Apocarotenoids

Subjects: Agriculture, Dairy & Animal Science
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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 and strigolactones, and have roles in plant defence against pathogens and herbivores. Others act as flavour and aroma compounds in fruit pericarp, flowers and seeds. The diverse variety of carotenoids (+700) means that the potential apocarotenoid products represent a significant number of natural compounds.

Keywords: Apocarotenoids ; flavour ; aroma ; therapeutic

1. Apocarotenoid Biosynthesis is Planta

In the late 1980s, the routes for the formation of apocarotenoids were poorly understood. However, their chemical structure and studies carried out analysing volatiles produced during the ripening of mutant tomato varieties accumulating unusual carotenoids indicated that apocarotenoids were likely derived from the oxidative carotenoid cleavage [1].

In the years following, a family of carotenoid cleavage dioxygenases (CCDs) that are able to cleave carotenoid at an assortment of double bonds were identified [2]. The first enzyme of the CCD family was identified from *Arabidopsis thaliana* (Arabidopsis) and named VP14 (EC.1.13.11.51), which was shown to cleave 9-cis neoxanthin at the 11,12 double bond to form xanthoxin, the precursor of abscisic acid (**Figure 1**) [3][4].

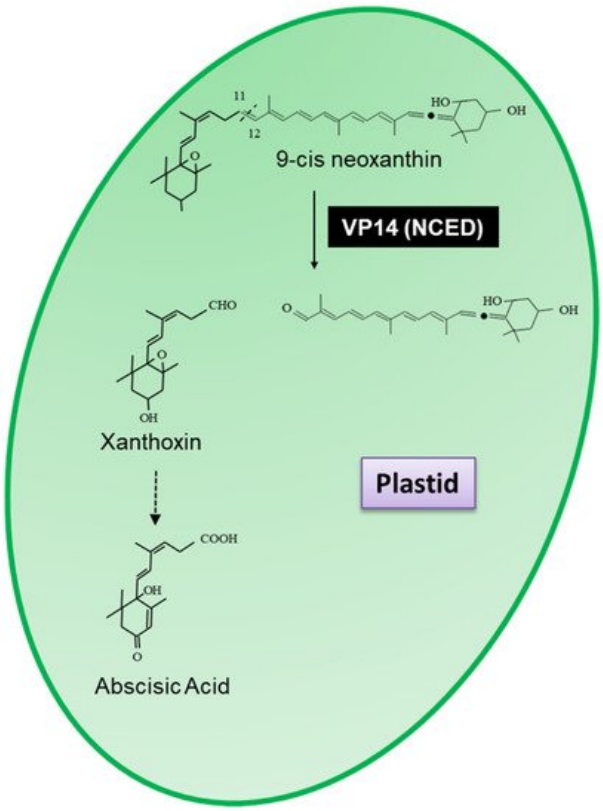

Figure 1. Scheme for the 11,12-cleavage reaction catalysed by VP14 (9-cis-epoxycarotenoid dioxygenase) resulting in the formation of xanthoxin, the precursor of abscisic acid.

Tan et al. [5] identified nine members of the VP14 family in Arabidopsis, five of which have been shown to cleave neoxanthin at the 11,12 double bond and have thus been renamed as neoxanthin cleavage dioxygenases (NCED2, NCED3, NCED5, NCED6(VP14) and NCED9). These enzymes have been extensively studied and are involved in the biosynthesis of the phytohormone abscisic acid (ABA). ABA regulates plant growth, development and stress responses and plays essential roles in multiple physiological processes, including leaf senescence, osmotic regulation, stomatal closure, bud dormancy, root formation, seed germination and growth inhibition among others. The four remaining NCED were shown to cleave a variety of carotenoids generating a variety of (di)aldehydes and ketones and were renamed carotenoid cleavage dioxygenases/oxygenases (CCD1 (EC.1.13.11.71), CCD4 (EC.1.13.11.n4), CCD7 (EC.1.13.11.68) and CCD8 (EC.1.13.11.69)).

The recombinant CCD7 protein from Arabidopsis exhibited a 9′-10′ asymmetrical cleavage activity converting β-carotene into β-ionone (9-apo-β-caroten-9-one) and 10-apo-β-carotenal (C_{27} compound; **Figure 2**) [5]. When the AtCCD8 gene was expressed in *Escherichia coli* with AtCCD7, the 10-apo-β-carotenal was subsequently cleaved into 13-apo-β-carotenone and a C_9 dialdehyde [5]. Since no cleavage activity has been associated with CCD8 when it has been expressed in carotenoid accumulating *E. coli* lines to date, Schwartz et al. [5] concluded that CCD8 functions as an apocarotenoid cleavage enzyme working sequential with CCD7 as the first steps in the formation of 13-apo-β-carotenone.

