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Kaempferol as a precursor for ubiquinone (coenzyme Q) biosynthesis: An atypical node between specialized metabolism and primary metabolism

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Abstract

Ubiquinone (coenzyme Q) is a vital respiratory cofactor and liposoluble antioxidant. Studies have shown that plants derive approximately a quarter of 4-hydroxybenzoate, which serves as the direct ring precursor of ubiquinone, from the catabolism of kaempferol. Biochemical and genetic evidence suggests that the release of 4-hydroxybenzoate from kaempferol is catalyzed by heme-dependent peroxidases and that 3-O-glycosylations of kaempferol act as a negative regulator of this process. These findings not only represent an atypical instance of primary metabolite being derived from specialized metabolism but also raise the question as to whether ubiquinone contributes to the ROS scavenging and signaling functions already established for flavonols.

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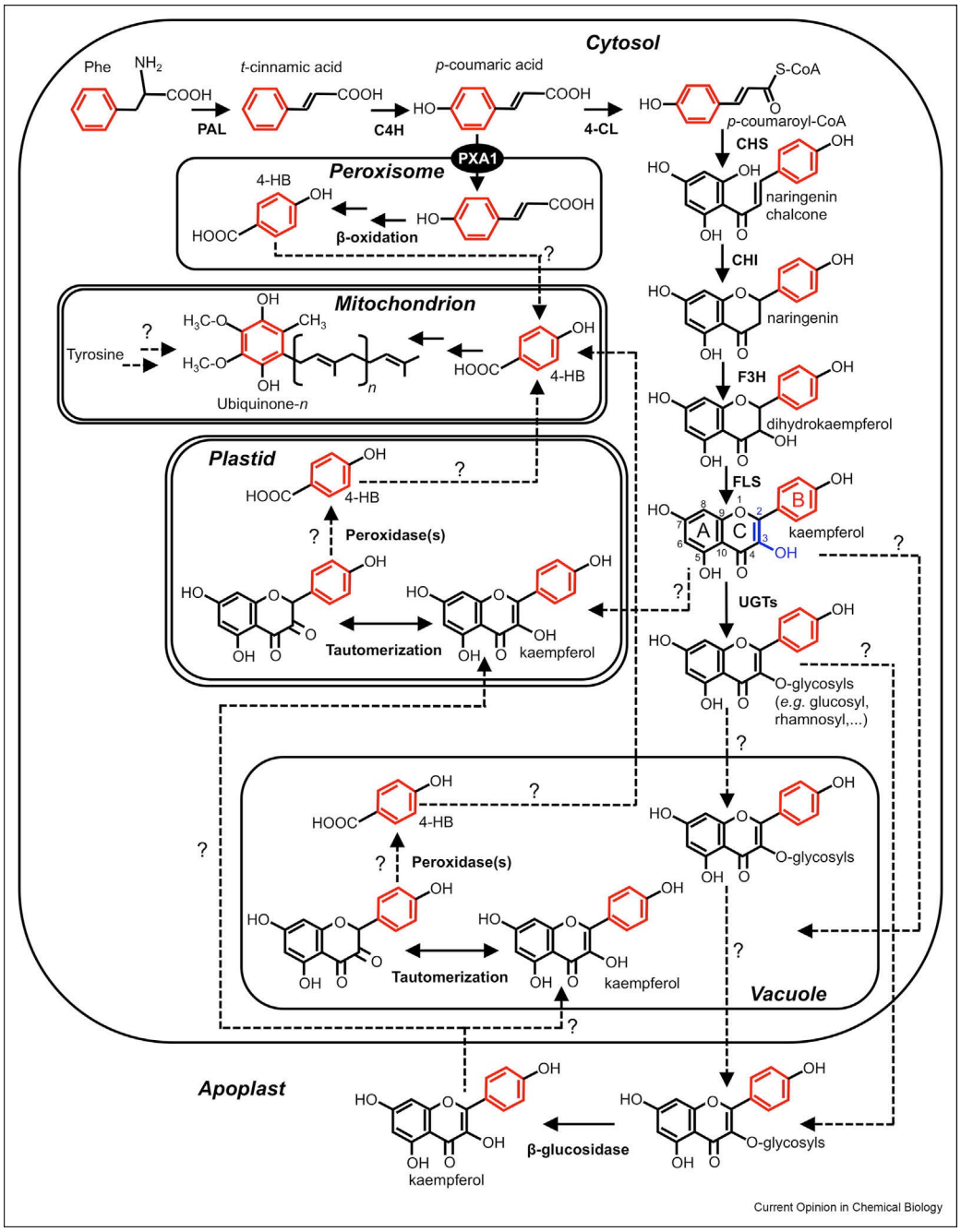
Introduction

