Vitamin E synthesis and response in plants

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Vitamin E, also known as tocochromanol, is a lipid-soluble antioxidant that can only be produced by photosynthetic organisms in nature. Vitamin E is not only essential in human diets, but also required for plant environment adaptions. To synthesize vitamin E, specific prenyl groups needs to be incorporated with homogentisate as the first step of reaction. After decades of studies, an almost complete roadmap has been revealed for tocochromanol biosynthesis pathway. However, chlorophyll-derived prenyl precursors for synthesizing tocochromanols are still a mystery. In recent years, by employing forward genetic screening and genome-wide-association approaches, significant achievements were acquired in studying vitamin E. In this review, by summarizing the recent progresses in vitamin E, we provide to date the most updated whole view of vitamin E biosynthesis pathway. Also, we discussed about the role of vitamin E in plants stress response and its potential as signaling molecules.

KEYWORDS
vitamin E, VTE, tocopherol, tocochromanol, biosynthesis, pathway, stress, signal

Introduction

Vitamin E (also called tocochromanols) is an essential micronutrient for humans, which is produced by phototrophs such as plants, and some algae (Falk and Munné-Bosch, 2010). As antioxidant, vitamin E can convert free radicals into less reactive compounds, playing a pivotal role in human health (Zingg, 2007). Insufficient consumption of vitamin E could cause many diseases, including cancers, Alzheimer’s disease and cardiovascular disease, but not limited (Sen et al., 2007; Falk and Munné-Bosch, 2010; Sozen et al., 2019).

Tocochromanol molecule contains a polar chromanol ring head and a prenyl side chain. According to the various types of side chains, tocochromanols can be defined as tocopherol, tocotrienol, plastochromanol-8 (PC-8) and tocomonoenol (Figure 1). Tocopherol contains fully saturated aliphatic side chain, while the side chain of tocotrienol contains three extra trans double bonds. PC-8 has similar unsaturated as
tocotrienol but longer side chain, whereas tocopherol has only one double bond on its side chain (Tian et al., 2007; Sadre et al., 2010; Stacey et al., 2016). Based on the differences in numbers and positions of methyl groups on the chromanol ring head, tocochromanol isomers can be classified as α, β, γ, and δ (Figure 1). While for PC-8, only δ-form was found in nature (Kamal-Eldin and Appelqvist, 1996).

Tocopherols are ubiquitously synthesized in all plant species and especially abundant in photosynthetic tissues and seeds. Tocotrienols are mostly concentrated in monocot species like maize (Zea mays) embryo (Falk and Munné-Bosch, 2010), and the three extra double bonds in tocotrienols were believed to be able to confer greater potential for scavenging peroxyl radicals (Suzuki et al., 1993). PC-8 was first identified in the leaves of the rubber tree and later found to be also enriched in Brassica napus, tomato fruit, and tuber of Dioscorea alata (Goffman and Mollers, 2000; Cheng et al., 2007; Zbierak et al., 2010), and the concentrations of leaf PC-8 are differed by species and developmental stages (Whittle et al., 1965; Kruk et al., 2014). Studies of tocochromanol suggested that they were mainly accumulated in the seed oil from palm, Slovenia pumpkin and sunflower (Matsumoto et al., 1995; Butinar et al., 2011; Hammann et al., 2015), but the exact function of tocotrienols in planta are yet to be thoroughly verified.

In the past few decades, Arabidopsis thaliana has been employed as a plant model for dissecting tocopherol function and its biosynthesis pathway, and many key VTE (Vitamin E) enzymes were identified. Recently, by applying EMS-based forward genetic screening and genome-wide association study (GWAS), several key chlorophyll metabolic enzymes were identified to be required for tocopherol biosynthesis, including POR, CLD1 and VTE7 etc. (Lin et al., 2016; Diepenbrock et al., 2017; Wang et al., 2018; Hershberger et al., 2022; Wu et al., 2022). In this review, we summarize the recent progresses in tocochromanol biosynthesis, discussing the role of tocochromanol in plant stress response, and its potentials in signal transduction.