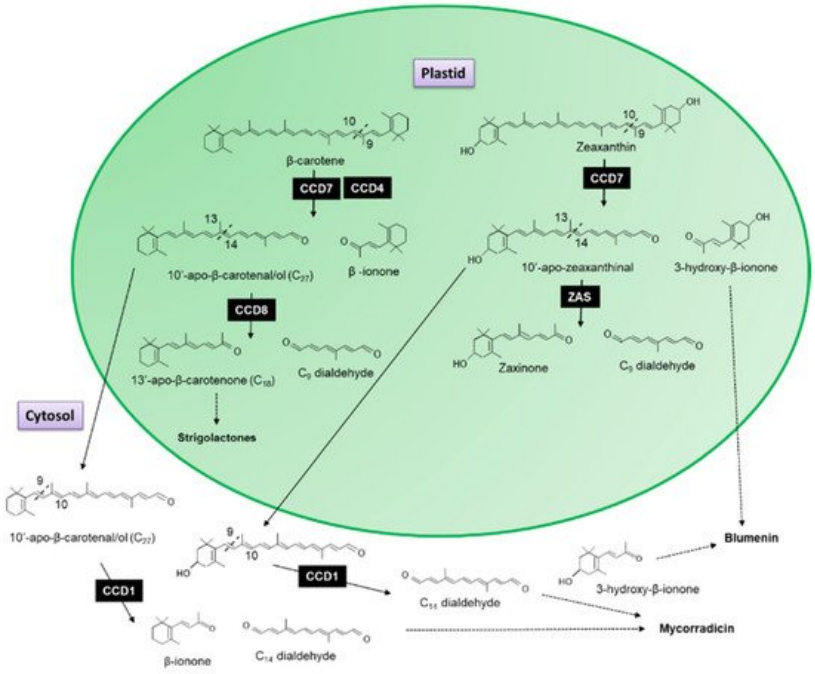

Figure 2. Scheme for the 9,10-cleavage of β-carotene and zeaxanthin catalysed by CCD7 and CCD4 into β-ionone and 10-apo-β-carotenal (C_{27} compound) and 3-hydroxy-β-ionone and 10-apo-β-zeaxanthinal (C_{27} compound). The 13,14 cleavage by CDD8 resulting in the formation of 9-apo-β-caroten-9-one (C_9 dialdehyde) and the 13-apo-β-carotenone, the precursor of strigolactones. The 13,14 cleavage of 10-apo-β-zeaxanthinal by Zaxinone Synthase (ZAS) forms Zaxinone and the C_9 dialdehyde. The C_{27} compound is cleaved by CCD1 in the cytosol into β-ionone, 3-hydroxy-β-ionone and rosafluene-dialdehyde (C_{14} dialdehyde—see **Figure 3**), the precursor for mycorradicin.

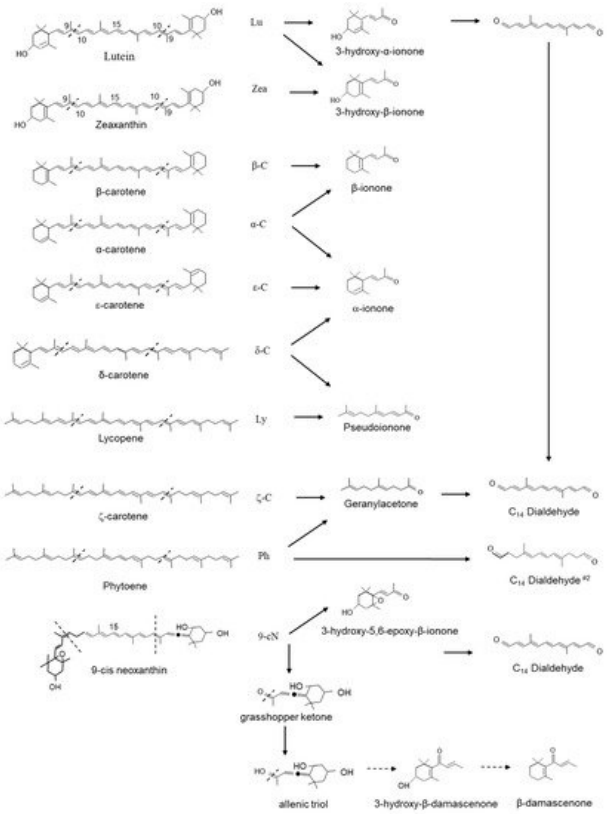

Figure 3. Scheme for the 9,10(9′,10′,) reactions catalysed by the recombinant CCD1 proteins with various substrates. C_{14} rosafluene-dialdehyde (4,9-dimethyldodeca-2,4,6,8,10-pentaene-1,12-dial). CCD1 activities are carried out in the cytosol.

2. Carotenoid Cleavage Dioxygenase 1 (CCD1) Enzymes Cleave a Broad Category of Carotenoids and Apocarotenoids at Multiple Double Bonds in the Cytosol

It has been shown that this sequential cleavage is the origin of the biosynthesis of strigolactones, a new class of plant hormones essential for plant development (**Figure 2**; for review see [6][7][8][9]). The recently characterized Zaxinone Synthase (ZAS), previously classed as CCD8b, cleaves 3-OH-all trans-β-apo-10′-carotenal (apo-10′-zeaxanthinal), the C27 cleavage product of zeaxanthin into zaxinone (3-OH-all-trans-apo-13-carotenone), a metabolite that regulates strigolactone biosynthesis in rice and the C_9 dialdehyde [10]. In contrast, CCD1 and CCD4 enzymes have been shown to catabolize a variety of carotenoids and produce volatile and non-volatile apocarotenoids, which are important for the aromas and flavours of flowers and fruits. The following sections of this review will focus exclusively on these two CCDs.

The majority of CCDs/NCEDs have been shown to reside within plastids. The one exception is CCD1, which acts in the cytosol to generate C_{13} and C_{14} apocarotenoids [11][12]; however, we cannot rule out a tight association with the outer envelope, as has been reported, for the tomato hydroperoxide lyase [13], which would potentially give CCD1 access to carotenoids stored in the envelope [11][12]. Significant amounts of β-carotene have been identified in the outer envelopes of spinach (*Spinacia oleracea*; [14]) and pea (*Pisum sativum*; [15]) chloroplasts, where they have been reported to stabilize chloroplast membranes [16].

Orthologs of AtCCD1 have been identified in a number of species, including tomato (*Solanum lycopersicum)* [11], strawberry (*Fragaria vesca*) [17], petunia (*Petunia hybrida*) [18], pepper (*Capsicum annum* L.) [19], coffee (*Coffea canephora/C. arabica)* [20][21], carrot (*Daucus carota* L.) [22], rice (*Oryza sativa*) [23], melon (*Cucumis melo*) [24], fig (*Ficus carica*) [25], grape (*Vitis vinifera*) [26][27][28], rapeseed (*Brassica napus*) [29], and roses (*Rosa damascena*) [19]. CCD1 has been shown to cleave both cyclic and acyclic carotenoids [30][11][23][31] forming apocarotenoid aldehydes and ketones, indicating that CCD1 may have a more complex reaction tunnel than other CCDs that cleave either cyclic carotenoids or apocarotenoids alone. Using AtCCD1, beta-apo-8′-carotenal as a substrate, isotope labelling experiments have shown that these cleavage activities arise due to a dioxygenase mechanism [32] requiring only Fe^2 as a cofactor.

Recombinant CCD1 enzyme and assayed multiple carotenoid substrates in vitro and characterized the cleavage products by thin-layer chromatography and HPLC. CCD1s have been shown to symmetrically cleave the 9,10(9′,10′) double bonds of a large category of carotenoids to form two C_{13} compounds and a central C_{14} rosafluene-dialdehyde (4,9-dimethyldodeca-2,4,6,8,10-pentaene-1,12-dial) (**Figure 3**) [30][11][33] In assays containing lutein, zeaxanthin and β-

carotene, 3-hydroxy-α-ionone (3-hydroxy-9-apo-α-caroten-9-one); 3-hydroxy-β-ionone (3-hydroxy-9-apo-β-caroten-9-one) and β-ionone are formed, whereas α-carotene led to the production of both β-ionone and α-ionone and ε-carotene formed α-ionone (9-apo-α-caroten-9-one) (**Figure 3**).

