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Health Benefits of Vitamins and Secondary Metabolites of Fruits and Vegetables and Prospects To Increase Their Concentrations by Agronomic Approaches

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Fruits and vegetables (FAVs) are an important part of the human diet and a major source of biologically active substances such as vitamins and secondary metabolites. The consumption of FAVs remains globally insufficient, so it should be encouraged, and it may be useful to propose to consumers FAVs with enhanced concentrations in vitamins and secondary metabolites. There are basically two ways to reach this target: the genetic approach or the environmental approach. This paper provides a comprehensive review of the results that have been obtained so far through purely agronomic approaches and brings them into perspective by comparing them with the achievements of genetic approaches. Although agronomic approaches offer very good perspectives, the existence of variability of responses suggests that the current understanding of the way regulatory and metabolic pathways are controlled needs to be increased. For this purpose, more in-depth study of the interactions existing between factors (light and temperature, for instance, genetic factors × environmental factors), between processes (primary metabolism and ontogeny, for example), and between organs (as there is some evidence that photooxidative stress in leaves affects antioxidant metabolism in fruits) is proposed.

KEYWORDS: Carbohydrates; carotenoids; glucosinolates; maturity; nitrogen; organic farming; phenolic compounds; stress; vitamin C

INTRODUCTION

Plants produce a very diverse set of organic molecules, some of which are traditionally considered not to participate directly in the major processes involved in growth and development. These substances are called secondary metabolites, an arguable term if one considers the importance of, for instance, lignin for all vascular plants or salicylic acid, a hormone. According to the nomenclature adopted by the British Nutrition Foundation, plant secondary metabolites can be divided into four major groups: terpenoids (about 25000 compounds), alkaloids (about 12000 compounds), phenolic compounds (about 8000 compounds), and sulfur-containing compounds (*1*). Unlike primary metabolites, so-called secondary metabolites are often unevenly distributed among taxonomic groups within the plant kingdom. Many secondary metabolites have positive effects on human health. Some of them are even essential to life, as are vitamins (such as tocopherols and tocotrienols, alias vitamin E). However, all vitamins are not considered to be secondary metabolites, like ascorbate, the major antioxidant in plants and for humans. A few other secondary metabolites are provitamins, that is, compounds that are converted into vitamins in animal bodies (such as β-cryptoxanthin, a carotenoid found in *Citrus* fruits, or β-carotene, found in several fruits and vegetables endowed with provitamin A properties). The vitamins and secondary metabolites this paper discusses are referred to by the generic term "phytochemicals" hereafter.

It is well established that fruits and vegetables (FAVs) represent the major source of phytochemicals and other useful compounds such as amino acids and fatty acids (*2*). Indeed, the much praised health benefits of FAVs are, at least partially, attributable to their high concentrations in phytochemicals. Even though no final evidence has been found that FAVs protect against cancer, there is vast consensus with regard to the positive role they play in preventing or controlling particular diseases or disorders (*3*), and it can be globally recommended to most people to substantially increase their consumption of FAVs.

In a report released jointly by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) in 2003, statistics are provided showing that, in 2001, chronic

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diseases contributed approximately 59% of the 56.5 million total reported deaths in the world and 46% of the global burden of disease (*4*). The report commissioned by WHO and FAO recommends increasing the amounts of fresh fruits and vegetables in the diet. At least 400 g, ideally 800 g, of fruits and vegetables should be consumed daily. Although the nutritional benefits of fresh FAVs have been well established for a long time, their consumption remains insufficient. In some developed countries, such as France, despite the numerous campaigns of information organized by the Ministries of Health or growers' organizations, quantities of FAVs bought by consumers even decreased over recent years. In developed countries, it may be tempting for the fruit and vegetable industry to propose to consumers FAVs with increased or guaranteed amounts of micronutrients. This could greatly help the cause of public health while contributing to the competitiveness of the industry in a more and more challenging global market. Similarly, FAVs with high concentrations in micronutrients could potentially help the cause of public health in developing countries where intake is generally in the range of 20−50% of the minimum recommended level, largely due to poverty and food insecurity, lack of nutritional knowledge, and some unfavorable food habits (*4*,*5*). In these countries, women and children, as well as the elderly and those infected with human immunodeficiency virus (HIV), suffer disproportionately because of their relatively higher need for vitamins and minerals while often being discriminated against in terms of food supply and availability. The situation is particularly critical in sub-Saharan Africa (*6*).

With regard to the issue of FAVs with increased concentrations in phytochemicals, several questions need to be answered. Can targets in terms of concentrations be defined, knowing that precise dietary recommendations cannot be currently made in the absence of sufficient understanding about the bioavailability of bioactive compounds, their interactions, their dynamic after ingestion and metabolization, and the variability of responses due to the existence of genetic profiles? If not, does it all the same make sense to try to produce FAVs with increased concentrations in phytochemicals? If the answer to the latter question is a positive one, what are the perspectives of genetic and agronomic approaches, respectively? Can genetic and environmental factors be considered as realistic levers? Is it realistic to imagine that innovative plant materials and growing techniques can supply FAVs with consistently increased concentrations in phytochemicals, without harming other important cropping objectives such as yield? What are the stumbling blocks, and what research needs to be done?

The first objective of this paper is to briefly review the dietary effects of phytochemicals. We shall argue that, even though no targets in terms of concentrations can be set, it is desirable to try to increase them within reasonable limits. We shall then consider the achievements and prospects of genetic approaches, before reviewing extensively the agronomic data accumulated about the effects of environmental factors on the concentrations of phytochemicals in FAVs. The prospects and challenges of agronomic approaches are eventually discussed in the light of some elements about interactions between factors, between processes, and between organs.

This review is focused mainly on vitamins C and E, phenolic compounds, carotenoids, and glucosinolates.

DIETARY EFFECTS OF PHYTOCHEMICALS CURRENTLY FOUND IN FAVs

Unlike carbohydrates, lipids, and proteins, which are hydrolyzed into small assimilable molecules upon ingestion by humans, most vitamins and phenolics are taken up directly and are subject to very weak biochemical modifications. Humans do not have the enzymatic arsenal to substantially modify these molecules after ingestion, which means that they can benefit in turn from the protective properties they have in the plants that synthesize them. On the contrary, glucosinolates and provitamin A carotenoids must be converted in the intestinal tract, into isothiocyanate and vitamin A respectively, before becoming active. Secondary metabolites and vitamins have positive dietary effects as this brief review tends to demonstrate. It must, however, be kept in mind that they may occasionally prove toxic or interact in an antagonistic way. For instance, an antagonistic effect of some flavonoids was observed on ascorbate uptake. The sodium-dependent vitamin C transporter 1 (SVCT1) is inhibited by flavonoids largely found in foods such as quercetin, fisetin, rutin, apigenin, and genistein (*7*,*8*).

Vitamins. Vitamin C, also known as ascorbate, is a vital micronutrient for humans. A lack of vitamin C hampers the activity of a range of enzymes and may lead to scurvy in humans (*9*). Unlike most animals, humans are unable to synthesize their own vitamin C, and they must therefore find it in plants, in particular, fruits and vegetables. In addition to its involvement in the production of collagen, ascorbic acid serves as a cofactor in several vital enzymatic reactions, including those involved in the synthesis of catecholamines, carnitine, and cholesterol, and in the regulation of transcription factors controlling the expression of important genes of the metabolism (*10*). Ascorbic acid is present in three forms: ascorbate, monodehydroascorbate (MDHA), and dehydroascorbate (DHA), which corresponds to the oxidized form of ascorbate. In most cellular functions, ascorbate acts as an electron donor, but it may also act directly to scavenge reactive oxygen species (ROS) generated by cellular metabolism. Due to the role of ascorbate in protecting cells against oxidative stress and the involvement of ROS in neurodegenerative disorders (Alzheimer's and Parkinson's diseases) or inflammatory response (arteriosclerosis), it is strongly suggested that vitamin C could prevent heart, chronic inflammatory, and neurodegenerative diseases (*11*).

Vitamin E (tocopherols and tocotrienols) is present in all cell membranes and plasma lipoproteins, especially in red blood cells of the human body. As the major lipid-soluble chain-breaking antioxidants in humans, vitamin E protects DNA, low-density lipoproteins, and polyunsaturated fatty acids from oxidative damage. It moreover plays a role in hemoglobin biosynthesis, modulation of immune response, and stabilization of the structure of membranes (*12*).

Vitamin K_1 is a liposoluble vitamin, synthesized from phylloquinone by bacteria in the intestinal tract. It plays a positive role in the control of blood clotting, bone formation, and repair. Deficiency of vitamin K_1 may result in hemorrhagic disease in newborn babies, as well as postoperative bleeding, muscle hematomas, and intercranial hemorrhages in adults (*13*). Vitamin K_3 menadione was shown to exhibit cytotoxic activity and inhibit growth of tumors in humans (*14*).