Flavonoids represent one of the largest classes of specialized metabolites and are often depicted as signature compounds of land plants [1*,2]. Functions most commonly attributed to the evolution and diversification of flavonoids include photoprotection [3,4], scavenging of reactive oxygen species (ROS) and redox homeostasis [5–8*], regulation of auxin transport [9–11], pollinator attraction [12], resistance to pathogens [13,14], and modulation of stomata aperture [6,15], pollen tube growth [8*], and root development [5,16**–18]. The recent finding that in Arabidopsis and tomato, the catabolism of the flavonol kaempferol generates 4-hydroxybenzoate (4-HB), the aromatic ring precursor of the vital respiratory cofactor and antioxidant ubiquinone (coenzyme Q), is not only a surprising addition to the functional repertoire of flavonoids but also blurs the historical classification of these compounds as archetypal specialized metabolites. Indeed, although it has long been known that flavonoids can serve as precursors for other specialized metabolites (e.g. anthocyanins, chalconoids), the atypical feature of the metabolic node discussed in this review is that one of the breakdown products of a flavonol is re-routed toward the biosynthesis of a primary metabolite.

Here, it must be said that kaempferol is not the exclusive supplier of 4-HB in plant cells and that the bulk of 4-HB for ubiquinone biosynthesis actually originates from the b-oxidation of p-coumarate in peroxisomes (Figure 1; [19,20]). There is also evidence that plants, like yeast and vertebrates, have evolved the ability to use tyrosine as a precursor of ubiquinone's ring [19]; none of the enzymes of this alternative pathway are known in plants. To put the contribution of each of these metabolic branches into perspective, heavy isotope feeding assays and reverse genetics indicate that in Arabidopsis, about 50% of the pool of ubiquinone's ring precursor originates from the b-oxidation of p-coumarate, while kaempferol cleavage and tyrosine metabolism each provides about 25% [19,20]. In tomato leaves, blockage of the flavonoid biosynthetic pathway upstream of flavonols indicates that at least 20% of the pool of ubiquinone's ring precursor comes from kaempferol [21**].

This review focuses on the branchepoint between the biosynthetic pathways of flavonols and ubiquinone, the mechanism of release of 4-HB from kaempferol, and the evolutionary and physiological significance of the metabolic connections between these compounds. For

Figure 1



Biosynthesis of the aromatic ring of ubiquinone (coenzyme Q) in plant cells. The double bond between C-2 and C-3 and the hydroxyl group on C-3 of the C-ring that are critical for the formation of the a-diketone tautomer of kaempferol are highlighted in blue. n designates the number of isoprenyl residues in the prenyl moiety of ubiquinone; this number can vary between species, e.g. n = 9 in Arabidopsis and rice, n = 10 in tomato and tobacco. Note that the subcellular compartmentalization of flavonol modifying enzymes and of peroxidases acting on kaempferol is a composite view reconstituted from studies in different plant taxa, and therefore that the corresponding steps may be species-specific. Dashed arrows indicate putative steps. 4-CL, p-coumaroyl-CoA ligase; 4-HB, 4-hydroxybenzoate; C4H, cinnamate-4-hydroxylase; CHI, chalcone isomerase; CHS, chalcone synthase; F3H, flavanone-3-hydroxylase; FLS, flavonol synthase; PAL, phenylalanine ammonia-lyase; PXA1, Peroxisomal ABC transporter 1; UGTs, UDP-carbohydrate-dependent glycosyltransferases.

more general considerations on the biosynthesis of flavonoids and ubiquinone, we refer the reader to the following comprehensive publications [22e24]. Additional examples of unusual metabolic arrangements, where specialized compounds re-enter primary metabolism as biosynthetic precursors (e.g. retrograde flow of sulfur from glucosinolates for cysteine biosynthesis [25]), are covered separately in this issue.