CCD1 has also been shown to cleave nonlinear carotenoids, δ-carotene yields α-ionone (9-apo-α-caroten-9-one) and pseudoionone (6,10-dimethyl-3,5,9-undecatrien-2-one); lycopene yields pseudoionone. Several linear carotenoids, including phytoene and ζ-carotene, are thought to be the precursors of geranylacetone (6,10-dimethyl-5,9-undecatrien-2-one), an important flavour volatile in tomato fruit, as well as precursors for a second C_{14} dialdehyde (4,9-dimethyldodeca-4,6,8-triendial). Finally, in assays containing violaxanthin or neoxanthin, 5′6-epoxy-3-hydroxy-β-ionone (5,6-epoxy-3-hydroxy-9-apo-β-caroten-9-one) was formed.

In assays containing neoxanthin, the asymmetric cleavage yielded a C_{27} allenic-apocarotenal and the C_{13} grasshopper ketone (3,5-dihdroxy-6,7-didehydro-9-apo-β-caroten-9-one). The grasshopper ketone is postulated to be the precursor for the formation of the potent odorants β-damascenone (1-2,6,6-trimethyl-1,3-cyclohexadien-1-yl-2-buten-1-one) and 3-hydroxy-β-damascenone (3-hydroxy-1-2,6,6-trimethyl-1,3-cyclohexadien-1-yl-2-buten-1-one) (**Figure 3**) [34][35]. β-damascenone has been shown to be formed from 9′-cis-neoxanthin by peroxyacetic acid oxidation and two-phase thermal degradation without the involvement of enzymatic activity [35]. Skouroumounis et al. [36] studied the possible hydrolytic pathway of β-damascenone and suggested formation and determined that allenic triol was the key intermediate.

CCD1s from tomato and maize (*Zea maize*) have also been shown to cleave the 5,6(5′,6′) double bonds of lycopene in vitro generating the apocarotenoid 6-methyl-5-hepten-2-one (MHO; **Figure 4**) [31]. Furthermore, Ilg et al. [23], using both in vitro and in vivo assays, demonstrated that the activity of OsCCD1 converts lycopene into pseudoionone (**Figure 3**) and MHO (**Figure 4**), suggesting that the 7,8(7′,8′) double bonds of acyclic carotenoid ends constitute a novel cleavage site for the CCD1 plant subfamily. Carballo-Conejo et al. [37] also identified a CCD1 lycopene-specific 5,6(5′,6′)-cleavage dioxygenase (BoCCD1-1) from *Bixa orellana*, responsible for the formation of bixin dialdehyde and MHO [38][39]. Bixin dialdehyde is the precursor for the formation of the dye bixin/annatto (**Figure 4**). BoCCD1-1 gene expression correlated with bixin accumulation in *B. orellana* [39], suggesting that BoCCD1-1 and its homologue BoCCD1-2 could be involved in the cleavage of lycopene in seed to form bixin. However, data from a study by Cárdenas-Conejo et al. [37][38] indicated that although BoCCD1-1 is expressed in immature seed, it is also expressed in green tissue (leaf), and BoCCD1-2 was preferentially expressed in leaf. These authors also identified two additional CCD1′s, BoCCD1-3 and BoCCD1-4, which were shown to be expressed in immature seeds at 1.5-fold and 10-fold the levels found in leaf, respectively suggesting that BoCCD1-3 and BoCCD1-4 are more likely involved in the cleavage of lycopene to form bixin dialdehyde in the seed (**Figure 4**).

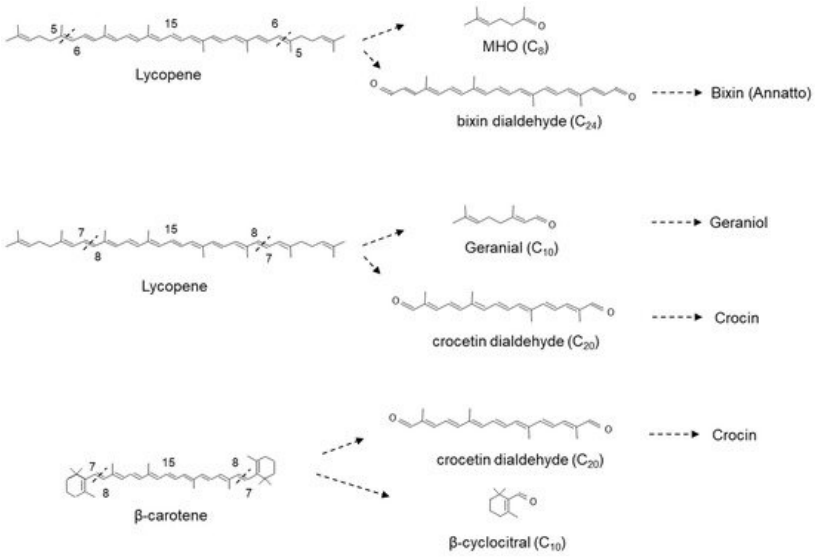

Figure 4. Scheme for the 5,6(5′,6′,) and 7,8(7′,8′,) reactions catalysed by the recombinant carotenoid cleavage deoxygenases (MHO; 6-methyl-5-hepten-2-one) carried out by CCD1 in the cytosol.

Meng et al. [44] showed that VvCCD1 also cleaved β-carotene at the 7,8(7′,8′) position into β-cyclocitral, an important flavour and aroma compound in planta. Interestingly, OsCCD1 was also shown to cleave the 7,8(7′,8′) double bonds of lycopene to form geranial (**Figure 4**) [27].

In the medicinal plant *Catharanthus roseus*, the formation of geraniol (isomer of geranial) from geranyl pyrophosphate by geraniol synthase [40] is a key step in the formation of a number of economically important monoterpene indole alkaloids

(MIA). Several of these MIA, such as vinblastine and vincristine, are valuable therapeutic compounds (anticancer drugs: [41]). CCD1 represents a possible alternate route in the generation of geraniol in planta.