Phenolic Compounds. The specific action of each plant phenolic compound is not easy to assess because only a very small part of them is really absorbed (*15*) and because they moreover potentially undergo transformations. Enterocyte and epathocyte can cleave glycoside moieties. They are responsible for glucuronidation, methylation, and sulfation of flavonoids. First, they protect some major cellular components from oxidation. Many dietary phenolics are antioxidants capable of quenching ROS and toxic free radicals formed from the peroxidation of lipids and, therefore, have anti-inflammatory and antioxidant properties at the body level. Several hydroxycinnamic acid derivatives, for instance, caffeic acid, chlorogenic acid, ferulic acid, *p*-coumaric acid, and sinapic acid, present strong antioxidant activities by inhibiting lipid oxidation and scavenging ROS (*16*). Flavonoids are known to prevent production of free radicals by chelating iron and copper ions to directly scavenge ROS and toxic free radicals

and to inhibit lipid peroxidation. Production of peroxides and free radicals, which may damage DNA, lipids, and proteins, has been linked to aging, atherosclerosis, cancer, inflammation, and neurodegenerative diseases such as Alzheimer's and Parkinson's. Flavonoids were also demonstrated to protect low-density lipoprotein (LDL) cholesterol from being oxidized, thus preventing the formation of atherosclerotic plaques at the level of the arterial wall. Many dietary flavonoids and hydroxycinnamic acids bind to human serum albumin, the main protein involved in lipid transportation within blood. This cotransport provides an efficient antioxidant protection to lipids. Additionally, when tannins form bond with enzymes, they inhibit part of the lipoxygenase and peroxidase activity, therefore exhibiting antioxidant effects. Chlorogenic acid and caffeic acid inhibit N-nitrosation reaction and prevent the formation of mutagenic and carcinogenic *N*-nitroso compounds (*17*). Without entering into details, it may be said that the range of activities of phenolic compounds encompasses protection against coronary heart diseases, anti-inflammatory effects, and inhibition of the development of cancer cells.

Some phenolics are known to modulate other enzymes of the metabolism (see the review in ref *18*). In particular, some flavonoids, such as quercetin, myricetin, and fisetin, inhibit the intestinal glucose transporter isoform 2 (GLUT2), thus exerting an antiglycemic effect (*7*, *19*). This inhibition is reversible and noncompetitive as far as quercetin is concerned. Chicoric acid has also an antidiabetic effect, but its cellular target has not yet been discovered. Flavonoid fractions of numerous plant extracts have been found to have a hypoglycemic effect that remains to be elucidated. Hydrosoluble tannins such as gallic acid esters and condensed tannins such as catechin polymers and many flavonoids accumulating in plant organs are known to exert an antifeeding effect by binding to the enzymes and other proteins of defoliating insects and other pests.

Flavonoids modulate signaling pathways (*20*). Among signaling roles, isoflavones such as daidzein and genistein have received considerable attention due to their ability to bind to mammalian estrogen receptors (α and β) and mimic estrogen and anti-estrogen actions. They modulate the endocrine system and may exert a preventive role against breast cancer and osteoporosis.

Middleton et al. (*18*) stated that dietary flavonoids, such as quercetin, affect each immune cell line specifically (T cells, B cells, macrophages, NK cells, basophils, mast cells, neutrophils, eosinophils, and platelets). In particular, dietary flavonoids have an antihistaminic action. During allergic reactions, when IgE binds to its specific receptors on the plasma membrane of mast cells and basophils, these cells are induced to produce histamine. Both quercetin and apigenin inhibit anti-IgE-induced histamine release (*21*). Many flavonoids that are inhibitors of histamine release are also good lipoxygenase inhibitors.

Many flavonoids protect plants against their pathogenic bacteria and fungi. Some phenolic acids such as benzoic acid, hydrobenzoic acid, caffeic acid, and vanillic acid possess antifungal and antimicrobial properties (*22*). These properties are useful during postharvest storage and are conserved after assimilation. They may also exhibit antiviral properties by limiting the multiplication of viruses.

Carotenoids. Carotenoids endowed with provitamin A activity are vital components of the human diet. Vitamin A is implicated in hormone synthesis, immune responses, and the regulation of cell growth and differentiation (*13*). It can be produced within certain tissues from carotenoids such as β-cryptoxanthin present in *Citrus* fruits, β-carotene present in carrots, spinach, and sweet potatoes, and α-carotene found in carrots, pumpkin, and red and yellow peppers (*23*). A carotenoid-deficient diet can lead to night blindness and premature death. Carotenoid-rich diets are correlated with a significant reduction in the risk for certain cancers, coronary heart disease, and several degenerative diseases.

Carotenoids have demonstrated anticancer and antimutagenic properties (*24*). Underlying mechanisms are not well understood, but the dietary importance of carotenoids is discussed, at least in part, in terms of antioxidant properties (*13*, *25*). Carotenoids are known for their capacity to efficiently quench $^1O_2$ singlet oxygen by energy transfer (*26*). $^1O_2$ is a particularly active ROS, capable of damaging DNA (*27*) and provoking genetic mutations (*28*). Eventually, $^1O_2$ can damage lipids and membranes (*29*).

Beutner et al. have classified carotenoids on the basis of three criteria: the dependence on the partial pressure of molecular oxygen, the potential for inhibiting the formation of peroxide, and the potential for quenching of $^1O_2$ (*25*). Astaxanthin, a xanthophyll produced by some algae, is an excellent antioxidant capable of quenching free radicals in either their standard or excited form. β-Carotene and lycopene are efficient antioxidants, capable of inhibiting strongly the formation of peroxide. They are prone to degradation after ingestion, but their breakdown product seems to have interesting properties that may explain the cancer preventive activity of these carotenoids (*30*). ζ-Carotene is a poor antioxidant.

When lipophilic antioxidants such as lutein or lycopene are associated with hydrophilic antioxidants such as rutin, a supra-additive protection of low-density lipoprotein occurs (*31*). When rutin is associated with ascorbic acid, a synergetic protection also occurs.

Phytosterols. Phytosterols are found in high amounts in broccoli, Brussels sprouts, cauliflower, and spinach (*32*). They regulate the fluidity and permeability of the phospholipid bilayers of plant membranes (*33*). Certain phytosterols are precursors of brassinosteroids, plant hormones involved in cell division, embryonic development, fertility, and plant growth (*34*). Some sterols are provitamins: upon skin exposure to UV radiation, they may give rise to calciferol, also known as vitamin D_2, which is involved in the absorption of calcium and bone growth. Plant sterols possess, morevoer, cholesterol-lowering properties and play a positive role by decreasing the incidence of cardiovascular diseases. Being structurally similar to cholesterol, they can compete with cholesterol, thus limiting its absorption from fat matrices into the intestinal tract (*35*). Plant sterols have been hypothesized to have anticancer, antiatherosclerosis, anti-inflammation, and antioxidant activities (*36*).

Saponins. Saponins are attributed with cardioprotective, immunomodulatory, antifatigue, and hepatoprotective physiological and pharmacological properties (*37*). Antifungal activity is generally ascribed to the ability of saponins to complex with sterols in fungal membranes, thus causing pore formation and loss of membrane integrity (*38*). They also affect membrane fluidity (*39*). Dietary saponins have been observed to reduce blood cholesterol, stimulate the immune system, and inhibit the growth of cancer cells (*40*). Saponins inhibit active transport by increasing the general permeability of the enterocytes (*41*). Saponins can also form insoluble complexes with minerals such as zinc and iron (*42*).

Glucosinolates. A reduction in the prevalence of certain forms of cancer has been attributed to the anticarcinogenic properties of certain glucosinolates and their breakdown products (*43*). Glucosinolates act by activating enzymes involved in the detoxification of carcinogens and by providing protection against oxidative damage (*44*) [see also the recent review of Traka and Mithen (*45*)]. Certain glucosinolates have been observed to inhibit enzymes involved in the metabolism of steroid hormones.

INCREASING THE CONCENTRATION OF VITAMINS AND SECONDARY METABOLITES OF FAVs

Although there is compelling evidence that vitamins and secondary metabolites are essential for human health, many questions

remain unresolved. Assessing the nutritional benefits of food with enhanced concentrations of specific biologically active substances is not an easy task, which, in turn, makes it impossible to define precise targets in terms of concentrations. Biologically active substances found in FAVs always come as part of a mixture in the diet. In a mixture, metabolites may have potentiating, antagonizing, or synergistic effects (*46*). Moreover, health benefits may be influenced by other ingredients such as dietary fibers, monounsaturated fatty acids, agents stimulating the immune system, minerals, and even ethanol (*47*). Then there is the issue of the so-called bioavailability of biologically active substances, which is affected by several factors such as tannin and lignin concentrations that differ greatly from one species to another. Tannins have antifeeding effects, due to their protein-binding properties, whereas lignin decreases the digestibility of plant material. The bioavailability of β-carotene, for instance, ranges from 47% in kiwi fruits to 2% in red grapefruits (*48*). Besides, it is now established that not all individuals respond identically to bioactive food components because of the existence of genetic profiles that modulate the responses. Finally, very little is known about the dynamics of food components after they are ingested and then metabolized in the body. A major challenge for researchers in the future will consist of working out the best combinations of beneficial components of FAVs according to existing genetic profiles while minimizing antagonistic interactions and determining the duration of exposure and timing. Meanwhile, it is very clear that no precise recommendations in terms of concentrations in phytochemicals can be formulated.

