Carotenoids in Planta

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Carotenoids are important natural pigments found in all plants and some bacteria, algae and fungiand constitute one of the largest families of natural products, with more than 750 distinct compounds classified to date. Carotenoids have also been shown to have a significant impact on a number of human diseases, improving the survival rates of some cancers and slowing the progression of neurological illnesses.

carotenoids flavour nutrition

1. Carotenoid Biosynthesis in Planta

The carotenoid biosynthetic pathway has been intensely studied since the early 1960s [1][2][3]. While the carotenoid biosynthetic genes are located in the nucleus, their precursor protein products are imported into the chloroplast where the mature proteins synthesis carotenoids [4]. In chloroplasts, carotenoids accumulate in the photosynthetic membranes in association with the photosynthetic reaction centres and light-harvesting complexes [5][6][7][8]. In fruits and flowers, petals chloroplasts differentiate into chromoplasts and carotenoids accumulate in the membranes or in oil bodies such as plastoglobules [9][10] and fibrils [11], or in other structures within the stroma.

Phytoene (**Figure 1**A), the first true carotenoid, is formed by the condensation of two molecules of geranylgeranyl diphosphate by the enzyme phytoene synthase (PSY; EC.2.5.1.32). Phytoene undergoes four consecutive desaturation steps catalysed by two enzymes, phytoene desaturase (PDS; EC.1.3.99.28), resulting in the formation of ζ-carotene (**Figure 1**B) via the intermediate phytofluene [12][13] and ζ-carotene desaturase (ZDS; EC.1.14.99.30) to form lycopene (**Figure 1**C), the red pigment responsible for the colour of tomatoes, via the intermediate neurosporene [14][15]. To maintain carotenoids in their trans form, ζ-carotene isomerase (Z-ISO; EC.5.2.1.12) [16] converts 9,15,9′-cis-z-carotene to 9,9′-cis-ζ--carotene via the isomerization of the 15-cis-double bond, and carotene isomerase (CRTISO; EC.5.2.1.13) [17][18][19] transforms 9,15,9′-tricis-ζ--carotene into 9,9′-dicis-ζ-carotene, 7,9,9′-tricis-neurosporene into 9-cis-neurosporene and 7,9-dicis-lycopene into all-trans-lycopene. These desaturation steps require the presence of the plastid terminal oxidase (PTOX; EC.1.10.3.11) as a co-factor [20][21][22][23][24].

Lycopene undergoes two cyclization reactions forming α- and β-carotene. Lycopene β-cyclase (LβCY; EC.5.1.1.19) introduces two β-rings to the ends of the Lycopene carbon chain forming β-carotene (β,β-carotene; **Figure 1**D) via the intermediate γ-carotene (β,ψ-carotene), which contains a single β-ring and one uncyclized end, known as psi (ψ) [25]. LβCY and lycopene ε-cyclase (LεCY; EC.5.1.1.18) form α-carotene (β,ε-carotene) (**Figure 1**E) by introducing one β-ring and one ε-ring respectively to lycopene via the intermediate δ-carotene (ε,ψ-carotene) with one ε-ring and one uncyclized ψ end [26].

In *Lactuca sativa* (lettuce), LεCY introduces two ε-rings, resulting in the formation of ε-carotene (ε,ε-carotene; **Figure 1**F) [27]. LεCY genes have been identified in plants, green algae and cyanobacteria (Prochlorococcus marinus), and likely arose following gene duplication of the β-cyclases and later functional divergence [28][29][30][31].

Oxygenated carotenoids are formed by the hydroxylation of the β- and ε-rings of the carotene carotenoids. β-carotene is converted to zeaxanthin (3,3′-dihydroxy-β,β-carotene) via cryptoxanthin (**Figure 1**G) by the action of β-carotene hydroxylase (βCHY; EC.1.14.15.24) [32][33][34][35][36], and α-carotene (β,ε-carotene) is hydroxylated by βCHY to form zeinoxanthin and then the ε-ring is hydroxylated by ε-carotene hydroxylase (εCHY; EC 1.14.99.45) to form lutein (dihydroxy-ε,ε-carotene) (**Figure 1**H) [37][38][39]. Lutein is essential for the assembly of the light-harvesting photosystems and plays a role in non-photochemical quenching [40][41][42][43][44][45].