Biosynthesis of vitamin E

To produce tocochromanol, homogenitase (HGA) will be condensed with different prenyl chains by homogenitase phytyltransferase [HPT, also named VTE2 (Vitamin E 2 loci)], in one-to-one ratio (Figure 1). HPT genes can be found in all green plants, and some algae including cyanobacterium Synechocystis (Collakova and DellaPenna, 2001; Savidge et al., 2002). For tocopherols, HGA and phytyl diphosphate (PDP) are catalyzed by VTE2 to generate 2-methyl-6-phytyl-1,4-benzoquinol (MPBQ). VTE2 can also use the tetrahydrogeranylgeranyl pyrophosphate (THGGPP) to generate 2-methyl-6-tetrahydrogeranylgeranyl-1,4-benzoquinol (MTHGGBQ) for producing tocopherol in Arabidopsis seeds (Pellaud et al., 2018). In monocots, homogenitase geranylgeranyl transferases (HGGTs) are seed-specific and plastid-targeted, which can condense geranylgeranyl pyrophosphate (GGDP) instead of PDP with HGA to generate 2-methyl-6-geranylgeranyl-1,4-benzoquinol (MGGBQ) for tocotrienol biosynthesis (Cahoon et al., 2003; Yang et al., 2011). Although HGGT and VTE2 are close in structure, their enzyme activities toward different substrates vary quite much. For example, the activity of barley HPPT toward GGDP is 6 times higher than that of PDP; the VTE2 enzyme confers 9 times higher activity toward PDP than that of GGDP. Interestingly, barley HPPT can restore the levels of both tocopherols and tocotrienols in Arabidopsis vte2 mutant (Yang et al., 2011). Moreover, homogenitase solanesyltransferase (HST) can condense HGA and solanesyl pyrophosphate (SPP) to produce the 2-methyl-6-solanesyl-1,4-benzoquinol (MSBQ), the precursor of PC-8 (Sadre et al., 2006; Tian et al., 2007).

The downstream of vitamin E biosynthesis pathway is divided into two branches. In one branch, the MPBQ, MGGBQ, MSBQ, and MTHGGBQ are methylated by a methyltransferase (MT, VTE3) to produce DMPBQ, DMGGBQ, DMTHGBQ, and DMSBQ (PQ-9), respectively, the precursors of α- and γ-tocochromanols (Cheng et al., 2003; Van Eenennaam et al., 2003). Then the methylated compounds are cyclized by tocopherol cyclase (TC, VTE1) to produce γ-tocochromanols (Cheng et al., 2003). In the other branch of this pathway, the demethylated compounds (MPBQ, MGGBQ, MSBQ, and MTHGGBQ) are cyclized directly by VTE1 to produce δ-tocochromanols (Cheng et al., 2003). In the final step, the γ- and δ-tocochromanols, respectively, are methylated to produce α- and β-tocochromanols by γ-tocopherol methyltransferase (γ-TMT; VTE4) (Shintani and DellaPenna, 1998; Bergmüller et al., 2003).

Biosynthesis of tocochromanol is mainly carried out in the plastid, but one of its main precursors HGA, which provides the chromanol ring head for tocochromanol, is produced during L-tyrosine (Tyr) degradation in the cytoplasm (Figure 1). Through the shikimate pathway, tyrosine aminotransferases (TATs) catalyze reversible reaction between Tyr and 4-hydroxyphenylpyruvate (HPP), and at least two homologous genes TAT1 and TAT2 were identified in the genome of Arabidopsis thaliana (Siehl et al., 2014; Stacey et al., 2016; Wang et al., 2016). Arabidopsis TAT1 gene loss of function mutant showed reduced tocopherols under normal condition (Riewe et al., 2012), but the tat2 single mutants have no effect on Tyr and tocopherol levels. In the tat1 tat2 double mutants, compared with wild-type and tat single mutants, more Tyr were accumulated and fewer tocopherols were maintained, and this effect was amplified under high-light stress (Wang et al., 2019). TAT1 and TAT2 thus work redundantly in Tyr degradation and tocopherol biosynthesis, with TAT1 playing a major role. Then, HPP is converted to HGA by the 4-hydroxyphenylpyruvate dioxygenase (HPPD), which is encoded by a single-copy gene
FIGURE 1
Plant tocochromanol biosynthesis pathway and sources of metabolites. Metabolite names were colored for recognizing different tocochromanol synthesis pathways. Abbreviations of metabolites: HPP, 4-hydroxyphenylpyruvate; HGA, homogentisate; Phytol-P, phytol-phosphate; PDP, phytol-diphosphate; THGGPP, tetrahydrogeranylgeranyl pyrophosphate; GGDP, geranylgeranyl pyrophosphate; SPP, solanesyl pyrophosphate; MPBQ, 2-methyl-6-phytyl-1,4-benzoquinol; DMPBQ, 2,3-dimethyl-6-phytyl-1,4-benzoquinol. Abbreviations of enzymes: TAT1, tyrosine aminotransferase 1; TAT2, tyrosine aminotransferase 2; HPPD, 4-hydroxyphenylpyruvate dioxygenase; CLD1, chlorophyll dephytylase 1; PPH, pheophytin pheophorbide hydrolase; VTE, vitamin E biosynthetic enzyme.