CCD1 has also been shown to cleave apocarotenoids generated by the asymmetric cleavage of a carotenoid. *Medicago truncatula* CCD1 antisense plants have been shown to accumulate 10′-apo-β-carotenal/ol (C_{27}) in root material [42]. This C_{27} dialdehyde is generated by the asymmetric 9′10 cleavage of β-carotene by CCD7, which is subsequently cleaved by CCD8 to form 13-apo-β-carotenone, the precursor of strigolactones (**Figure 2**). This indicates that (1) CCD7 result in the accumulation of 10′-apo-β-carotenal/ol, possibly due to a low turnover by CCD8 in the strigolactone pathway; and (2) that CCD1 may act to mop up apocarotenoid generated by previous reactions. Such a role for CCD1 has been previously hypothesized (for review, see Floss et al. [43]).

The multisite cleavage of lycopene by CCD1 enzymes may be linked to the absence of a terminal ring structure found on the cyclic and oxygenated carotenoids . With no ring, linear carotenoids such as lycopene may penetrate deeper into the reaction tunnel compared to cyclic carotenoids with no stop measure to prevent it. This may well result in a random cleavage pattern and the generation of multiple products from a single linear substrate (**Figure 3** and **Figure 4**). The aldehydes and ketones generated by the activity of CCD1 enzymes represent important flavour and fragrance compounds themselves (**Figure 3** and **Figure 4**) and act as substrates for the formation of others [11][31][44][45].
Finally, we also cannot exclude photooxidation as an additional mechanism for the formation of 9′10(9′10′) CDCs β-ionone, pseudoionone, geranylacetone or any of the 5,6(5′6′) and 7,8(7′8′) CDCs generated by the activity of CCD1. It should be noted that the formation of β-ionone from β-carotene by free radical-mediated cleavage of the 9–10 bond has been demonstrated in vitro [51]. In pepper leaves, natural oxidative turnover accounts for as much as 1 mg of carotenoids day-1 g-1 DW [52]. During tomato fruit ripening, carotenoids concentration increases by 10- and 14-fold, mainly due to the accumulation of lycopene [53]. Given the overall quantity of carotenoids that accumulate during fruit ripening, the rates of CDC emission remain very low.

3. Carotenoid Cleavage Dioxygenase 4

Like CCD1, a common feature of CCD4 subset is a 9–10 or 9–10/9′–10′ cleavage activity [46][47]; however, unlike CCD1, CCD4 is localized to the plastid where it has been detected in the plastoglobules [47]. Plastoglobules have been identified as a site of carotenoid cleavage by a functionally active CCD4 with β-carotene, lutein and violaxanthin being the principle substrates of CCD4 in vivo [48]. Huang et al. [46] cloned CCD4 cDNAs from rose (*Rosa damascena*, RdCCD4), chrysanthemum (*Chrysanthemum morifolium*, CmCCD4a), apple (*Malus domestica,* MdCCD4) and osmanthus (*Osmanthus fragrans*, OfCCD4) and expressed them along with AtCCD4 in *Escherichia coli* engineered to accumulate carotenoids [49]. No cleavage products were observed for any of the five CCD4 genes when they were co-expressed in *E. coli* strains that accumulated either cis-ζ-carotene or lycopene. Additional trials using β-carotene as a substrate showed that CmCCD4a and MdCCD4 both cleaved the 9–10 double bond of β-carotene to yield β-ionone; however, OfCCD4, RdCCD4, and AtCCD4 were almost inactive towards this substrate. In the case of RdCCD4 and AtCCD4, the formation of β-ionone was observed in the presence of an apocarotenoid substrate, 8′-apo-β-caroten-8′-al (**Figure 5**), while this apocarotenal was barely degraded by MdCCD4, OfCCD4 or CmCCD4a [46]. It has also been suggested that CCD1 cleaves 10-apo-β-carotenal, a C_{27} compound generated by the activity of CCD7 (**Figure 2**), suggesting that CCDs also act to further catabolize down-stream products of other CCDs [43]. From the published data, it also appears that two individual classes of the CCD4 subset exist in planta. Sequence analysis showed that RdCCD4 and AtCCD4 contain no introns, whilst MdCCD, OfCCD4 and CmCCD4a contain one or two introns [50][46]. It’s interesting to note that the two intronless CCD4s displayed apocarotenoid cleavage dioxygenase activity (ACD) rather than the carotenoid cleavage dioxygenase activity (CCD) observed for the two of the three CCD4s containing introns.

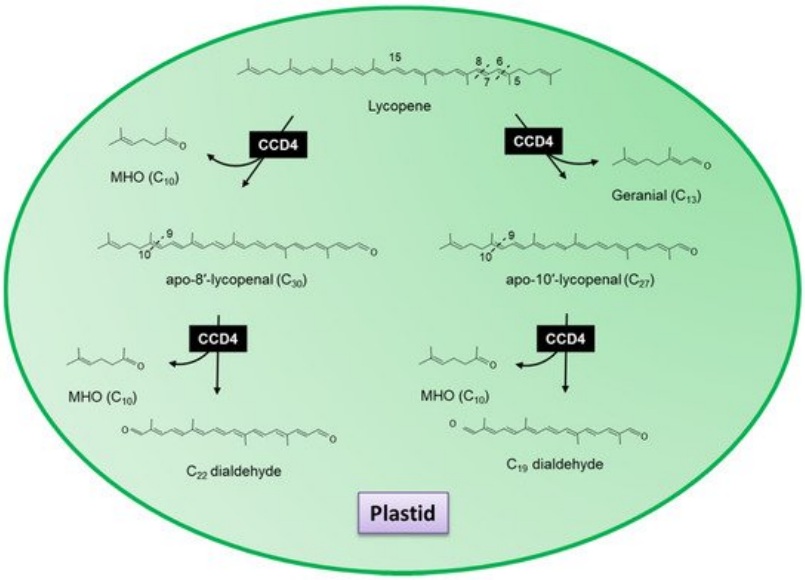

Figure 5. Scheme for the 5,6(5′,6′,) and 7,8(7′,8′,) cleavage of lycopene by CCD4 (MHO; 6-methyl-5-hepten-2-one) and the 9,10(9′,10′,) cleavage of the generated apocarotenoids in a second step.