Lutein has also been shown to enhance the stability of the antenna proteins [46], play a role in light harvesting by transferring energy to chlorophyll (Chl) [47] and to quench Chl triplet states in the light-harvesting complex, protecting it from photo-oxidative damage [48].

Zeaxanthin epoxidase (ZEP: EC.1.14.13.90) catalyses the epoxidation of the two hydroxylated β-rings of zeaxanthin in two steps to generate antheraxanthin (**Figure 1**J) and violaxanthin **(Figure 1**K; [49][50]. In high light, violaxanthin is converted back to zeaxanthin by the activity of violaxanthin de-epoxidase (VDE: EC.1.10.99.3). This inter-conversion of violaxanthin to zeaxanthin is called the xanthophyll cycle and is implicated in the adaptation of plastids to changing light conditions [51][52][53]. In a similar mechanism, ZEP and VDE catalyse the inter-conversion of Lutein to Lutein epoxide (**Figure 1**L) in a process first reported in green tomato fruit in 1975 [54].

The final carotenoid, neoxanthin (**Figure 1**M), is synthesized from violaxanthin by the enzyme neoxanthin synthase first cloned from tomato and potato (NYS: EC.5.3.99.9) [55][56]. In Capsicum annum, antheraxanthin and violaxanthin are modified by a unique enzyme, capsanthin/capsorubin synthase (CCS: EC.5.3.99.8), induced at the onset of ripening [57], resulting in the synthesis of capsanthin and capsorubin from antheraxanthin and violaxanthin, respectively (**Figure 1**N) [58][59]. CCS possesses 86.1% amino acid sequence similarity with the tomato βCHY, suggesting that the two genes evolved from a common ancestral form and that the CCS functional activity diverged at a later date [60][61].

