwer Academic Publishers, Dordrecht, Netherlands, 1999), pp. 245–269.
4. J. A. Mares-Perlman, A. E. Millen, T. L. Ficek, S. E. Hankinson, *J. Nutr.* **132**, 518S (2002).
5. W. W. Adams III, B. Demmig-Adams, T. N. Rosenstiel, V. Ebbert, *Photosynth. Res.* **67**, 51 (2001).
6. B. Demmig-Adams, W. W. Adams III, *Nature* **403**, 371 (2000).
7. K. K. Niyogi, *Curr. Opin. Plant Biol.* **3**, 455 (2000).
8. X.-P. Li *et al.*, *Nature* **403**, 391 (2000).
9. P. Dominici *et al.*, *J. Biol. Chem.* **277**, 22750 (2002).
10. C. Külheim, J. Ågren, S. Jansson, *Science* **297**, 91 (2002).
11. K. K. Niyogi, A. R. Grossman, O. Björkman, *Plant Cell* **10**, 1121 (1998).
12. B. J. Pogson, K. K. Niyogi, O. Björkman, D. DellaPenna, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 13324 (1998).
13. B. Demmig-Adams, W. W. Adams III, *Trends Plant Sci.* **1**, 21 (1996).
14. P. A. Davison, C. N. Hunter, P. Horton, *Nature* **418**, 203 (2002).
15. B. J. Pogson, H. M. Rissler, *Philos. Trans. R. Soc. London B* **355**, 1395 (2000).
16. J. S. Josue, H. A. Frank, *J. Phys. Chem. A* **106**, 4815 (2002).
17. P. Mullineaux, S. Karpinski, *Curr. Opin. Plant Biol.* **5**, 43 (2002).
18. C. Reinbothe, B. Parthier, S. Reinbothe, *Planta* **201**, 281 (1997).
19. M. Maccarrone, G. Melino, A. Finazzi-Agro, *Cell Death Differ.* **8**, 776 (2001).
20. M. Havaux, K. K. Niyogi, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 8762 (1999).
21. ______, J.-P. Bonfils, C. Lütz, K. K. Niyogi, *Plant Physiol.* **124**, 273 (2000).
22. A. V. R. Rao, S. Agarwal, *J. Am. Coll. Nutr.* **19**, 563 (2000).
23. J. T. Landrum, R. A. Bone, *Arch. Biochem. Biophys.* **385**, 28 (2001).
24. S. Dharmapuri *et al.*, *FEBS Lett.* **519**, 30 (2002).
25. R. G. Allen, M. Tresini, *Free Radic. Biol. Med.* **28**, 463 (2000).
26. K. Nose, *Biol. Pharm. Bull.* **23**, 897 (2000).
27. T. D. Dalton, H. G. Shertzer, A. Puga, *Annu. Rev. Pharmacol. Toxicol.* **39**, 67 (1999).
28. P. Maher, D. Schubert, *Cell. Mol. Life Sci.* **57**, 1287 (2000).
29. R. E. Shakelford, W. K. Kaufmann, R. S. Paules, *Free Radic. Biol. Med.* **28**, 1387 (2000).
30. Y. Lavrovsky, B. Chatterjee, R. A. Clark, A. K. Roy, *Exp. Gerontol.* **35**, 521 (2000).
31. E. Ho, T. M. Bray, *Soc. Exp. Biol. Med.* **222**, 205 (1999).
32. F. Battaini, *Pharm. Res.* **44**, 353 (2001).
33. R. Gopalakrishna, S. Jaken, *Free Radic. Biol. Med.* **28**, 1349 (2000).
34. A. Denys, A. Hichami, N. A. Khan, *J. Lipid Res.* **42**, 2015 (2001).
35. R. A. Siddiqui, C. A. Labarrere, R. J. Kovacs, *Curr. Org. Chem.* **4**, 1145 (2000).
36. J. M. Seddon *et al.*, *Arch. Opthalmol.* **119**, 1191 (2001).
37. W. E. Connor, *Am. J. Clin. Nutr.* **71**, 171S (2000).
38. N. W. Solomons, *Asian Pac. J. Clin. Nutr.* **9**, S41 (2000).
39. H. N. Basu, A. J. Del Vecchio, F. Flider, F. T. Orthoefer, *J. Am. Oil Chem. Soc.* **78**, 665 (2001).
40. V. N. Sumantran, R. Zhang, D. S. Lee, M. S. Wicha, *Cancer Epidemiol. Biomark. Prev.* **9**, 257 (2000).
41. K. Müller, K. L. H. Carpenter, I. R. Challis, J. N. Skepper, M. J. Arends, *Free Radic. Res.* **36**, 791 (2002).
42. L. Lomnitski, S. Grossman, M. Bergman, Y. Sofer, D. Sklan, *Int. J. Vitam. Nutr. Res.* **67**, 407 (1997).
43. D. Trono, D. Pastore, N. Di Fonzo, *J. Cereal Sci.* **29**, 99 (1999).
44. A. D. Hieber, R. C. Bugos, H. Y. Yamamoto, *Biochim. Biophys. Acta* **1482**, 84 (2000).
45. L. Logdberg, L. Wester, *Biochim. Biophys. Acta* **1482**, 284 (2000).
46. N. I. Krinsky, *J. Nutr.* **132**, 540S (2002).
47. P. S. Bernstein, N. A. Balashov, E. D. Tsong, R. R. Rando, *Investig. Ophthalmol. Vis. Sci.* **38**, 167 (1997).
48. B. R. Hammond Jr., B. R. Wooten, J. Curran-Celentano, *Arch. Biochem. Biophys.* **385**, 41 (2001).
49. A. Vershinin, *Biofactors* **10**, 99 (1999).
50. W. W. Adams III, B. Demmig-Adams, B. A. Logan, D. H. Barker, C. B. Osmond, *Plant Cell Environ.* **22**, 125 (1999).
51. C. S. Yang, J. M. Landau, M.-T. Huang, H. L. Newmark, *Annu. Rev. Nutr.* **21**, 381 (2001).
52. S. C. Sahu, *J. Environ. Sci. Health Part C Environ. Carcinog. Ecotoxicol. Rev.* **20**, 61 (2002).
53. M. Paolini *et al.*, *Carcinogenesis* **22**, 1483 (2001).
54. S. N. Williams *et al.*, *Chem.-Biol. Interact.* **128**, 211 (2000).

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