The issue of target concentrations for phytochemicals in FAVs is made even more complicated by the existence of some secondary metabolites that can be toxicants. Not all secondary metabolites are micronutrients. Some are natural food toxicants, such as furanocoumarins, which are found in grapefruit juice. Psoralens can generate hazardous drug interactions (*49*). Moreover, psoralens are recognized as skin photocarcinogens (*50*). It has been hypothesized that the increase in cutaneous melanoma incidence may be attributed to the increase in consumption of grapefruit and orange juices in developed countries (*50*). Similarly, some saponins, such as sapotoxin, can be toxic to humans by causing irritations of the skin and membranes (*40*). Eventually, extreme overconsumption of glucosinolate-rich food can cause inflammation of the mucous membranes of the stomach and disrupt synthesis of the thyroid hormone (*51*).

At this stage, one may conclude, rather hastily, that promoting the consumption of bioactive compounds of fruits and vegetables may be dangerous or, at least, beside the point. Several attitudes may be adopted. The first one consists of waiting for dieticians to come up with more precise recommendations in terms of doses or combinations of doses of bioactive food compounds. This will take some time, perhaps even a lot of time, considering the importance of the scientific challenges created by the issues of the bioavailability, the dynamics and the interactions of bioactive compounds, and the genetic diversity of consumers' responses. Clearly the issue of human health requires urgent measures to be taken. A more down-to-earth attitude consists of considering that enough evidence has been accumulated respectively through epidemiologic and clinical studies, first about the global benefits of FAVs in the human diet and second about the dietary effects of their bioactive compounds, especially vitamins and secondary metabolites. On the basis of such undisputed evidence, even in the absence of precise recommendations, it makes sense to encourage people to consume more FAVs. Unfortunately, the five-a-day campaigns in developed countries to persuade people to eat at least five portions of FAVs every day have proven to be a relative failure so far, and the situation is no better in developing countries. Taking these facts into account, it appears reasonable to try to improve the current situation by encouraging, besides the consumption of FAVs, the consumption of foods and food supplements with enhanced concentrations in phytochemicals, or, as we may say in the case of phenolic compounds at least, restored concentrations when compared to the concentrations that prevailed in the FAVs before centuries of breeding to obtain bigger, less lignified, less astringent, and less indigestible edible plant parts resulted in strongly impoverishing food. Within this view, the proposition to produce FAVs with increased concentrations in useful bioactive compounds makes sense. Prudence demands that potentially toxic secondary metabolites should not be included in studies aiming at designing innovative plant materials or techniques to increase the concentration in phytochemicals of FAVs, or at least that they are not given the priority. Moreover, it may be argued that prudence also demands that targets in terms of concentrations remain in the range of those observed as the consequence of natural genetic variability or of the influence of not-too-extreme variations or levels of environmental factors (note that such a strategy probably excludes nutraceuticals). To throw light on both the issues of the potential of genetic and agronomic approaches (does it work?) and the limits to keep in mind when trying to enhance the concentrations in bioactive compounds (how much is too much?), it is necessary to review the achievements of genetic and agronomic approaches and discuss their respective prospects.

ACHIEVEMENTS AND PROSPECTS OF CONVENTIONAL BREEDING AND METABOLIC ENGINEERING

Our objective is not to review all genetic approaches but to focus on FAVs. See the review of Newell-McGloughlin (*52*) for a broader approach to the issue of nutritionally improved crops. The reader can also refer to the AGBIOS crop database (http://www.agbios.com/dbase.php?action=ShowForm). Moreover, we shall not consider here the suppression of toxic compounds by metabolic engineering (*53*).

There are two basic approaches to modifying a biosynthetic pathway with the objective of increasing the amounts of desirable compounds. It may be tempting either to manipulate the pathway flux or to introduce novel biosynthetic activities from other organisms. Increasing, preventing, or redirecting the flux into or within the pathway may rely on such methods as increasing the levels of identified or suspected rate-limiting biosynthetic enzymes, inhibiting the activity of genes that code for enzymes competing for limited substrate supply, and up- or down-regulation of regulatory factors (*54*).

The experience gained with regard to the flavonoid pathway demonstrates that all of the above-mentioned approaches can be applied successfully to modify the production of plant metabolites (*55*−*57*). More specifically, up-regulation of the flavonoid pathway has been obtained by using transgenes for biosynthetic enzymes as well as for transcription factors.

Ascorbate. Ascorbate (AsA) is essential not only to humans but also to the plants that synthesize it. Indeed, AsA plays an important role in many plant physiological processes, acting as a regulator of growth and plant development and as an electron donor in such essential adaptative processes as nonphotochemical quenching. AsA is also an major antioxidant, playing a pivotal role in the maintenance of the redox status of cells. AsA is abundantly found in fruits and vegetables. Its concentration depends on the type of tissue (leaves, fruits, and roots) and the age of organs. It also varies greatly as a function of species and cultivar, besides environmental conditions (light, drought, ozone, ...). Considering genetic factors, Johnston et al. (*58*) reported that AsA ranges from 20 to 300 mg/kg in apple and from 300 to 500 mg/kg in orange and reaches up to 17.5 g/kg in *Acerola*. In kiwi, AsA concentration

ranges from 290 to 800 mg/kg, depending on cultivar. It was suggested that genotypes with very high potential could be used for breeding objectives to reach very high concentrations, up to 21 g/kg of fresh weight in *Actinidia latifolia* (*59*). In tomato, the highest concentrations were observed in the smaller fruit varieties (*60*) and in wild species. There is up to 5 times more AsA in *Solanum penneli* compared to *Solanum lycopersicum* (*61*).

The AsA concentration in plant cell depends on biosynthesis, recycling (*62*), and degradation (*63*). The different biosynthetic pathways of vitamin C have been elucidated recently and the genes involved identified (*64*). The genetic molecular (GM) approaches have helped us to identify the limiting steps in the AsA pathway. Two important regulatory steps were identified: GDP-mannose epimerase (GME) (*65*, *66*) and GDP-L-galactose phosphorylase (GGP) (*67*), with two genes coding for the latter enzyme, vtc2 and vtc5. A 4-fold increase in AsA was observed when the kiwifruit GGP was overexpressed in *Arabidopsis*, and an up to 7-fold increase in AsA was observed when both the GGP and the GME genes were overexpressed (*66*). Similarly, the overexpression of the GGP gene from *Actinidia chinensis* in tobacco resulted in a 3-fold increase in foliar AsA (*67*). Stevens et al. (*61*) revealed that the gene coding for GME is present in the quantative trait loci (QTLs) responsible for high levels of AsA in tomato. Another promising way to manipulate AsA content might be achieved via regulatory genes of this pathway. It was observed that an ascorbic acid mannose pathway regulor mutant (AMR1 mutant) (it was found that the AMR1 gene regulated the Smirnoff−Wheeler pathway) with reduced expression of AMR1 had 2−3-fold higher foliar AsA concentrations due to increased expression of limiting-step enzymes such as GME, GPP, and vitamin C defective 2 (VTC2) (*68*). Other attempts to manipulate AsA concentration via up-regulation of plants' AsA recycling also proved to be efficient. For example, GM approaches showed that overexpression of wheat dehydroascorbate reductase (DHAR) increased AsA content in tobacco or wheat chloroplast up to 3.9-fold (*69*).

Synthesis, transport, and accumulation of AsA in the different cell and tissue compartments appear tightly regulated. Moreover, the pivotal role played by AsA in the cell balance suggests that increasing AsA concentration in plant parts of interest represents a difficult task ahead. Due to the complexity of AsA regulation in plants, producing FAVs with increased concentrations in AsA will clearly require a deeper understanding of AsA metabolism (*70*) .

Carotenoids. Several surveys and studies have revealed the potential of conventional breeding to increase the concentration in carotenoids of carrot, spinach (*71*), and tomatoes (*72*). Increases of 120, 30, and 50%, respectively, have been reported. Results from breeding programs at the Asian Vegetable Research and Development Center and the U.S. Department of Agriculture suggest that it is possible to obtain lines of tomatoes with 10−25 times the concentration in β-carotene of conventional varieties (*73*, *74*).

There have been numerous attempts to engineer carotenoid biosynthesis (*75*), but they have not been very successful so far. The carotenoid biosynthetic pathway is well-known, and carotenogenic genes have been isolated from a variety of organisms, which facilitates manipulation of this pathway (*76*). Consequently, most attempts consisted of overexpressing one or more specific genes, selected for coding for enzymes thought to catalyze key controlling steps of the biosynthetic pathway. They generally did not result in the accumulation of the targeted carotenoid or produced detrimental collateral effects.