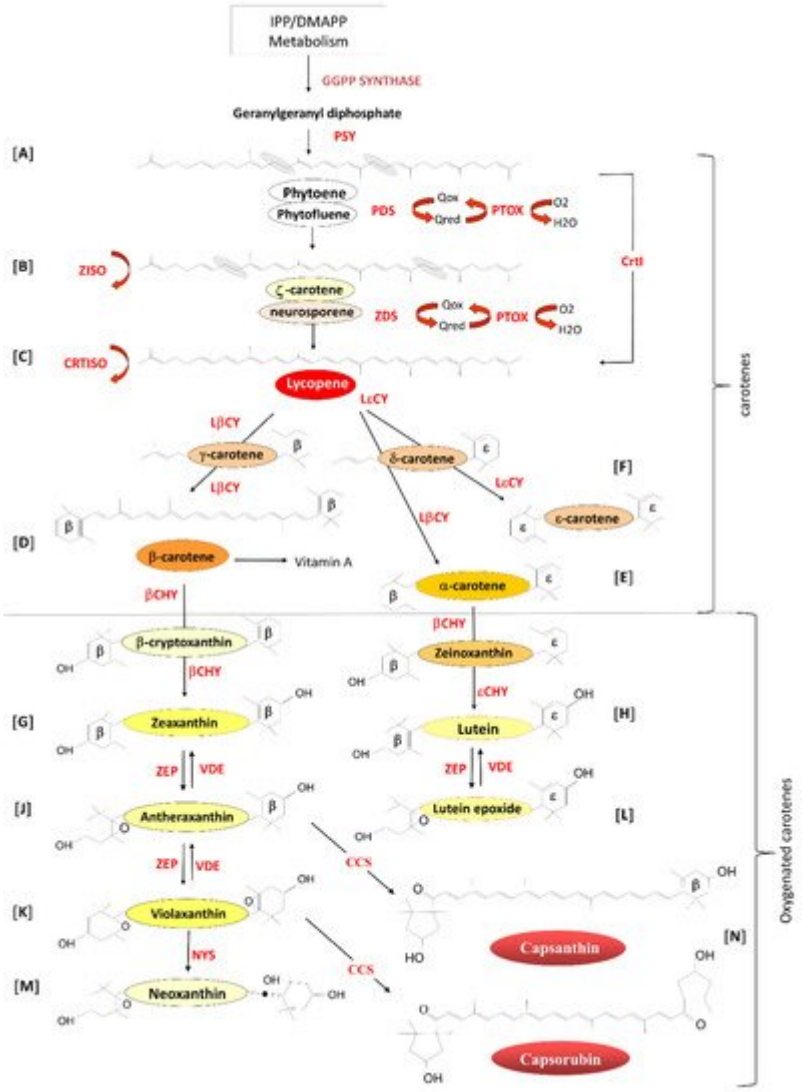

Figure 1. Overview of the biosynthesis of isoprenoids in plastids. PSY: Phytoene synthase. PDS: phytoene desaturase. ZDS: ζ-carotene desaturase. Z-ISO: ζ-carotene isomerase. PTOX: plastid terminal oxidase. CRTISO: carotene cis-trans isomerase. LβCY: lycopene β-cyclase. LεCY: lycopene ε-cyclase. βCHY: β-carotene hydroxylase. εCHY: ε-carotene hydroxylase. ZEP: zeaxanthin epoxidase. VDE: violaxanthin de-epoxidase. NYS: neoxanthin synthase. CCS: capsanthin/capsorubin synthase (adapted from Simkin et al. [62]. Letters A-N represent specific biosynthetic steps highlighted in the text.

2. Manipulating Carotenoid Content in Planta

Metabolic engineering has been used to generate a large number of crops with substantial increases in carotenoid content. Since carotenoid levels are determined by the rate of biosynthesis, the means of carotenoid sequestration and finally the rate of degradation, multiple avenues exist to increase carotenoid content in planta. The ‘push’ strategy uses methods to increase metabolic flux by over-expression of carotenoid biosynthesis enzymes. The ‘pull’ strategy increases carotenoid sink capacity and finally, the ‘block’ strategy seeks to reduce the rate of carotenoid turnover.

2.1. ‘Push’ Strategies for Increasing Carotenoid Content in Planta

Using genetic engineering to increase carotenoid content in fruit and staple crops has the potential to increase the availability of carotenoid substrates for the generation of a host of important volatile and non-volatile organic compounds and important nutritional components of foods. Genetic engineering of the carotenoid biosynthesis has been shown to create high carotenoid varieties of key staple crops such as flaxseed (*Linum usitatissimum*) [63][64], wheat (*Triticum aestivum*) [65], Sorghum [66][67], canola (*Brassica napus*) [68] and rice (*Oryza sativa*) [69][70][71], and root crops such as potato (*Solanum tuberosum*) [72][73][74] and cassava (*Manihot esculenta*) [73]. In addition, work to produce high carotenoid varieties of tomato (*Solanum lycopersicum*) has been well studied [10][75][76].

Key staple crops such as rice (*Oryza sativa*), wheat, cassava and potato, which constitute a significant part of the diets of poorer communities, contain little or no carotenoids or carotenoid-derived compounds (CDCs). Early efforts to generate β-carotene enriched-rice (*Oryza sativa*), termed “golden rice” [69][70][71], by over-expressing multiple enzymatic steps in the pathway (**Figure 1**) successfully resulted in rice variety accumulating up to 18.4 µg/g of carotenoids (up to 86% β-carotene) [70]. In this instance, these authors over-expressed PSY with the expression of the *Pantoea ananatis* CrtI (EC 1.3.99.31). CrtI carries out the activities of four plant enzymes, namely PDS, Z-ISO, ZDS and CRTISO (**Figure 1**).

2.2. ‘Pull’ Strategies for Manipulating Carotenoid Storage in Planta

In transgenic tomato, expression of the Arabidopsis Or was shown to promote chloroplast to chromoplast differentiation inducing carotenoid accumulation at early fruit developmental [77]. Expression of AtOR under the control of an endosperm-specific promoter increased carotenoid content in corn by promoting the formation of carotenoid-sequestering plastoglobuli [78]. However, these authors showed that these increases were seen when the carotenoid pool was limited, but it had no effect when carotenoid levels where abundant [78]. In Arabidopsis, Zhou et al. [79] demonstrated that the Or protein interacts directly with PSY (see **Figure 1**), post-transcriptionally regulating carotenoid biosynthesis. Chayut et al. [80] demonstrated in melon (*Cucumis melo*) that CmOr is required to stabilize flux through the carotenoid biosynthetic pathway, but the increase in carotenoids is due to the inhibition of downstream metabolic turnover of β-carotene [80]. Or expression has also been shown to increase carotenoid content in the seeds of rice [81] and maise [78]. In rice, these increases in carotenoids were observed in conjunction with the over-expression of two photosynthetic genes ZmPSY and PaCrtI. When ZmPSY and PaCrtI were expressed together, rice grain accumulated up to 5.5 µg/g DW, increasing to 2.5µg/g DW when these genes were expressed along with the *AtOr* gene [81]. This is the first demonstration that a multi-gene approach, targeting both carotenoid synthesis and sequestration, has the potential to dramatically increase carotenoid levels in grain.