In Chrysanthemum 'Jimba' (*Chrysanthemum morifolium*), CmCCD4a contributes to the development of white petals by cleaving carotenoids into their apocarotenoid products [50]. RNAi interference of CmCCD4a resulted in the development of pale-yellow petals due to the accumulation of carotenoids in the petal tissue [51]. Brandi et al. [52] found that CCD4 contributed to the colour of peach flesh and aroma profile, white-fleshed mutants had both a lower carotenoid content and a higher apocarotenoid aroma concentration compared to non-CCD4 expressing yellow flesh peaches, demonstrating the strong link between carotenoids and carotenoid derived aroma volatiles.

In Satsuma mandarin (*Citrus unshiu*), CitCCD4 converts zeaxanthin into 3-hydroxy-β-cyclocitral and the C_{30} apocarotenoids β-citraurin (3-hydroxy-β-apo-8′-carotenal), which is responsible for the reddish colour in the peel. CitCCD4 was also shown to use β-cryptoxanthin as an alternate substrate (**Figure 6**). However, CitCCD4 cleavage of β-cryptoxanthin generates two possible C_{30} apocarotenoids: β-apo-8′-carotenal or β-citraurin, although their relative abundance may indicate that the reaction favours the formation of β-apo-8′-carotenal. In the same experiments, CitCCD4 showed no activity with the substrates, lycopene, α-carotene, β-carotene or violaxanthin [53].

Related work by Rodrigo et al. in the Washington Navel sweet orange (*C. sinensis* L. Osbeck), Clemenules mandarin (*C. clementina*), In silico data mining identified five CCD4-type genes in Citrus. One of these genes, CCD4b1, was expressed in different Citrus species in a pattern correlating with the accumulation of β-citraurin. In contrast to the activity identified for CitCCD4, CCD4b1 was also shown to cleave β-carotene into β-apo-8′-carotenal and β-cyclocitral (**Figure 6**); α-carotene into one single C_{30} product, ε-apo-8′-carotenal and β-cyclocitral. When lutein was used as a substrate, only α-citraurin (3-OH-8′-apo-ε-carotenal) was identified, suggesting that 3-hydroxy-β-cyclocitral is also formed. In this instance, Rodrigo et al. showed that CCD4b1 cleaves carotenoid structures with an ε-ring but only on the extremity containing the β-ring. These C_{30} products of lutein, α-carotene and lycopene are not detected in Citrus extracts, which is not unexpected, as lutein and α-carotene are typical only found in green fruits.

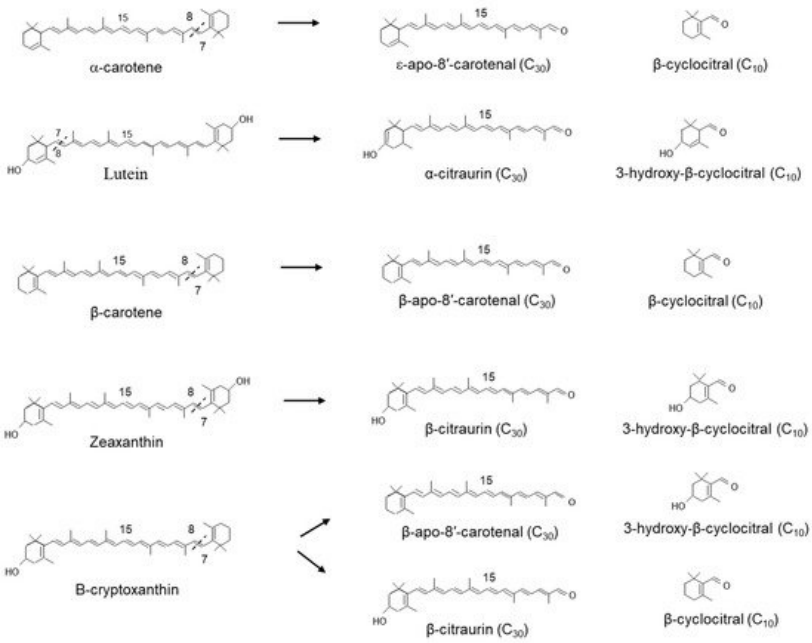

Figure 6. Scheme for the 7,8(7′,8′,) reactions catalysed by the recombinant carotenoid cleavage deoxygenase 4 in the plastid.

When lycopene was used as a substrate, CCD4b1, two different apocarotenoids, apo-10′-lycopenal (C_{27}) and apo-8′-lycopenal (C_{30}), were identified to have derived from the 5,6 and 7,8 cleavage, respectively (**Figure 5**). CCD4b1 has also been shown to cleave linear apocarotenoids apo-8′-lycopenal and apo-10′-lycopenal at the 5,6 double bonds generating the C_{22} and C_{19} dialdehydes (**Figure 5**) [54]. These data show that the absence of the ionone ring can substantially alter the cleavage position, as has been suggested for CCD1.

MdCCD4 (*Malus domestica*), CmCCD4a (*Chrysanthemum morifolium* Ramat), RdCCD4 (*Rosa damascena*), OfCCD4 (*Osmanthus fragrans*) and AtCCD4 (*A. thaliana*) were all detected in their respective flowers. The expression levels of CCD4 in rose flowers were 42 times higher than those in leaves, indicating that CCD4s may play integral roles in the aroma profile of flowers [55].

4. Novel Carotenoid Cleavage Dioxygenases

In addition to the nine carotenoid cleavage dioxygenases initially identified, authors have also identified a group of novel cleavage dioxygenases with specific activities. CCD2 is a novel carotenoid cleavage dioxygenase from *C. sativus* that catalyses the first dedicated step in saffron and crocin biosynthesis [56]. Localized in the plastid, CCD2 sequentially cleaves zeaxanthin at the 7,8(7′,8′) forming 3-hydroxy-β-cyclocitral and crocetin dialdehyde, the precursor for the formation of crocin and the spice saffron (**Figure 7**) [56][57]. Ahrazem et al. [57] demonstrated that CsCCD2 requires a 3-hydroxy-β-ring and does not use β-carotene or lycopene as a substrate. Crocetin dialdehyde has previously been shown to accumulate in the flowers of *Jacquinia angustifolia* [58] and the roots of *Coleus forskohlii* [59].