The majority of the plants of the first transgenic tomato line, generated with the tomato phytoene desaturase (PSY) under the control of the constitutive cauliflower mosaic virus 35S promoter, showed a dwarf genotype (*77*). It was probably due to a competition between carotenoids and gibberellins for geranylgeranyl diphosphate (GGPP). Interferences with other processes address the question of a tissue-specific or constitutive promoter for constructions used to generate transgenic plants and underscore the lack of information on metabolic cross-talk between carotenoid and other pathways. The problems encountered originate from the complexity of the regulation of biosynthesis of isoprenoids in plant cells, at both the gene and enzyme levels, and the poor understanding we have of the existing mechanisms (*78*, *79*). It has been observed, for instance, that overexpression of PSY, which is believed to exert the greatest control over pathway flux, in genetically modified tomato plants obtained by inserting homologous bacterial genes reduced the control exerted by this enzyme on the flux, eventually shifting it from one step of the metabolic pathway to another (*80*). Therefore, a modest (almost 2-fold) increase in lycopene content was achieved with bacterial *psy* transgene under a fruit-specific promoter (*80*). Higher increases in carotenoid levels have been seen for plant tissues with low carotenoid levels or for plants with carotenoid-free tissues. It was reported that overexpression of a bacterial *psy* gene under a seed-specific promoter results in a significant increase in total carotenoid and β-carotene contents in canola seed (*81*). More recently, tissue-specific coexpression of *psy* and phytoene désaturase (*crtI*) led to Golden Rice (*82*) and to Golden Potato (*83*) with β-carotene enhancement of up to 23 times in Golden Rice 2.

The central role of carotenoids in plant development and adaptation suggests that their synthesis is coordinated with development processes such as plastid differentiation and fruit development (*78*). Only a few regulatory genes involved in carotenoid biosynthesis have been isolated so far (*84*). It was shown that a transcription factor, AtRAP2.2, a member of the APETALA2 (AP2)/ethylene responsive element-binding protein transcription factor family, binds to a regulatory region of psy promoter and modestly regulates *psy* and *pds* expression (*85*). Some genes involved in the light signal pathway (*de-etiolated1* (*DDB1*) and *UV-damage DNA-binding protein 1* (*DET1*) or in chromoplast differentiation (*orange* (*Or*)) were reported to control carotenoid metabolism (*84*). There are many forms of control and many controlling points, presumably at each branch point of the isoprenoid pathway. The dominant form of control is thought to be at the transcriptional level (*78*, *86*), but others probably exist. For instance, Marty et al. (*87*) attributed the decorrelation they observed between β-carotene accumulation and expression of ζ-carotene desaturase (ZDS) in the white apricot variety 'Moniqui' to a post-transcriptional modification of the ZDS, which may have resulted in an inactive form (*87*). Post-transcriptional regulation over key steps of the biosynthetic pathway may also involve redox status and external signals, such as light. Eventually, observations also suggest that feedback control mechanisms and metabolic channeling between each branch of the isoprenoid pathway play a key role and may be behind unexplained hindering of endproduct formation or unwanted side effects. The organization of carotenoid enzymes into metabolons may explain such observations (*80*), and it has been argued that understanding the interactions within the enzymatic complexes catalyzing biosynthesis of carotenoids and their conversion is as important as understanding the regulation at the level of gene expression (*88*). In addition to transcriptional and post-transcriptional regulations, a certain form of regulation may be exerted by the sequestration of carotenoids within the cell. Observations made on tomato and cauliflower suggest that the accumulation of carotenoids depends on genes involved in sequestration (*79*, *89*). Preventing the degradation of carotenoids and exploiting pleiotrophic collateral effects by interfering in the light signal transduction pathway (*90*) have been suggested as promising strategies that could allow the difficulties arising

from the complexity of the regulation of the biosynthetic pathway of carotenoids to be bypassed (*91*). For instance, the expression of the *Or* gene in potato tuber causes high levels of β-carotene accumulation and a 6-fold increase in total carotenoids (*92*).

Glucosinolates. The potential of conventional breeding to increase the concentration in glucosinolates in *Brassica* seems to be considerable. Kushad et al. (*93*) observed huge variability among the 50 cultivars of broccoli they screened. In this study, the concentration in glucosinolates was 20 times higher in the best performing cultivar compared to the least one.

There have been several attempts to breed broccoli for enhanced concentrations of glucosinolates (*94*, *95*). Cultivars have been developed by introgression of two genomic segments from *Brassica villosa* that present a 4-fold increase in 3-methylsulfinylpropyl and 4-methylsulfinylbutyl glucosinolates, as well as an increased conversion of glucosinolates to isothiocyanates associated with a reduction in nitrile production (*95*). It has been hypothesized that enhanced glucosinolate synthesis is associated with allelic forms of the methylalkylmalate synthase genes in these genomic segments which are involved in the control of chain elongation of methionine-derived glucosinolates and appear to be associated with QTLs involved in the total amount of glucosinolates in both *Brassica* (*96*) and *Arabidopsis* (*97*). Although there have been no attempts so far to engineer commercial *Brassica* cultivars with enhanced concentrations in glucosinolates, metabolic engineering looks promising when considering what has been achieved on *Arabidopsis* and the way our understanding of glucosinolate molecular genetics, particularly of the role played by transcription factors, has progressed (*98*). See also Desjardins for a review (*91*). According to Traka and Mithen, metabolic engineering should focus on 3-methylsulfinylpropyl and 4-methylsulfinylbutyl glucosinolates because of their biological activity and because the isothiocyanates that derive from them, iberin and sulforaphane, respectively, are not volatile and thus do not contribute to the unpleasant flavor of *Brassica* foods, unlike those deriving from most other glucosinolates (*45*).

Phenolic Compounds. Anthocyanin content has been an important target of FAV breeding for long time. Generally speaking, conventional breeding looks promising as far as polyphenols are concerned. Kalt et al. (*99*), for instance, found in the some 250 blueberry genotypes they surveyed that there was a 1.2−1.6-fold difference in the total phenolic and anthocyanin contents, respectively, between the 10th and the 90th percentiles. Anttonen and Karjailanen (*100*) observed a 2-fold difference in total phenolics and a 3-fold difference in quercetin and ellagic acid in the 17 cultivars of raspberry they analyzed. In studies conducted on strawberry, 2−3-fold differences in the anthocyanin content were reported by Wang and Lin (*101*) and Cordenunsi et al. (*102*), respectively. Atkinson et al. (*103*) reported a 5-fold difference in concentration in ellagic acid among the 45 strawberry cultivars they studied. Several breeding programs exist that aim at releasing cultivars with enhanced concentrations of phenolic compounds. Successful improvements have been registered in cranberry, strawberry, peach, and plum (*104*). We are certainly entitled to expect breeding programs to yield interesting results in the coming years.

There have been several attempts to exploit studies of the biosynthetic pathway of flavonoids in flowers, dating back to the early 1990s, to engineer tomatoes with higher concentrations in phenolic compounds. Target genes identified during these early studies belong to two categories: those involved in the biosynthetic pathway itself, such as chalcone synthase (CHS), chalcone flavanone isomerase (CHI), flavanone-3 hydroxylase (F3OH), and flavonol synthase (FLS), and those involved in the control of the pathway (*56*). Concomitant expression of CHS, CHI, F3OH, and FLS increases dramatically the level of quercetin glycosides in the peel of tomato (*105*). Tomatoes transformed with a heterologous double gene construct from a *Petunia* chalcone isomerase and a *Gerbera hybrida* flavone gene exhibited an 18-fold increase in flavonol quercetin-3-rutinoside and a >36-fold increase in kaempferol-rutoside when compared to the wild type (*106*). Several regulatory genes of flavonoid biosynthesis have been identified. Most of them belong to the MYB and MYC families. Overexpression of transcription factors of the MYB and MYC families was found to result in a 60-fold increase in flavonoid and, especially kaempferol biosynthesis in tomato (*107*). Other examples of metabolic engineering include the introduction of a stilbene synthase gene from grapevine in tomato and the subsequent accumulation of not only *trans*-resveratol and glycosylated forms of stilbene but also ascorbate and glutathione (*108*). Down-regulation of cinnamoyl-CoA reductase (CCR), the first committed enzyme of the lignin biosynthesis pathway, resulted in an increase in the availability of the coumaroyl-CoA precursors of kaempferol rutinoside and actually in the accumulation of the expected endproduct (*109*). But the CCR transformants exhibited altered phenotypes, demonstrating that rerouting of a metabolic flow may come at a price (*110*). See also the review of Chopra et al. (*111*).