In Arabidopsis (Tsegaye et al., 2002). However, HPPDs possess different subcellular localizations according to studies in various plant species (Pellaud and Mène-Saffrané, 2017). For example, HPPD proteins of Spinacia oleracea, Lemma gibba and maize are targeted to plastids, while in carrot and Arabidopsis they are located in the cytoplasm (Löffelhardt and Kindl, 1979; Fiedler et al., 1982; Garcia et al., 1997; Siehl et al., 2014; Wang et al., 2016).

Another main precursor of tocopherols comes from phytol diphosphate (PDP), which is generated from two steps of phosphorylation relay using phytol (Gutbrod et al., 2019). The first step is to generate phytol-phosphate via VTE5 (phytol kinase), which accounts for 80% and 50% total tocopherol biosynthesis in Arabidopsis seeds and leaves, respectively (Valentin et al., 2006). The second step is executed by VTE6 (phytol phosphate kinase), and due to over accumulation of phytol-phosphate, vte6 mutant plant confers severe growth defects. By introducing vte5 into the vte6 background, the vte5 vte6 double mutant resembles wild-type in plant growth, but showing tocopherol deficient and high levels of accumulated chlorophylls (Vom Dorp et al., 2015). GGDP, SPP and THGGPP are the polypropenyl chain precursors of...
tocotrienols, PC-8 and tocomicronoens, respectively (Méné-Saffrané, 2018). Of note, all of the four tocochromanol isoprenoid side chains can be produced by GGDP synthases (Pellaud and Méné-Saffrané, 2017).

However, accumulated studies have suggested that the phytol group used for tocopherol biosynthesis mostly comes from the chlorophyll degradation (Valentin et al., 2006; Guibrod et al., 2019). Thus, finding the relevant hydrolases that can bring down phytol group from chlorophyll and/or chlorophyll derivatives is key for dissecting tocopherol biosynthesis pathway. The first chlorophyllase (CLH) was isolated from Citrus sinensis, which shows activity toward chlorophylls, and two CLH genes (AtCLH1 and AtCLH2) were found in Arabidopsis (Jacob-Wilk et al., 1999; Tsuchiya et al., 1999). The highest transcripts of AtCLH1 and AtCLH2 were found in young leaves and their levels decline gradually during leaf maturation (Chen et al., 2014; Tian et al., 2021). However, previous studies had shown that the two Arabidopsis CLHs were not required for chlorophyll breakdown during leaf senescence. In addition, CLH proteins are targeted to vacuole instead of chloroplasts. Based on functional genomic approach with the features of senescence-regulated gene expression and chloroplast targeting, Schelbert et al. identified a hydrolase called pheophytin phosphatase hydrolyase (PPH) in Arabidopsis. The PPH mutant showed stay-green phenotype during senescence, compared with its wild-type control. In vitro, PPH confers specific activity toward pheophytin but not chlorophylls (Schelbert et al., 2009). Recently, through EMS screening for Arabidopsis heat-sensitive progenies, an Arabidopsis CHLOROPHYLL DEPHYTYLASE1 (CLD1) gene was identified. A G-to-A transition at position 957 of cld1 gene results in the replacement of Gly-193 by Asp (G193D), which confers much higher activity of cld1 toward both chlorophylls and pheophytin than that of its native CLD1 (Lin et al., 2016). Following studies found about 15% tocopherol increase in CLD1 and cld1 overexpression plants, but no significant difference in its miRNA lines (Lin and Chiang, 2017). Although CLHs, PPH and CLD1 can cleave phytol directly from chlorophyll and/or pheophytin, none of the single or high order mutants (clh1/clh2, pph, and pph/clh1/clh2) significantly affect tocopherol contents. Moreover, overexpression of the four genes only moderately increased the levels of tocopherol, suggesting the relevant alpha/beta hydrolase is yet to be identified (Zhang et al., 2014; Lin and Chiang, 2017). Recently, GWAS of seed tocopherols was applied using 814 Arabidopsis natural variation lines (part of the 1001 Arabidopsis Genome Panel, Alonso-Blanco et al., 2016), a novel seed-specific alpha/beta hydrolase gene AtVTE7 was identified. AtVTE7 is targeted to the chloroplast envelope and accounts for 55% of total seed tocopherols. Consistent with the results in Arabidopsis, the maize orthologous gene ZmVTE7 controls 38% and 49% total tocopherols in kernel and leaf, respectively (Albert et al., 2022). Of note, Arabidopsis AtVTE7 is only detected in seed, does not affect tocopherol trait in leaf. Although VTE7 can provide phytol from chlorophyll degradation for tocopherol biosynthesis, this enzyme mainly affects the levels of chlorophyll biosynthetic intermediates, instead of bulk chlorophyll levels (Albert et al., 2022).