Furthermore, the over-expression of the pepper fibrillin in transgenic tomato showed that fibrillin proteins play a crucial role in development of plastoglobules and fibrils in differentiating chromoplast [10]. In transgenic tomato, over-expression of Fibrillin was shown to delay thylakoid loss during chloroplast to chromoplasts differentiation, increase plastoglobuli number and thereby increase the concentrations of carotenoids including β-carotene (+64%) and lycopene (+118%) [10]. These carotenoids were further shown to increase the pool of substrates for volatile

formation, and fruit were shown to generate a 36% and 74% increase in β-carotene-derived volatiles β-ionone and β-cyclocitral, respectively. Furthermore, an increase in the lycopene-derived volatiles citral (+50%), 6-methyl-5-hepten-2-one (MHO; +122%) and the ζ-carotene-derived geranylacetone (+223%) were observed to be consistent with the increases in carotenoids in these fruit [10]. These results demonstrate that increasing carotenoid content in fruits, vegetables and other crops provides a substrate for the formation of important volatile and non-volatile organic compounds important to plant development, flavour and aroma.

2.3. 'Block' Strategies for Manipulating Carotenoid Storage in Planta

Carotenoid cleavage dioxygenases 4 knockout (ccd4-1) had an even higher impact on seed carotenoid levels. Total carotenoids in ccd4-1 increased by 270% and β-carotene alone increased by a remarkable 840% compared with the wild type [82]. The more significant carotenoid turnover in ccd4-1 mutants compared to ccd1-1 mutants may be linked to their subcellular location. CCD1 has been shown to be localized in the cytosol, where it may have access to carotenoids stored in the plastid envelope [83][84][85], whereas CCD4 has been shown to be localized to the chloroplast and plastoglobules [86] where carotenoids are stored, giving them easier access to these substrates. Combining ccd4-1 and ccd1-1 into a single background increased carotenoid levels in Arabidopsis seed by 360% compared with ~170% and 270% for ccd1-1 and ccd4-1 alone.

These data suggest that CCD1 and CCD4 are important actors in carotenoid turnover and that whilst CCD4 has a more important role, likely due to its chloroplastic localisation, the two work together, and combined ccd1 and ccd4 mutants have a synergistic effect on the accumulation of carotenoids in Arabidopsis seeds. Furthermore, a mutation in ccd4 in peach (Prunus persica) was shown to result in a yellow fleshed variety due to the accumulation of carotenoids compared to the white flesh of the wild type [87].

Furthermore, work to evaluate the impact of CCDs on carotenoid turnover, authors used transgenics to knockout (KO) CCD1 or CCD4 in planta. Ohmiya et al. [88] used RNAi to silence CCD4a in Chrysanthemum (Chrysanthemum morifolium) resulted in a change of petal colour from white to yellow and Campbell et al. [89] down-regulated CCD4 in potato tubers resulting in a yellow flesh variety .

Down-regulation of CCD1A and CCD1B in tomato (antisense construct) resulted in a significant reduction in the rates of emission of pseudoionone, geranylacetone and β-ionone in cut tomato fruits, volatiles generated by the 9–10(9′–10′) cleavage of lycopene, ζ-carotene and β-carotene, respectively. However, these authors did not observe significant changes in the carotenoid content of these fruits [83]. In tomato, CCD1A and CCD1B are not plastid-localized, and it is not unexpected that plants with greatly reduced CCD1 expression showed insignificant alterations in carotenoid content, given that tomato fruit accumulate a significant amount of carotenoids during ripening, and any small turnover may go unnoticed.

These areas of exploitation thus require additional research to explore the contribution of jointly manipulating 'push', 'pull' and 'block' mechanisms to increase carotenoid content to improve the nutritional quality of food stuffs. Carotenoids have furthermore been shown to have important health benefits when consumed as part of a balanced

diet . Manipulating carotenoid biosynthesis and sequestration also offers the potential to modify the flavour and aroma of fruit, grain or leaves. However, it should be noted that blocking the carotenoids turnover could negatively impact CDCs nutritional importance. Carotenoids, via these activities of carotenoid cleavage enzymes, provide the building blocks for a number of volatile and non-volatile organic compounds of physiological importance for plant development.