Besides numerous attempts to increase the concentration in flavonoids in FAVs through metabolic engineering, there have been some very interesting achievements with hydroxycinnamic acids. Overexpression of hydroxycinnamoyl-CoA:shikimate/quinate hydroxycinnamoyl transferase in tomato was found to cause plants to accumulate more chlorogenic acid with no side effects in terms of concentrations of other soluble phenolic compounds (*55*).

Technically, the potential of metabolic engineering and conventional breeding appears to be huge, even though, at this stage, we are not capable of quantifying what this potential will be when the other usual breeding criteria are taken into account. Then there is the issue of the commercial potential. Metabolic engineering and conventional breeding probably do not have the same perspectives. European consumers have expressed repeatedly that they do not trust genetically modified food. On the contrary, the same consumers should not express reluctance to accept new cultivars with enhanced concentrations in phytochemicals obtained by conventional breeding or by marker-assisted breeding for that matter (*112*). The problem is that breeding is a time-consuming process. Coming up with a new cultivar endowed with enhanced desirable traits takes years, which means that the impact of breeding will not express itself quickly and remain strictly restricted to only cultivars that were designed with the objective of increasing the concentration in phytochemicals. Breeders of FAVs should certainly be encouraged to find new cultivars meeting this objective. Meanwhile, it seems useful to evaluate the other major option, namely, the environmental one. From the farmer's point of view, the question is to assess whether it is technically and economically feasible to increase the content in phytochemical of FAVs by relying on cropping techniques.

ACHIEVEMENTS AND PROSPECTS OF AGRONOMIC APPROACHES

The idea that it is possible to increase the content in secondary metabolites of edible plant parts is a relatively ancient one. It has been demonstrated since the late 1980s that deficit irrigation improves grape quality by increasing the concentration of phenolic compounds and, more specifically, anthocyanins (see ref *113* for a review). More recent studies have started to focus on the effect of climatic factors on the content in micronutrients of FAVs. To date, there are more than 100 papers dealing with this issue. Convincing evidence has been collected which proves clearly that the environment can be manipulated to substantially increase the

Table 1. Effect of Environmental Factors, Light, Temperature, Carbon Supply, Drought, Salinity, and Nitrogen Fertilization, on Concentration, Expressed on a Fresh Matter Basis, If Not Indicated Otherwise, in Ascorbic Acid[a]

environmental factor	crop	effect	ref
high mean daily temperature	several crops	−	*159*
high light intensity combined with low mean daily temperature	*Pisum sativum* L.	+	*180*
low mean temperature	*Brassica oleracea* L. var. *italica* Plenck	++	*114*
increased fruit temperature	*Solanum lycopersicum* L.	−	*181*
high daily sum of light	*Brassica oleracea* L. var. *italica* Plenck	+	*114*
high light intensity	*Fortunella crassifolia* Swingle	+	*182*
high light intensity	*Spinacia oleracea* L. cv. Carambola	+++	*124*
high light exposure	*Malus domestica* Borkh.	++	*123*
high light exposure	*Solanum lycopersicum* L.	+ ?	*125*
high light exposure	several fruit species	+ ?	*183*
high light exposure	*Citrus aurantium* L. (leaves)	+++ (DW basis)	*184*
high light exposure	*Malus domestica* Borkh. cv. Gala (peel)	+++	*185*
high UV-B radiation	*Spinacia oleracea* Mill.	+++	*139*
high UV-B radiation	*Spinacia oleracea* Mill.	+++	*141*
long vs short days	*Fragaria* × *ananassa* Duch.	unclear	*186*
elevated CO_2	*Fragaria* × *ananassa* Duch.	+ (AA) − − (DHA)	*132*
elevated CO_2	*Citrus aurantium* L.	+	*187*
elevated CO_2	*Citrus aurantium* L. (leaves)	0	*184*
high leaf to fruit ratio	*Fortunella crassifolia* Swingle	+	*182*
drought	*Solanum lycopersicum* L.	+	*144*
drought	*Solanum lycopersicum* L.	depending on cv.	*188*
drought	*Spinacia oleracea* L.	+ to ++ depending on cv.	*155*
drought/high salinity	*Solanum lycopersicum* L.	− ?	*150*
high salinity	*Solanum lycopersicum* L.	+	*149*
high salinity	*Solanum lycopersicum* L.	0	*158*
high salinity	*Solanum lycopersicum* L.	variable	*188*
high salinity	*Solanum lycopersicum* L.	+ depending on cv.	*145*
high salinity	*Capsicum annuum* L.	−	*147*
high salinity	*Fragaria* × *ananassa* Duch.	−/− −	*148*
high salinity (fall−winter season)	*Solanum lycopersicum* L.	++ (AA) ++ (DHA)	*189*
high salinity (spring−summer season)	*Solanum lycopersicum* L.	+± (AA depending on cv. −(DHA)	*189*
high salinity	*Pisum sativum* cv. Puget	+++	*190*
high EC	*Cucurbita pepo* L.	+	*191*
low nitrogen	several crops	+	*159*
low nitrogen	citrus, potato, tomato	+	*160*
low nitrogen	*Capsicum annuum* L.	0	*163*
low nitrogen	*Solanum lycopersicum* L.	+	*144*
low nitrogen	*Solanum lycopersicum* L.	+ strong seasonal impact	*165*
boron stress	*Solanum lycopersicum* L.	+++	*192*
boron stress	*Citrus reshni* Hort ex Tan	+++	*193*

[a] EC, electrical conductivity; +, up to +30%; ++, +30 to +100%; +++, >+100%; −, up to −30%; − −, −30 to −100%; − − −, <−100%; 0, no significant effect.

concentrations of vitamins and secondary metabolites in a large array of FAVs. The global picture we can draw is the following (**Tables 1**−**5**).

Low temperatures during the growth period are generally very favorable to the accumulation of ascorbic acid, phenolic compounds, carotenoids, and glucosinolates. However, all compounds are not affected to the same extent. Ascorbic acid seems to be the less sensitive, with a maximal potential gain of +60% found in broccoli when the mean daily temperature is decreased from 15/20 to 7/12 °C, whereas lutein has the potential to be increased up to 150% (*114*) and anthocyanins up to +240%, as observed in certain cultivars of strawberry when temperatures were decreased from 30 to 18 °C (*115*). The positive effect of low temperatures on ascorbic acid and glucoraphanin seems to be enhanced in broccoli in the presence of high light (*114*), which suggests that photooxidative stress is behind the effect of low temperatures (see below). Interestingly, a positive effect of low temperatures was also observed after harvest for carotenoids in tomatoes (*116*, *117*) and for anthocyanins in apples, the former submitted to UV-B radiation (*118*).

The effect of high temperatures after harvest has been investigated in several species of FAVs. The global picture is the following: with the exception of the skin of mango fruits (*119*), high temperatures have an effect ranging from insignificant to negative on the concentration in total ascorbic acid of tomatoes (*120*−*122*). A similar effect, ranging from insignificant to negative, was observed on the concentrations of carotenoids and α-tocopherol in tomatoes (*121*, *122*). On the contrary, positive effects of high temperatures have been reported on the concentration in total phenolics of tomatoes (*120*) and the skin of mango and banana fruits (*119*).

Generally, good exposure or high light intensity is a positive factor for the accumulation of ascorbic acid as observed in apple (*123*), broccoli (*114*), spinach (*124*), and tomatoes (*125*). A similar positive effect was observed on phenolic compounds in apple (*126*), lettuce (*127*), and tomatoes (*128*), for instance, and also on carotenoids [ca. +70% in well-exposed mangoes (*129*)] and glucosinolates [+200% at low temperature in broccoli (*114*)]. Differences between the different forms of phenolic compounds were observed by Ju et al. (*130*): flavonoids were not affected by high light