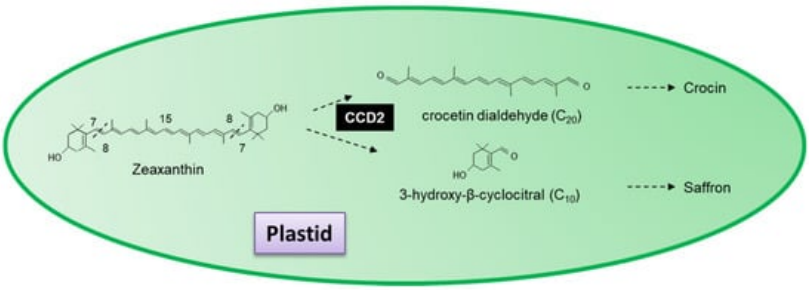

Figure 7. Scheme for the 7,8(7′,8′,) reactions catalysed by the recombinant carotenoid cleavage deoxygenases 2 in *Crocus sativus*.

A second novel carotenoid cleavage enzyme, the *Zea maize* CCD10a, cleaved neoxanthin, violaxanthin, antheraxanthin, lutein, zeaxanthin and β-carotene in planta at 5,6(5′,6′) and 9,10(9′,10′) positions, generating MHO (6-methyl-5-hepten-2-one) and the C_{13} apocarotenoids, geranylacetone, α-ionone and β-ionone [60]. ZmCCD10 over-expression and down-regulation led to alterations in the expression of phosphate starvation response regulators (PHR1) and phosphate transporters, whereas down-regulation of CCD10a made plants susceptible to Pi deficiency, over-expression in

Arabidopsis enhanced plant tolerance to phosphate limitation [60], further demonstrating that CCD-generated apocarotenoids have important regulatory functions in planta. Finally, Wang et al. [10] have reported that CCD10 is found in mycorrhizal plants only. As C_{13} apocarotenoids promote arbuscular mycorrhizal symbiosis ([42][61][62]); over-expression of CCD10 under low phosphate increases C_{13} formation, which may promote phosphate acquisition via the mycorrhiza fungal pathway (see [60]).

5. Apocarotenoids Are Important to Flavour and Aroma

Terpenoid flavour volatiles are generally present in plants at relatively low levels, but possess strong effects on the overall human appreciation of the flavour of [1][44][63][64][65][66][67][68]. These CDCs are considered to be among the most significant contributors to the flavour and aroma of many fruits and vegetables. For example, α-ionone, β-ionone, β-cyclocitral and β-damascenone have been estimated to contribute as much at 8% to the aroma profile of Valencia orange juice and as much at 78% of the total floral aroma [69]. Peak levels of β-ionone and geranylacetone emissions from ripe tomato fruit have previously been calculated to be 1.25 pg/g fw^{-1} h^{-1} and 40 pg/g fw^{-1} h^{-1}, respectively [44]. Although found in low concentrations compared to other more abundant volatiles such as cis-3-hexenal and hexenal, β-ionone and geranylacetone have much lower odour thresholds, 0.007 nL/L^{-1} and 60 nL/L^{-1}, respectively [44]. These odour thresholds are more than 10,000-fold lower than other flavour contributing volatiles; thus, these carotenoid-derived volatiles α-ionone, β-ionone, β-cyclocitral and β-damascenone have the potential to greatly impact aroma and flavour, even at low concentrations. Bladwin et al. [44] determined that β-ionone is the second most important volatile contributor to tomato fruit flavour. The major volatile present in lycopene-containing tomatoes (and watermelons) were geranial, MHO, pseudoionone and geranylacetone, seemingly derived from lycopene [70]. β-ionone and β-cyclocitral were identified in both tomato and watermelon fruits containing beta-carotene. Furthermore, α-ionone was detected only in an orange-fleshed tomato mutant *Delta,* that accumulates ζ-carotene [70].

β-ionone has also been identified as one of the major components of henna leaves (*Lawsonia inermis* L.) [71], melon [24] and as a constituent of a number of Moroccan herbs (*Montpellier cistus, Myrtus communis, Cistus ladanifer*) [72], and Yahyaa et al. [22] identified β-ionone in orange and purple carrot (*Daucus carota*) roots. β-ionone has also been shown to be an important contributor to fragrance in the flowers of *Boronia megastigma* [73], *Petunai hybrida* [18] and *Rosa damascene* [74] (see Paparella et al. [75] for review).

β-damascenone, which was first identified in the oil of the Bulgarian rose (*R*. *damascena*) [76], has been described as a potent odorant with an odour threshold of 2 ppt in water [45]. β-damascenone is one of the most ubiquitous natural odourants, commonly occurring in processed foodstuffs and beverages, where it has also been shown to contribute to the aroma profile of black tea [77][78], tomato [64][79], apples [80], grapefruit juice [81] and more. It has also been reported to be key component of alcoholic beverages, including wines [82][83], apple brandy [84] and beer [85][86], as well as a primary odorant in Kentucky bourbon [87]. β-damascenone has also been identified in raw coffee beans [88], which was not unexpected given the previous identification of carotenoid in raw coffee beans [21]; however, during the roasting process, β-Damascenone increased strongly [88].

Another group of volatiles synthesised by CCD1 and CCD1-like enzymes, MHO [31], and β-cyclocitral [89] are associated with tomato-like flavour [90] and sweet floral aroma [91] of tomato fruit and contributes a sweet/citrus aroma to tomato [91]. The CCD1-derived geranylacetone and pseudoionone [11] have also been identified in tomato and contribute to the overall aroma profile. Pseudoionone has been described as having a balsamic-type odour and a floral-type flavour, and geranylacetone has been described as having a floral-type odour and floral-type flavour.

Geranylacetone, α-ionone, β-ionone, β-cyclocitral and β-damascenone were all found in mango fruit [92]. Interestingly, mango fruit also contained geranial. Whether this accumulation is related to the cleavage of lycopene by CCD1 (**Figure 4**) or through the activity of an endogenous geraniol synthase is unknown. As noted above, geranial has also been identified in the headspace of red tomato fruit [70]. The distillation of apple brandy was also shown to enhance the concentration of two carotenoid-derived flavour compounds, β-damascenone and β-cyclocitral [84], and MHO has been shown to be present as a component of the floral scent of 50% of all flowering plants analysed [93], and β-ionone contributes to the aroma profile of petunia flowers [18]. Baldermann et al. [94] functionally characterized CCD1 from *Osmanthus fragrans* Lour and found it cleaved α- and β-ionone, contributing to the aroma of flowers.