In addition to the alpha/beta hydrolases that are directly involved in phytol production, many chlorophyll-metabolism-related genes also contribute to tocopherol homeostasis. For instance, plant NYE [Non-Yellowing, also named SGR (Stay-Green)] are chloroplast-localized Mg-dechelatase proteins, and during chlorophyll degradation NYEs closely cooperate with other chlorophyll catabolic enzymes including PPH (Armstead et al., 2007; Sato et al., 2007; Zhang et al., 2014). Indeed, the seed tocopherol levels of the Arabidopsis double mutant nye1 nye2 modestly reduced, compared with that in the wild-type (Zhang et al., 2014). Chlorophyll synthesis needs the esterizing of chlorophyllide with either GGDP or PDP. The RNAi lines of CHLOROPHYLL SYNTHASE (CHLSYN) exhibit significantly reduced chlorophylls but up to 2 times increased tocopherols (Zhang et al., 2015). Moreover, two QTLs that encode homologs of protochlorophyllide reductase (POR1 and 2) were revealed in maize, and the two por loci had the highest phenotypic variance explained for all four forms of tocopherols calculated (Diepenbrock et al., 2017; Wang et al., 2018). Thus, disturbing the genes involved chlorophyll metabolism can affect tocopherol biosynthesis, suggesting a precise mechanism for balancing chlorophyll metabolism and tocopherol biosynthesis in plants.

**Vitamin E in stress response**

As important antioxidants, tocopherolins can be boosted to high levels during various biotic and abiotic stresses (Figures 2, 3) (Bao et al., 2020). Meanwhile, plants with low levels of tocopherolins are more susceptible to different stressful treatments, suggesting a crucial role of vitamin E in plant environment adaptions.

Temperature and light intensity are the two key environmental factors that can affect crop yield (Pretty et al., 2010). During high light and heat stress, tocopherolins (especially α-tocopherolins) are induced to accumulate at high levels, and elevated α-tocopherolins were believed to be required for protecting photosystem from savaging singlet oxygen and maintaining the stability of chloroplast (Kruk et al., 2005). Indeed, tocopherol deficient Arabidopsis mutants are more vulnerable to high light (Kobayashi and DellaPenna, 2008). When grown under low temperature, vitamin E deficient mutants are retarded in plant growth (Maeda et al., 2006), which mainly attributes to defects in phloem loading, coincide with the findings in maize and potato (Solanum tuberosum) (Russin et al., 1996; Hofius et al., 2004). The combination of high light and high temperature causes strong lipid peroxidation and photooxidative stresses to Arabidopsis, and this effect was exemplified in vte1 mutant (Havaux et al., 2005). In
plants display a strong chlorotic phenotype with low levels of α-tocopherol under the stress combined with high-light and high-temperature (Spicher et al., 2017). Moreover, high-light stress also triggers the expression of HPPDs in Medicago sativa and Lactuca sativa for counteracting and survival strategies (Ren et al., 2011; Jiang et al., 2017).

Drought is one of the most common stresses in limiting farming, which leads to significant yield losses (Godwin and Farrona, 2020). The capacity of HPPDs to resist drought has also been demonstrated in various plant species, including Lactuca sativa, Medicago and sweet potato (Ren et al., 2011; Jiang et al., 2017; Kim et al., 2021). In rice, OsVTE1 is induced to significantly high levels under drought stress (Ouyang et al., 2011), and ectopic overexpression of AtVTE1 in tobacco can enhance tolerance to drought stress via reducing lipid peroxidation, electrolyte leakage and \( \text{H}_2\text{O}_2 \) content (Liu et al., 2008). Moreover, overexpression of MsVTE4 increases the levels of both α-tocopherols and total tocopherols in alfalfa, alleviating oxidative damages, leading to higher tolerance to drought stress (Ma et al., 2020).