Table 2. Effect of Environmental Factors, Light, Temperature, Carbon Supply, Drought, Salinity, and Nitrogen Fertilization, on the Concentration, Expressed on a Fresh Matter Basis, If Not Indicated Otherwise, in Phenolic Compounds[a]

environmental factor	crop	compound	effect	ref
heat shock or short period of cold	*Lactuca sativa* L.	total phenolics	+++	*127*
cooling irrigation	*Malus domestica* Borkh.	anthocyanins	+++	*194*
low mean day temperatures	*Fragaria* × *ananassa* Duch.	anthocyanins and *p*-coumaroylglucose	+++	*115*
high light intensity	*Lactuca sativa* L.	total phenolics	+++	*127*
high light intensity	*Solanum lycopersicum* L.	soluble phenolics	+++	*128*
high light intensity	*Malus domestica* Borkh.	anthocyanins and flavonoids	+++	*126*
high light intensity	*Solanum lycopersicum* L.	quercetin	++	*195*
high light intensity	*Fortunella crassifolia* Swingle	hesperidin, naringin	+++/++	*182*
high light exposure	*Fragaria* × *ananassa* Duch.	total phenolics	0	*131*
high light exposure	*Malus domestica* Borkh.	anthocyanins	++	*130*
high light exposure	*Punica granatum* L.	anthocyanins	+ (peel) − (juice)	*196*
high light exposure	*Malus domestica* Borkh.	flavonoids	0	*130*
high light exposure	*Malus domestica* Borkh. cv. Gala (peel)	anthocyanins	+++	*185*
supplemental light (visible + UV-B)	*Malus domestica* Borkh.	anthocyanins, chlorogenic acid, quercetin and phloretin glycosides	+	*142*
red light	*Solanum lycopersicum* L.	anthocyanins	+	*197*
red light	*Vaccinium macrocarpon* Ait.	anthocyanins	++	*198*
elevated CO_2	*Fragaria* × *ananassa* Duch.	anthocyanins, *p*-coumaroylglucose, quercetin and kaempferol	+/+++	*132*
high leaf to fruit ratio	*Fortunella crassifolia* Swingle	hesperidin, naringin	+	*182*
drought	*Cynara scolymus* L.	total phenolics	0 to ++ according to harvest date	*156*
high salinity	*Capsicum annuum* L.	total phenolics	0	*147*
high salinity	*Fragaria* × *ananassa* Duch.	total phenolics	+	*148*
high salinity	*Lactuca sativa* L.	total phenolics	−	*146*
high salinity	*Solanum lycopersicum* L.	total phenolics	+	*149*
high EC	*Fragaria* × *ananassa* Duch.	ellagic acid, quercetin, kaempferol	+/++	*131*
high nitrogen	*Malus domestica* Borkh.	total phenolics	0	*199*
high nitrogen	*Capsicum annuum* L.	total phenolics	0	*163*
high nitrogen	*Prunus armeniaca* L.	total phenolics	+/++	*162*
high nitrogen	*Malus domestica* Borkh.	anthocyanins	−	*161*
high nitrogen	*Solanum lycopersicum L*	quercetin, kaempferol	0	*164*
high nitrogen	*Solanum lycopersicum* L.	caffeic acid derivates	− strong seasonal impact	*165*
high nitrogen	*Brassica oleracea* L. var. *italica*	quercetin, kaempferol	−− (DW basis)	*200*
selenium treatment	*Brassica oleracea* L.	caffeic acid, sinapic acid, ferulic acid	+++/++ (DW basis)	*201*
boron stress	*Solanum lycopersicum* L.	total phenolics	−−	*192*

[a] EC, electrical conductivity; +, up to +30%; ++, +30 to +100%; +++, >+100%; −, up to −30%; −−, −30 to −100%; −−−, <−100%; 0, no significant effect.

exposure, whereas anthocyanins responded very positively. The highest positive response to light intensity (ca. +200%) was found for total phenolics in lettuce submitted to $Q = 800$ μmol of photons m^{-2} s^{-1} for 1 day (*127*). At the other end of the response scale of phenolic compounds to light, one finds strawberry, a typical shade plant that does not respond positively to increasing light intensity (*131*). At any rate, the effect of high light exposure or intensity on the concentration of ascorbate, phenolic compounds, carotenoids, and glucosinolates of FAVs can generally be rated as very positive. This positive effect may be attributed either to enhanced photooxidative stress, as the synergic effect of combined high light intensity and low temperature would suggest (see above), or to increased photosynthesis, considering the positive effect of increased carbon supply on the concentration in phenolic compounds of strawberry (*132*), in total carotenoids of mango (*129*), and in glucoraphanin of broccoli (*133*).

After harvest, the effect of high intensity on tomatoes appears very positive for phenolic compounds (*117*, *134*). The highest effect (+123%) was found for tomatoes exposed for 5 h to high solar radiation (*134*). The picture is more contrasted for carotenoids with reports of effects either positive (*117*) or negative (*134*). Similarly, the effect of high light intensity ranges from negative (*134*, *135*) to positive (*117*) for ascorbic acid. At any rate, the effect of high light intensity seems to be highly mediated by temperature (*117*).

Strong positive effects of specific wavelength were observed before and after harvest (**Tables 1** and **2**). Lycopene content increased in tomatoes with blue light (*136*, *137*), but the effect of red light was even more marked (+133%) for carotenoids (*138*). UV irradiation either before or after harvest may have a very dramatic effect: +170% ascorbic acid in spinach leaves before harvest (*139*), +400% anthocyanins in apples after harvest (*118*), +400% anthocyanins in figs after harvest (*140*), and +700% α-tocopherol in leaves of spinach and lettuce before harvest (*141*). Carotenoids in tomatoes either before (*142*) or after (*143*) harvest seem, however, to be less responsive. Globally, it may be said that postharvest irradiation is very promising as far as ascorbic acid, phenolic compounds, and α-tocopherol are concerned, especially using UV radiation, but the lack of references clearly begs for more studies.

The picture becomes more complex when one considers the effect of drought and high salinity (**Table 1**). For ascorbic acid there is a global positive trend (*144*), probably strongly dependent on genetic × environmental interactions, as observed for tomato (*145*), whereas there are conflicting responses, that is, ranging from negative (*146*) to not significant (*147*) to positive (*131*, *147*−*149*), with regard to phenolic compounds. When observable, the positive effect to be expected is <+40%. Similarly, responses ranging from negative (*150*, *151*) to not significant (*152*) to positive (*146*, *147*, *149*, *153*−*155*) were observed for carotenoids.

Table 3. Effect of Environmental Factors, Light, Temperature, Carbon Supply, Drought, Salinity, and Nitrogen Fertilization, on the Concentration, Expressed on a Fresh Matter Basis, If Not Indicated Otherwise, in Carotenoids[a]

environmental factor	crop	compound	effect	ref
low mean daily temperature	*Solanum lycopersicum* L.	total carotenoids	+++	*202*
low mean daily temperature	*Solanum lycopersicum* L.	phytoene, phytofluene, β-carotene and lycopene	+/+++ with the exception of carotene (− −)	*203*
increased fruit temperature	*Solanum lycopersicum* L.	total carotenoids	−	*181*
high light exposure	*Malus domestica* Borkh.	total carotenoids	0	*123*
high light exposure	*Citrus aurantium* L. (leaves)	total carotenoids	++ (DW basis)	*184*
high light exposure	*Malus domestica* Borkh. cv. Gala (peel)	total carotenoids	+	*185*
high light exposure	*Citrus clementina* Tanaka	total carotenoids	+	*204*
light spectrum (glass or plastic vs open field conditions	*Solanum lycopersicum* L.	lycopene	−/− −	*205*
light spectrum	*Solanum lycopersicum* L.	lycopene and β-carotene	+ with blue light	*136*
high UV-B radiation	*Malus domestica* Borkh.	β-carotene	+	*142*
elevated CO_2	*Solanum lycopersicum* L.	lycopene and β-carotene	0	*152*
elevated CO_2	*Citrus aurantium* L. (leaves)	total carotenoids	− −	*184*
high leaf to fruit ratio	*Mangifera indica* L.	total carotenoids	++	*129*
high leaf to fruit ratio	*Citrus clementina* Tanaka	total carotenoids	++	*204*
high leaf to fruit ratio	*Citrus clementina* Tanaka	total carotenoids	− − − (DW basis)	*204*
high leaf to fruit ratio	*Citrus unshiu* [Mak.] Marc.	total carotenoids	++	*168*
high leaf to fruit ratio	*Fortunella crassifolia* Swingle	β-cryptoxanthine	+++	*182*
drought	*Solanum lycopersicum* L.	total carotenoids	+ according to cv.	*206*
drought	*Solanum lycopersicum* L.	lycopene, β-carotene, and xanthophylls	0	*188*
drought	*Solanum lycopersicum* L.	lycopene and β-carotene	−	*151*
drought	*Spinacia oleracea* L.	β-carotene, lutein, neoxanthin, and violaxanthin	+	*155*
drought/high salinity	*Solanum lycopersicum* L.	total carotenoids	−	*150*
high salinity	*Lactuca sativa* L.	total carotenoids	++/+++	*146*
high salinity	*Capsicum annuum* L.	lycopene	+	*147*
high salinity	*Solanum lycopersicum* L.	lycopene and β-carotene	++	*153*
high salinity	*Solanum lycopersicum* L.	lycopene and β-carotene	+/++	*149*
high EC	*Solanum lycopersicum* L.	lycopene and β-carotene	0	*152*
high EC	*Solanum lycopersicum* L.	carotene	++	*154*
high nitrogen	*Brassica oleracea* L.	lutein and β-carotene	0 (++ on a DW basis)	*166*
high nitrogen	*Capsicum annuum* L.	lycopene and β-carotene	+/++	*163*
high nitrogen	*Solanum lycopersicum* L.	lycopene	+/++	*167*
high nitrogen	citrus, potato, tomato	carotenes	+	reviewed in *160*
high nitrogen	*Citrus unshiu* [Mak.] Marc.	color index	−	*168*
boron stress	*Solanum lycopersicum* L.	lycopene	+++	*192*

[a] EC, electrical conductivity; +, up to +30%; ++, +30 to +100%; +++, >+100%; −, up to −30%; − −, −30 to −100%; − − −, <−100%; 0, no significant effect.