3. ’Hidden Hunger’ and the Health Benefits of Carotenoids

It has been reported that although humans had access to more than 50 carotenoids in their diet, six major carotenoids persisted in blood plasma, including the colourless carotenoids phytoene and phytofluene, and the coloured carotenoids α-carotene, β-carotene, lycopene, β-cryptoxanthin, zeaxanthin and lutein [90][91].

Carotenoids such as β-carotene, α-carotene and β-cryptoxanthin with provitamin A activity are essential in the human diet [92]. Vitamin A, also known as retinol, is an essential micronutrient and is required for growth, development and vision and is important for immune system function [93][94][95]. Vitamin A, in the form of retinal, combines with the protein opsin to form rhodopsin, a pigment containing sensory protein that absorbs light, converting it to an electrical signal, and it is required for colour vision [96]. Most people suffering from a Vitamin A deficiency are often unaware of that deficiency and show no clinical symptoms in a phenomenon often called ‘hidden hunger’ [97]. Vitamin A deficiencies are more common in areas where cereals and tubers are relied upon for the vast majority of calories consumed, as they are a poor source of provitamin A carotenoids [97].

Genetically modified maize (*Zea mays*) [98][99] engineered to accumulate provitamin A carotenoids has shown to be effective at increasing the stores of vitamin A in the bodies of 5- to 7-year-old children [100]. This work has shown that β-carotene-fortified maize is as effective at controlling vitamin A deficiency as taking supplements [100]. Palmer et al. [101] showed that the consumption of β-carotene from fortified maize improved the visual function of children with a vitamin A deficiency. As such, crops such as ‘golden rice’ biofortified with provitamin A, engineered by European scientists with the hope of combatting premature blindness, and in extreme cases, death by vitamin A deficiencies, have great potential to improve the health of populations that that subsist on nutrient-poor white rice [62]. However, 20 year later, golden rice is not readily available to those it was intended to help. Over the past 20 years, it has been reported that tens of millions of people across Asia (Bangladesh, China and South and Southeast Asia) have gone blind or died due to these delays [102]. Some critics described golden rice as a ‘hoax’ or ‘fool’s gold’ and eventually became a key piece of what supporters have described as propaganda against GM technologies, resulting in a 20-year delay in its introduction and what supporters have described as a crime against humanity [102].

Carotenoids, such as phytoene, phytofluene, lycopene, lutein and astaxanthin, have been associated with a decreased in the risk of certain cancers, including colon [103], lung [104], and prostate cancer [105][106][107]. In elderly patients (64–75), a high intake of tomatoes, carrots and lycopene was associated with a decreased risk of prostate cancer compared to patients with a lower intake of these foods (~50% less tomatoes and 125% less carrots and a 23% lower carotenoid intake overall) [108]. For example, these authors found that patients with prostate cancer

consumed 839 µg/day lycopene, 756 µg/day α-carotene and 4473 µg/day β-carotene compared to the general population with an intake of 1356, 919 and 5492 µg/day lycopene, α-carotene and β-carotene, respectively [108]. A low dietary intake of lycopene and a low plasma lycopene content have also been linked to increased mortality from oral cavity and pharynx cancer [109]. Furthermore, a study of 638 independently living 65–85 years old revealed that higher carotenoid (lycopene, lutein) serum levels and significantly higher levels of cholesterol adjusted α-tocopherol were correlated with higher cancer survival rates [110]. It has also been reported that lutein decreases the proliferation of breast cancer cells in a dose-dependent manner (6.25, 12.5, 25 and 50 µg/mL) and increases the expression of cellular antioxidant enzymes [111]. Further reports have shown that in human breast cell lines (e.g., MCF-7 or MDA-MB-235 cells) treatment with lycopene and β-carotene (0.5 to 10 µM), for 48 h and 96 h, inhibits cell proliferation [112]. Effectively, after 96h, treatment of MCF-7 cells with lycopene (2.5–10 µM) resulted in a 30% reduction in cell viability and a 20% reduction in MDA-MB-235 cell viability; however, the results obtained using MDA-MB-235 cells was only obtained with higher lycopene treatment [112]. Moreover, an additional cell line, MDA-MB-231, showed a 75% decrease in viability when treated with 10 µM lycopene after 96 h [112]. Similar results were found when these cell lines were treated with β-carotene. When treated with 10 µM β-carotene, a 40%, 30% and 70% reduction in MCF-7, MDA-MB-235 or MDA-MB-231 cell viability, respectively, was observed [112]. β-carotene at a concentration of 20 µM and has furthermore been shown to arrest the development of leukaemia cells (HL-60) by approximately 39% and significantly reduce their viability [113]. Phytofluene (10 µM) and ζ-carotene (10 µM) inhibited the cell growth of HL-60 cultures [114] (see Niranjana et al. [115] and Meléndez-Martínez et al. [90] for review).