6. Apocarotenoids Are Important Therapeutical Compounds

6.1. Bixin

Bixin is located in the seeds of a tropical perennial achiote tree (*Bixa orellana*) grown in Central and South America, India and East Africa. It contains about 5% pigment w/v, of which 70–80% is bixin, and it is extracted to form annatto. Annatto is a commercially important natural yellow-orange-red pigment used as a dye in dairy and bakery products, vegetable oils and drinks [95][96]. Bixin dialdehyde, the precursor for the formation of bixin/annatto, is formed by the 5,6(5′,6′)-cleavage of lycopene (**Figure 4**) and is in increasing world demand for use as a natural food dye. Furthermore, bixin has also been described as having anti-cancer properties towards osteosarcoma, anaplastic thyroid, breast, colon, prostate and papillary thyroid cancers [97] as well as various potent pharmacological activities, including antioxidant and anti-inflammatory properties. Moreover, it has been described as a promising candidate for the treatment of Multiple sclerosis (MS), an autoimmune and degenerative disease, due to its ability to prevent neuroinflammation and demyelination in experimental autoimmune encephalomyelitis in mice, primarily by scavenging ROS [98]. Bixin has been shown to restore the sensitivity of human melanoma A2058 cells to chemotherapy and have an antiproliferative (IC_{50} = 34.11–48.17 μM) and anti-migratory effects [99]. The IC_{50} is a quantitative measurement of how much of a drug, or substance, is needed to inhibit a biological activity or process by 50%.

6.2. Saffron and Crocetin

Crocus sativus L. is a perennial, stemless herb cultivated in Iran, Spain, India and Greece. Saffron, considered the world's most expensive spice, is extracted from the dried stigma of Crocus flowers. Crocus flowers also contain several important pharmacologically active compounds, bitter principles (e.g., picrocrocin), volatile agents (e.g., safranal), and dyes (e.g., crocetin and its glycoside crocin). Active compounds have been used as anticonvulsant, antidepressant, anti-inflammatory, antitumor and neuroprotective agents. Crocin has also been reported to act as an anti-alzheimer agent by inhibiting pro-inflammatory activity, triggered by the microglia, and to have a beneficial impact on the cardiovascular systems, immune system, endocrine system, and the gastrointestinal tract [100]. Saffron (30 mg/day^{-1}) has been used to treat mild to moderate depression in clinical outpatients with no side effects [101], and crocetin has been shown to have anti-proliferation effects on lung cancer cells in Swiss albino mice administered at 50 mg/kg^{-1} bodyweight [102]. It has also been used to suppress the proliferation of colorectal cancer cells in vitro (3 mg/mL^{-1}) [103]. Crocin has been described as having an IC_{50} of 2mM in cervical cancer cell lines [104]. For an extensive review on the uses of saffron and other compounds, see Moshiri et al. [105], Milani et al. [106] and Pashirzad et al. [107] (**Figure 7**).

6.3. Carotenoid-Derived Ionones

β-ionone has also been described has having important pharmacological properties benefiting human health, including antibacterial [108], antifungal [108] and antileishmanial [109] activities. β-ionone actively inhibits *Escherichia coli* and *Candida albicans* proliferation [110] and the growth of the fungus *Aspergillus flavus* and sporulation of *A. flavus* and *A. parasiticus* [111]. β-ionone has also been shown to have cancer-preventing [112][113] and anti-inflammatory roles [114]. β-ionone has been shown to suppress the proliferation of breast cancer cells [113], prostate cancer cell growth in both in *vitro* and in *vivo* models [115] and induce apoptosis in murine B16 melanoma cells, human leukaemia and suppress the proliferation of human colon adenocarcinoma cell lines [116], human colon cancer [117] and human gastric adenocarcinoma [118]. Liu et al. [119] reported that β-ionone was responsible for a dose-dependent inhibition of mammary gland carcinogenesis in rats—further indication that ionones have important therapeutic uses (for review, see Ansari et al. [112] and Aloum et al. [120].)

Other ionones and their derivatives have also been shown to have therapeutic value. 3-Hydroxy-β-ionone, for example, was shown to slow the proliferation colony formation and cell migration of squamous cell carcinoma [121]. α-ionone derivatives have also been shown to exhibit anti-inflammatory, anti-microbial and anticancer effects. However, it appears that the use of ionones in therapy might be complicated by their interaction. For example, α-ionone prevented or suppressed the effects of β-ionone [122][123], and Neuhaus et al. [122] found that α-ionone inhibited the β-ionone-induced anti-proliferative effect in prostate cancer cells.

7. Apocarotenoids Have Roles in Plant Development and Defense

In addition to their roles as aroma, flavour and colourants, apocarotenoids have been shown to have a variety of functions in planta, including having roles in plant–microbe interactions, plant—insect interactions and in plant development.

7.1. Apocarotenoids Promote Arbuscular Mycorrhizal Symbiosis and Have Antimicrobial Activities

The 9,10(9′10′) symmetric cleavage of diverse carotenoids by CCD1 results in the formation of a variety of C_{13} cyclohexone apocarotenoids, depending on the substrate, and rosafluene-dialdehyde (C_{14} dialdehyde) (**Figure 4**), corresponding to the central portion of the original carotenoid precursor [30]. Another route for the formation of C_{14} dialdehyde follows the cleavage of a C_{40} carotenoid by CCD7 or CCD4, resulting in a C_{27} apocarotenoid which is subsequently cleaved by CCD1 in the cytosol to form an addition C_{13} cyclohexone and rosafluene-dialdehyde (**Figure 2**) [42][62][124]. This C_{14} dialdehyde is thought to be the precursor of mycorradicin (10,10′-diapocarotene-10,10′-dioic acid), a yellow pigment that accumulates in the roots of plants infected with arbuscular mycorrhizal fungi [61]. Mycorradicin accumulates in the plastids in the roots and is stored as globules, which leads to changes in root morphology [125]. The accumulation of Mycorradicin seems to be associated with arbuscular mycorrhizal (AM) symbiosis [62][126]. The root symbiotic association of AM fungi (AMF) benefits the host plant by improving tolerance to biotic and abiotic stresses, mineral nutrition and impact plant developmental processes that effect root architecture flowering time, fruit and seed formation/quality [127][128][129].