Potential positive responses may be >150%. Results may depend on the stage of application of drought as suggested by observations made on phenolic compounds in artichoke (*156*). It may be speculated that the contradictory observations are due to the fact that drought and high salinity, because they induce stomatal conductance and photosynthesis to decrease, are responsible for depleted carbon supply (arguably a negative factor regarding synthesis of secondary metabolites; see above) while they exacerbate photooxidative stress, thus providing a positive stimulus for their synthesis. Moreover, the effect of high salinity is not totally assimilable to water stress. This may explain why drought has a negative effect on the concentration of glucoraphanin in *Lepidium campestre* L., whereas high salinity on the contrary may increase its concentration up to 67% (*157*). There are not many studies about the effect of drought or high salinity on the accumulation of α-tocopherol in FAVs. Recent observations suggest that the positive effect of high salinity depends on cultivar, as observed in strawberry (*148*), and on the stage of application of high salinity as suggested by observations made on tomato (*158*).

The effect of nitrogen depletion can generally be considered as positive with regard to the concentration in ascorbic acid of many FAVs (*144*, *159*, *160*) and in phenolic compounds of such fruits as apple (*161*) and peach (*162*). An increase in total phenolics of about 60% was observed in peaches, for instance, as the consequence of a reduction of nitrogen fertilization from 150 to 80 kg of N ha^{-1} (*162*). However, there are also less positive reports: it was reported, for instance, that nitrogen fertilization in a 4−20 mol of NO_3^- m^{-3} range does not affect the concentration in ascorbic acid and phenolic compounds of pepper (*163*). Similarly, nitrogen fertilization in a 79−405 μg of N g^{-1} range does not affect significantly the concentrations in quercetin and kaempferol of tomatoes (*164*). Even a negative effect of nitrogen depletion on accumulation of phenolic compounds in tomatoes has been reported recently (*165*). This negative effect was associated with a slightly positive effect on the concentration in ascorbic acid. The picture is somewhat different for carotenoids, with reports ranging from negative effects of nitrogen depletion on pepper (*163*), citrus, potato, and tomato (*160*) to the absence of effect on kale (*166*) to positive effects on tomato (*167*) and citrus (*168*). The highest positive effect of nitrogen depletion was observed in kale, with an increase of about 100% in β-carotene expressed on a dry weight basis. Besides the usual considerations about the interactions between environmental and genetic factors (*166*), it may be put forward that the effect of the timing of application of nitrogen depletion is crucial. When applied too early, nitrogen depletion arguably affects negatively photosynthetic capacity and thus carbon supply, a

Table 4. Effect of Environmental Factors, UV-B and Salinity, on the Concentration, Expressed on a Fresh Matter Basis, in Tocopherols[a]

environmental factor	crop	compound	effect	ref
high UV-B radiation	*Lactuca sativa* L. and *Spinacia oleracea* L.	α-tocopherol	+++	*141*
high salinity	*Solanum lycopersicum* L.	α-tocopherol and β-tocopherol	+/+++	*158*
high salinity	*Fragaria* × *ananassa* Duch.	α-tocopherol	0/++	*148*

[a] +, up to +30%; ++, +30 to +100%; +++, >+100%; −, up to −30%; − −, −30 to −100%; − − −, <−100%; 0, no significant effect.

Table 5. Effect of Environmental Factors, Light, Temperature, Carbon Supply, Drought, Salinity, and Nitrogen Fertilization, on the Concentration, Expressed on a Fresh Matter Basis, If Not Indicated Otherwise, in Glucosinolates[a]

environmental factor	crop	compound	effect	references
high mean daily temperature	*Brassica oleracea* L. var. *italica* Plenck	total glucosinolates	+ (low light) +++ (high light)	*114*
high mean daily temperature	*Brassica oleracea* L. var. *italica* Plenck	alkenyl glucosinolates	0	*114*
high vs low mean daily temperature	*Brassica oleracea* L. var. *italica* Plenck	glucoraphanin	+ (low light) +++ (high light)	*114*
high sum of light	*Brassica oleracea* L. var. *italica* Plenck	total glucosinolates	+++ (low temperature) − − (high temperature)	*114*
high sum of light	*Brassica oleracea* L. var. *italica* Plenck	alkenyl glucosinolates	0	*114*
high sum of light	*Brassica oleracea* L. var. *italica* Plenck	glucoraphanin	+++ (low temperature) − − (high temperature)	*114*
elevated CO_2	*Brassica oleracea* L. var. *italica* Plenck	total glucosinolates	+	*133*
elevated CO_2	*Brassica oleracea* L. var. *italica* Plenck	glucoraphanin	++	*133*
drought	*Brassica oleracea* L. var. *italica* Plenck	total glucosinolates	+++	*207*
drought	*Lepidium campestre* L.	glucoraphanin	−	*157*
high salinity	*Lepidium campestre* L.	glucoraphanin	++	*157*
low nitrogen	*Brassica rapa* ssp. *Rapifera* L.	total glucosinolates	0	*169*
low nitrogen	*Brassica oleracea* L. var. *italica* Plenck	total glucosinolates	+	*170*
high nitrogen	*Brassica oleracea* L. var. *italica*	glucobrassin, glucoraphin	+ ± − (DW basis)	*200*
selenium treatment	*Brassica oleracea* L.	total glucosinolates	− (DW basis)	*201*

[a] EC, electrical conductivity; +, up to +30%; ++, +30 to +100%; +++, >+100%; −, up to −30%; − −, −30 to −100%; − − −, <−100%; 0, no significant effect.

negative factor when it comes to synthesis of secondary metabolites. We found no references about the effect of nitrogen fertilization on vitamin E synthesis in FAVs. Whereas nitrogen fertilization (in contrast to sulfur) does not affect total glucosinolate concentration of turnip, it increases the proportion of N-containing tryptophan-derived indole glucosinolates (*169*). In contrast, N depletion results in an increase of 17% in the total glucosinolate concentration in broccoli (*170*).

We dealt mainly with such conventional environmental factors as light and temperature here. After harvest, the composition of the atmosphere of FAVs may also be modified. It is not possible to draw a clear picture of what might be achieved by either increasing or decreasing the concentration in O_2, for instance, considering the general lack of references (**Table 6**). However, as suggested by the observations of increased concentration in α-tocopherol made on kiwi fruits stored in NO conditions, modified atmospheres after harvest may be exploited to increase the concentrations in phytochemicals of FAVs (*171*).

Increases of 10−25-fold in carotenoids (*73*), 20-fold in glucosinolates (*93*), and 36-fold in kaempferol-rutoside (*106*) have been observed as the consequence of natural genetic variability, conventional breeding, and metabolic engineering. When compared to genetic factors, the potential of environmental factors clearly appears to be less. However, because it may not be useful, and even hazardous, to increase exceedingly the concentration in phytochemicals of food, it may be argued that the prospects provided by agronomic approaches, a ca. 2-fold increase, represent arguably the perfect balance between effectiveness and safety.

Of course, some of the questions raised by the prospects of genetic approaches apply to agronomic approaches as well. It is quite obvious that increasing the concentration in phytochemicals of FAVs must not come at the price of an exaggeratedly lowered yield. There are not many studies assessing the impact of the tested growing techniques on yield and quality criteria other than the concentration in vitamins and secondary metabolites, but there are some. Not too surprisingly, low nitrogen (*162*), as well as drought and high salinity, seems to reduce yield (*150*, *151*, *155*, *156*), whereas high carbon supply has the opposite effect. Interestingly, brief stress treatments seem to be especially promising because they apparently do not negatively affect yield (*127*). Similarly, the potential of postharvest treatments appears to be very promising because the latter do not affect yield at all (**Table 5**). At any rate, the negative side effects of agronomic techniques aiming at increasing the concentration in phytochemicals of FAVs do not seem to exceed the ones observed with genetic approaches.

UPCOMING CHALLENGES FOR AGRONOMIC APPROACHES

At this stage, we can state with confidence that agronomic approaches are credible. The most serious cause for concern lies in the variability of the responses observed because poor control of the processes involved may impair our capacity to design realistic and reliable cropping techniques, making it possible to produce FAVs with increased and controlled concentrations in phytochemicals. The variability in responses hints at the existence of uncontrolled interactions between factors, between processes, and between organs.

Let us consider factors first. It is quite clear that increasing light intensity will increase temperature as well, whereas drought or high salinity will have the same effect through their negative effect on stomatal conductance. The existence of responses varying as a function of genetic factors suggests that interactions between genetic and environmental factors also play an important role.