Soil with unfavorable high level of soluble salts causes salinity stress in plants, limiting crop yield and the area for farming. In tobacco (Nicotiana tabacum) VTE2 silenced plants, total tocopherols decreased 98%, and ion homeostasis was disturbed with sorbitol and methyl viologen treatment (Abbasi et al., 2007). Meanwhile, in tobacco VTE4 silenced plants, α- and γ-tocopherols were found to play diversified roles in plant stress tolerance (Abbasi et al., 2007). On the other hand, overexpressing AtVTE4 can reduce superoxide contents, lipid peroxidation and ion leakage under salt stress (Jin and Daniell, 2014). By employing Arabidopsis tocopherol deficient mutants vte1 (deficient in α- and γ-tocopherols) and vte4

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FIGURE 2
Representative HPLC traces of Arabidopsis leaf tocopherols subjected to different growth conditions (high light, heat, and dark). Tocol is used as internal standard (based on Bao et al. (2020), with modification).

FIGURE 3
A proposed working model of the vitamin E in signal transduction. Chilling stress can be sensed by COLD1 to regulate calcium signal and tocochromanol homeostasis for transcriptional reprogramming in the nucleus. Other stresses including high-light and heat can also transduce retrograde signaling between chloroplast and nucleus for miRNA biogenesis, via manipulating PAP (3′-phosphoadenosine-5′-phosphate) and tocochromanols.
Vitamin E in signal transduction

Vitamin E has long been assessed and studied as an antioxidant, but emerging evidences strongly suggested that vitamin E may also serve as signaling molecules in plants. Reactive oxygen species (ROS) such as hydroperoxide and single oxygen that produced in the photosystem have been shown as important signals in the communications between chloroplast and gene expression in the nucleus (Figure 3) (Foyer and Noctor, 2003, 2005). When single oxygen accumulated in the chloroplast, tocopherols will be oxidized to produce tocopheryl radical and hydroperoxide. Reversibly, these two products can be reduced to tocopherols by introducing ascorbate (also known as vitamin C) (Neely et al., 1988). Thus, through eliminating ROS, vitamin E may also serve as signaling molecules in plants.

For instance, tocopherol deficient \textit{vte1} mutants, Cela et al. found that altered tocopherol compositions could reduce plant tolerance and delay the activation of defense pathway (Cela et al., 2018).

Studies in human and animals suggested that tocopherol-binding protein (TBP) is important for the distribution and transport of \(\alpha\)-tocopherol among different tissues. In the latest research, Bermúdez et al. identified the \textit{SITBP} (\textit{Solanum lycopersicum} tocopherol-binding protein) as a homolog of the human \(\alpha\)-tocopherol transfer protein (HsTTP). In vitro biochemical assay suggested that \textit{SITBP} possesses \(\alpha\)-tocopherol binding ability. \textit{SITBP} is chloroplast-targeted, and knocking down \textit{SITBP} expression in tomato confers disorders in tocopherol, carotenoid and lipid compositions.

Future perspectives

Studies in \textit{Arabidopsis} indicated that 90% and more of the total tocopherols (~5 ng/mg fresh weight) in leaves are \(\alpha\)-tocopherol, while in \textit{Arabidopsis} seeds, tocopherols (~370 ng/mg dry seed) are dominated by the \(\gamma\) isofrom. Crucial physiological functions of vitamin E for plants were exemplified by the observation that tocopherol defective \textit{Arabidopsis} mutants were severely affected in seed longevity, germination and seedling growth (Sattler et al., 2004). Differential regulation of the same cassette of genes for tocochromanol biosynthesis in different tissues warrants for future explorations.
in green plants, and accumulated evidences suggested that chlorophyll-derived phytol groups are the main source for vitamin E biosynthesis (Gutbrod et al., 2019). VTE7 is a novel alpha/beta hydrolase that fits in the missing gap between chlorophyll metabolism and vitamin E production, accounting for more than 50% of total tocopherol biosynthesis in seeds. However, its exact targets still need to be verified. In recent years, tocopherols were found to be involved in both cold response and PAP-mediated retrograde signal transduction. In addition, tocopherol binding protein (TBP) was identified in tomato. Thus, role of tocopherols in acting as signaling transducers are promising and deserved to be investigated in depth. More importantly, as an essential nutrient, engineering balanced vitamin E in crops like soybean, rapeseed will advance plant breeding and benefit human health.

Author contributions

YB concepted the topic of this manuscript and revised the manuscript. YN and QZ drafted the manuscript with YB. All authors contributed to the article and approved the submitted version.

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