Lycopene treatment (0–30 µM) over 0, 24, 48, and 96 h decreased the proliferation of SW480 cells 96 h after treatment with increasing effectiveness as lycopene levels increased from 10 to 30 µM [116]. Several other studies have also shown that lycopene (0–100 µM) inhibited cell growth in colorectal cancer cells (CRC) in a dose-dependent manner [117], and the proliferation of CRC was reduced by lycopene treatment to as low as 12 µM by Huang et al. [118]. A lycopene treatment of 20 mg/kg^{-1} in female Wistar rats has been shown to inhibit tumour growth [119] and protect against spontaneous ovarian cancer formation in laying hens (lycopene 26–52 mg/day/hen) [120].

It has been suggested that the preventive role of carotenoids against cancer is linked to their antioxidant activity and that regular consumption of carotenoids may alleviate oxidative stress. Lutein, zeaxanthin, and lycopene, for example, have been reported to decrease the inflammatory mediator's production, as lycopene has been shown to have an anti-inflammatory effect on human colorectal cancer cells [116]. Lycopene and lutein have also been described as having the capacity to prevent oxidative stress-induced diseases such as cardiovascular disease in vivo (CVD) [121][122][123][124][125] and reduce LDL-cholesterol plasma levels [126]. Lutein has also been shown to reduce the risk of coronary artery disease [127] and may prevent atherosclerosis (condition where arteries become clogged with fatty deposits) development due to its anti-inflammatory and antioxidant properties and its ability to reduce the build-up of oxidized low-density lipoprotein (LDL) in the blood [128]. Lycopene has also been described as having preventive effects in atherosclerosis pathology [125]. High plasma lutein levels have also been found to reduce the risk of coronary heart disease and stroke [129] and decrease oxidative stress and apoptosis, protecting the myocardium from ischemia injury (inadequate blood supply to an organ i.e heart muscles) [124].

Carotenoids, lutein, zeaxanthin and β-carotene limit neuronal damage from free radicals, delaying the progression of neurological diseases, and dietary supplementation with lutein and zeaxanthin (2.02 mg/day) may prevent cognitive decline in those aged ≥ 60 years [130]. β-carotene has also been described as an Alzheimer's disease antagonist [131], and high serum levels of lycopene, zeaxanthin and lutein have been linked to a reduction in mortality of Alzheimer's sufferers [132].

It should also be noted that carotenoids have been linked to preventative roles in diabetes mellitus and osteoporosis, and numerous studies have suggested that carotenoids, including lutein and astaxanthin, could decrease age-associated decline in human skin cells and have a positive impact on the human life span (see Tan et al. [133], Rivera-Madrid et al. [134] and Milani et al. [135] for review), as well as having a beneficia effects on eye health and improving cognitive function (see Eggersdorfer et al. [136]).

The benefits noted above have suggested that increasing the levels of these beneficial carotenoids in the human diet could have a significant contribution to human health, and manipulating their metabolism would contribute greatly to this goal. Furthermore, manipulating terpenoid biosynthesis, either by increasing or decreasing specific carotenoid subsets, can lead to increases in nutritionally important compounds and flavour/aroma volatiles that could be used as a way to improve the quality in fresh produce such as tomatoes [10].

Carotenoid-derived apocarotenoids (CDCs) are formed by the oxidative cleavage of carbon–carbon double bonds in the carotenoid backbones either by carotenoid cleavage enzymes (CCDs) or via the exposure of carotenoids to ROS. Many of these apocarotenoids play key regulatory roles in plant development as growth simulators and inhibitors, signalling molecules, including as abscisic acid [137][138][139] and strigolactones [140][141][142][143][144], and have roles in plant defence against pathogens and herbivores [145]. Others act as flavour and aroma compounds in fruit pericarp, flowers and seeds [83][146][84][147][148][149][150][86][151]. The diverse variety of carotenoids (+700) means that the potential apocarotenoid products represent a significant number of natural compounds.

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