The issue of interactions between processes can be illustrated by the observations made on *Citrus* fruits in ref *168*. Iglesias et al. (*168*) observed that maturity and biosynthesis of carotenoids

Table 6. Effect of Postharvest Factors, Light and Temperature, on the Concentrations of Ascorbic Acid, Phenolic Compounds, Carotenoids, and Glucosinolates in Several FAVs[a]

compound	environmental factor	crop	effect	references
total ascorbic acid	high light	*Solanum lycopersicum* L.	−	*135*
total ascorbic acid	high light for a brief period	*Solanum lycopersicum* L.	−	*134*
total ascorbic acid	high light	*Solanum lycopersicum* L.	+	recalcd from *117*
total ascorbic acid	UV-C	*Solanum lycopersicum* L.	++	*143*
total ascorbic acid	high temperature during a brief period	*Solanum lycopersicum* L.	0	*122*
total ascorbic acid	high temperature during a brief period	*Solanum lycopersicum* L.	− − −	*121*
total ascorbic acid	high temperature	*Solanum lycopersicum* L.	0	*122*
total ascorbic acid	high temperature	*Mangifera indica* L. (skin)	++	*119*
total ascorbic acid	high temperature	*Solanum lycopersicum* L.	− − −	*120*
total ascorbic acid	nitric oxide 1 μmol L^{-1}	*Actinidia chinensis* Planch. cv. Xuxiang	+	*171*
dehydroascorbate	high nitric oxide	*Prunus persica* L.	−	*208*
total ascorbic acid	2% O_2, 5% CO_2	*Pyrus communis*	− −	*209*
total ascorbic acid	irradiation stress	*Mangifera indica* L.	−	*210*
total ascorbic acid	dehydratation process	*Capsicum annuum* L.	− − − (DW basis)	*211*
anthocyanins	low mean daily temperature	*Malus domestica* Borkh.	+++	*118*
total phenolics	high temperature	*Mangifera indica* L. (skin)	++	*119*
total phenolics	high temperature	*Musa* spp. (skin)	++	*119*
total phenolics	high temperature	*Solanum lycopersicum* L.	++	*120*
caffeic acid derivates	high light	*Solanum lycopersicum* L.	+ (DW basis)	*117*
flavonoids	high light	*Solanum lycopersicum* L.	+++	*134*
rutin	high light	*Solanum lycopersicum* L.	++	*117*
anthocyanins	pulsed visible and UV light	*Ficus carica* L.	+++	*140*
anthocyanins	UV-B	*Malus domestica* Borkh.	+++	*118*
quercetin	UV-C	*Allium cepa* L.	++	*140*
total phenolics	UV-C	*Solanum lycopersicum* L.	+ (DW basis)	*143*
total phenolics, anthocyanins	100% O_2	*Myrica rubra* Sieb. & Zuce	++/+	*212*
total carotenoids mainly lycopene	relatively low mean daily temperature	*Solanum lycopersicum* L.	+ (depending on light conditions/DW basis)	*117*
lycopene and β-carotene	low mean daily temperature	*Solanum lycopersicum* L.	++	*116*
lycopene	high temperature	*Solanum lycopersicum* L.	++	*120*
lycopene	high temperature	*Solanum lycopersicum* L.	++	*213*
total carotenoids mainly lycopene	high light	*Solanum lycopersicum* L.	++	*117*
lycopene	UV-C	*Solanum lycopersicum* L.	0 (DW basis)	*143*
total carotenoids	high light for a brief period	*Solanum lycopersicum* L.	−	*134*
lycopene	red light	*Solanum lycopersicum* L.	+++	*138*
lycopene and β-carotene	high temperature during a brief period	*Solanum lycopersicum* L.	−/0	*122*
lycopene	high temperature during a brief period	*Solanum lycopersicum L*	− − −	*121*
lycopene and β-carotene	high temperature	*Solanum lycopersicum* L.	+++	*122*
total carotenoids	high nitric oxide	*Prunus persica* L.	0	*208*
total carotenoids	irradiation stress	*Mangifera indica* L.	− − −	*210*
β-carotene, zeaxanthin, antheraxanthin/violaxanthin, β-cryptoxanthin	dehydratation process	*Capsicum annuumm* L.	− − −/− − (DW basis)	*211*
α-tocopherol	high temperature during a brief period	*Solanum lycopersicum* L.	−	*122*
α-tocopherol	high temperature	*Solanum lycopersicum* L.	+	*122*
α-tocopherol	nitric oxide 1 μmol L^{-1}	*Actinidia chinensis* Planch. cv. Xuxiang	++	*171*

[a] +, up to +30%; ++, +30 to +100%; +++, >+100%; −. up to −30%; − −, −30 to −100%; − − −, <−100%; 0, no significant effect.

both depend strongly on sucrose supply. It is generally admitted that the carbon status influences the biosynthesis of vitamins and secondary metabolites, although the way it works is not so clear. It has been said that precursor availability is essential for biogenesis of secondary metabolites (*172*). Within this view, ecologists trying to predict how plants will allocate resources over a broad range between differentiation-related processes (including production of secondary metabolites) and growth-related processes have proposed theories such as the growth differentiation−balance hypothesis (*173*). Besides deterministic theories from ecologists, there are more mechanistic ones based on sugar signaling (*174*). The currently emerging view of physiologists is one of a modulating rather than a conditioning role of carbohydrates concerning biogenesis of secondary metabolites. It may be inferred from this literature that the positive effect of sucrose feeding on carotenoid concentration of *Citrus* fruits reported in ref *168* originates from a direct effect on the synthesis pathway of carotenoids. At the same time, it must remembered that biosynthesis of many secondary metabolites and, to a lesser extent, ascorbate is strongly regulated during ontogenesis of organs, especially in fruits. This is the case of

carotenoids, which always accumulate during ontogenesis. High carbon supply accelerates maturity in fruits (*129*), so it is eventually unclear whether high sucrose has a positive effect on synthesis of carotenoids in *Citrus* fruits directly (the carbon supply/sucrose control theory) or indirectly through its stimulating effect on maturity, or both.

The example of tomato and orange will help us to illustrate the issue of interactions between organs. It is now well established that most stresses result in oxidative stress (*175*). All factors that increase the imbalance between incoming energy and its utilization by photochemistry, such as drought, high electrical conductivity and salinity, high light, and, even better, the combination of high light and low temperature, will increase the risk of producing ROS. ROS and hormones have been demonstrated to systematically interact in signaling pathways controlling adaptative responses (*176*). Moreover, direct implication of either ROS or variations in redox status has been evidenced in the carotenoid biosynthesis pathway (*177*). Similarly, there is some evidence that synthesis of phenolic compounds is redox controlled (*178*). The role played by oxidative stress per se or the associated variations in redox status in the synthesis of phytochemicals raises a very interesting question. If we consider that the redox status or the concentration in ROS plays a key role in controlling biosynthesis of phytochemicals in the pulp of fruits, as suggested by several studies, then where do the ROS come from? They cannot originate from photosynthesis because the pulp has lost its photosynthetic machinery during maturation, when chloroplasts were converted into chromoplasts. Do ROS originate from NADPH oxidase, the respiratory electron transport chain of mitochondria of the pulp, or do they originate from the photosynthetic electron transport chain of the chloroplasts of the peel of fruits or of leaves close to them? Observations made on tomato (*179*) as well as our own observations on orange (unpublished data) clearly demonstrate that stressed leaves induce stress responses in nearby unstressed fruits, in other words, that signals are transmitted from the leaves to the fruits.

CONCLUSION AND PERSPECTIVES

Agronomic approaches offer very good perspectives to increase the concentrations in secondary metabolites of FAVs and, to a lesser extent ascorbic acid, and this probably without risking attaining undesirable levels. It is reasonable to expect agronomic approaches to have a more global reach than genetic approaches, at least in the short term. However, the response variability hints that we lack true control over metabolic and regulatory pathways. To improve the current situation, in addition to fundamental studies, it seems highly recommendable to develop quantified and integrated views of the way environmental factors affect the biosynthesis of phytochemicals. More specifically, we consider it desirable (i) to quantify more precisely the effects of environmental factors, (ii) to include response curves in mathematical models of production capable of dealing with interactions between environmental factors (light and temperature for instance), between processes (carbon metabolism, ontogeny of organs, and response to oxidative stress, as they are known to be intertwined), and between organs (because there is some evidence that photooxidative stress in leaves affects antioxidant metabolism in fruits), and (iii) to build models of genetic × ecophysiological interactions (i.e., models in which parameters of ecophysiological models are included in genetic models). It must be emphasized that such studies will not only help the cause of agronomic approaches but also be useful to genetic approaches. Moreover, what is at stake here in the long term is the capacity to design innovative cropping techniques or even combinations of varieties/terroirs/cropping techniques bringing to FAVs a clear added value in terms of nutritional benefits. In the meantime, it is desirable to explore more systematically the genetic variability of the concentrations in phytochemicals of a large range of FAVs, whereas it seems tempting to test simple and practical ideas, such as modifying the environment of harvested organs or imposing to plants stressing conditions limited in time and intensity at the end of the cropping cycle, maybe just by withholding irrigation for a while, at a time when no harm to yield is likely.

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