Several C_{13} cyclohexone derivatives have also been identified in the same root tissue [61][126][130][131]. Application of blumenin (Blumenols), a C_{13} 3′-hydroxy cyclohexone carotenoid-derived product (likely derived from 3′-hydroxy-β-ionone; **Figure 2**) that accumulates in roots [61][130][132], strongly inhibits early fungal colonization and arbuscule formation, implying that cyclohexenone derivatives might act in the plant to control fungal spread [133]. Blumenols are classified into three groups: blumenol A, B and C. However, it is blumenol C glycosides that accumulate during mycorrhizal colonization, including in the roots of several plant species, i.e., tomato, barley and potato [134]. Wang et al. [134] also reported that blumenols accumulate in the shoots and leaves of plants with symbioses with arbuscular mycorrhizal fungi. These authors suggested that this accumulation may be useful, and potentially a universal indicator, of symbioses between different plants and fungi and that measuring blumenol levels in leaves, which would be quicker and simpler than trying to identify fungal symbioses in root soil samples, could be used by crop breeders to select cultivars that have better interactions with beneficial fungi (see [134] for review).

α-Ionone, derived from the 9′10 cleavage of α-carotene, inhibits the growth of multiple pathogenic fungi, including *Fusarium solani, Botrytis cinerea*, and *Verticillium dahliae* [135], *Colletotrichum musae* [136] and *Peronospora tabacina* [137]. β-ionone, derived from the 9′10 cleavage of β-carotene by CCD1/CCD4, has been shown to inhibit the sporulation and growth of *Peronospora tabacina,* a plant pathogenic fungus infecting tobacco [137][138]. Thus, it is possible that expression of CCD1A and CCD1B in vegetative tissues and fruit may have a role in the formation of multiple antimicrobial compounds.

7.2. Apocarotenoids Attract and Repel Insects

β-Ionone has been shown to repel both the flea beetle and the spider mite and provide a significant oviposition deterrence to whiteflies [139]. Moreover, β-ionone (and geraniol (isoform of geranial generated by CCD1)) has been shown to repel the crucifer flea beetles (*Phyllotreta cruciferae* (Goeze)) from *Brassica napus* (L.) leaves [140] and conversely attract Euglossa mandibularis (*Hymenoptera, Apidae*) males [141], suggesting that it could be used in ‘push’ and ‘pull’ strategies for controlling pests in different crops dependent on the predominant pest (for review on β-Ionone, see Paparella et al. [75]). Geranylacetone has also been shown to attract Longhorn beetles (*Asemum caseyi*) and is a constituent, along with fuscumol, in traps used to attract a related Longhorn beetle, *Asemum nitidum* [142]. β-cyclocitral emissions from strawberries have been shown to attract spotted wing drosophila (*Drosophila suzukii* (Matsmura)), a pest causing damage to ripening fruit [143]. Furthermore, additional studies showed that males had higher responses to β-cyclocitral than females, suggesting that males have a greater sensitivity to this compound [144]. α-ionone induces tomato plant resistance to western flower thrips (*Frankliniella occidentalis*, see [145]) and MHO increases in wheat seedlings following infestation by the aphid *Rhopalosiphum padi*, repelling the aphid [146]. MHO is also released after infestation of the aphid *Uroleucon jaceae*, attracting a parasitoid wasp (*Aphidius ervi*) [147]. Vogel et al. [31] suggested that the activity of the insect would disrupt chloroplast integrity, exposing the CCD1 enzymes located outside of the chloroplast to the lycopene substrate localized inside, causing the rapid increase in MHO upon infestation.

The potential for engineering volatile production in specific plant tissues could be a viable strategy to repel pest and/or attract pest predators that could result in a reduced requirement for pesticides. The over-expression of AtCCD1 in Arabidopsis, for example, was shown to induce β-ionone emission [139][148], reducing feeding damage by the crucifer flea beetle, suggesting that the over-expression of CCD1 in crop plants could provide a natural repellent for some pests.

7.3. Developmental Roles of Apocarotenoids

CDCs also play roles in plant development and plant defence. The most well-known CDCs, ABA and strigolactoes, formed by NCEDs and CCD7/CCD8, respectively, from neoxanthin (**Figure 1**) and β-carotene (**Figure 2**) are the most well studied. Other CDCs have also been shown to affect plant development. β-Cyclocitral, formed by the 7,8(7′8′) cleavage of β-carotene by CCD1/CCD4 activity, is an endogenous root compound that has been found to promote cell divisions in root meristems and to stimulate lateral root branching in Arabidopsis [149].

In *ccd1/ccd4* double mutants, β-Cyclocitral was shown to rescue meristematic cell division [149]. Application of β-cyclocitral to tomato and rice seedlings showed that it is a conserved root growth regulator across plant species resulting in a denser crown root systems in rice [149]. The positive effects of β-cyclocitral were also observed in plants grown in conditions of elevated salt and, and it was able to rescue rice roots, improving plant root depth and plant vigour [149]. This is consistent with the reports that β-cyclocitral mediates resilience to photooxidative stress [150][151] and initiates acclimation to high-light conditions [151]. Studies carried out in Arabidopsis have shown that β-cyclocitral acts as a messenger, conveying a singlet oxygen ($^1O_2$) stress signal to the nucleus, regulating the expression of $^1O_2$ responsive genes [151][152]. A similar activity has also been described for dihydroactinidiolide, a volatile formed by the oxidation of the carotenoid derived β-ionone by singlet oxygen [151]. The accumulation of β-Cyclocitral in root tissue is consistent with the expression of CCD1 [11] and CCD4 [153] in tomato and potato roots, respectively (For review, see D'Alessandro and Havaux, [154]).

Furthermore, the symmetrical cleavage of lutein and zeaxanthin at the 9,10(9′,10′) positions leads to the formation of 3-hydroxy-β-ionone and 3-hydroxy-α-ionone (**Figure 3**). The 3-hydroxy-β-ionone (also formed by the 9,10(9′,10′) cleavage of zeaxanthin; (**Figure 3**). accumulates in etiolated bean seedlings on exposure to light. This compound may have a function in the light-induced inhibition of hypocotyl elongation [155][156]. Kato-Noguchi and Seki [157] showed that 3-hydroxy-β-ionone, produced by the moss *Rhynchostegium pallidifolium* (Mitt.), which typically forms large colonies on rocks and soils, inhibited the growth of *Lepidium sativum* L. (cress). Applied exogenously, 3-hydroxy-β-ionone was shown to inhibit the growth of hypocotyls (conc. 1 µM) and roots (conc. 1 µM) of cress [157]. These data suggest that 3-hydroxy-β-ionone plays a role in maintaining pure *R*. *pallidifolium* colonies by acting as a defence mechanism to suppress the growth competitors.

This entry is adapted from 10.3390/plants10112321

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