Kaempferol is the node metabolite between the biosynthetic pathway of flavonols and that of ubiquinone

Hints of the existence of a functional connection between the metabolism of flavonoids and that of ubiquinone in plants originate from gene coexpression analyses in Arabidopsis [21**]. Quantification of ubiquinone in a series of Arabidopsis flavonoid biosynthetic mutants showed that blockage of the pathway up to the flavanone-3-hydroxylase (F3H) catalyzed-reaction resulted in a decrease in ubiquinone content, while null mutations downstream of this step did not (Figure 1; [21**]). Furthermore, when added to axenic cultures of F3H knockout plants, dihydrokaempferol or kaempferol, but not naringenin, boosted ubiquinone content at or above wild-type level [21**]. Isotopic tracer experiments using ^{13}C-labeled phenylalanine and ^{13}C-labeled-kaempferol in Arabidopsis confirmed these findings while simultaneously pinpointing the B-ring of kaempferol as the part of the flavonoid scaffold that was incorporated into ubiquinone (Figure 1; [21**]). There is also evidence that the tomato anthocyanin reduced (are) mutant, which carries a point mutation in the F3H gene, displays a decrease in ubiquinone content similar to that observed in the Arabidopsis F3H mutant [21**]. Conversely, tomato fruits engineered to boost flavonol content were found to accumulate up to twice as much ubiquinone than their wild-type counterparts [21**].

Heme-dependent peroxidases likely release 4-hydroxybenzoate from the a-diketone tautomer of kaempferol

The immediate precursor of ubiquinone's benzenoid ring is 4-HB. A mechanistic model based on the peroxidative cleavage of kaempferol has been proposed to explain the release of 4-HB from this flavonol's B-ring [21**]. Notably, this model predicts that it is not kaempferol itself that is cleaved, but its a-diketone tautomer (Figure 1). Two structural features of the C-ring of kaempferol dictate this process: the presence of a double bond between C-2 and C-3 and a free hydroxyl group on C-3 (Figure 1). Compelling biochemical and genetic evidence supports the model: (i) The H_2O_2-dependent release of 4-HB from kaempferol is readily detected in Arabidopsis leaf extracts; this activity is saturable and is highly sensitive to sodium azide, a prosthetic-heme group inhibitor [21**]. The corresponding heme-dependent peroxidases have not yet been identified. (ii) Blockage of the hydroxyl group on C-3 via glycosylation prevents the H_2O_2-dependent cleavage of kaempferol in vitro [21**]. There is indirect evidence that the same mechanism operates in vivo [26, see next section]. (iii) Naringenin, which lacks a double bond between C-2 and C-3 and a hydroxyl group on C-3 (Figure 1), and dihydrokaempferol, which lacks the C-2/C-3 double bond (Figure 1), are also fully resistant to peroxidative cleavage in vitro [21**].

3-O-glycosylations of kaempferol represent a bottleneck in ubiquinone biosynthesis in vivo

That chemical modification of the C-3 hydroxyl of flavonols prevents the formation of the corresponding a-diketone tautomers, and thus, protects these molecules from peroxidative cleavage is physiologically significant because in plant tissues, kaempferol occurs almost exclusively as glycosyl conjugates [10,27]. In Arabidopsis, loss of function of flavonol 3-O-glucosyltransferase and of flavonol 3-O-rhamnosyltransferase, which together bear the bulk of the activities of 3-O-glycosylation of kaempferol, has been shown to result in an increase in the incorporation of phenylalanine into the benzenoid moiety of ubiquinone, as well as in an increase in ubiquinone content [26]. In contrast, knocking out flavonol 3-O-arabinosyltransferase did not have any impact on ubiquinone biosynthesis [26]. Interestingly, the boost in ubiquinone content in the flavonol 3-O-glucosyltransferase/flavonol 3-O-rhamnosyltransferase double knockout was virtually identical to that observed for axenic cultures of wild-type plants fed with saturating doses of 4-HB [26]. These observations suggest that the supply of 4-HB limits ubiquinone biosynthesis in plant tissues and that the glycosylation of kaempferol contributes to such a bottleneck in the pathway. Conversely, it is logical to expect that deglycosylation of kaempferol at the C-3 hydroxyl position would increase the availability of 4-HB for ubiquinone biosynthesis. There are reports of plant b-glucosidases that hydrolyze kaempferol 3-O-b-glucoside [28,29], but the extent to which these enzymes may impact ubiquinone biosynthesis is not known.

Evolutionary and physiological significance of the connection between the catabolism of kaempferol and the biosynthesis of ubiquinone

Flavonols are widely distributed and even possibly ubiquitous in Angiosperms, Gymnosperms, ferns, and liverworts, while in other groups of Archaeplastida, flavonols are either absent (e.g. hornworts, lycophytes) or seem to occur only sporadically and/or at trace levels (e.g. Chlorophytes, Rhodophytes, mosses) [30–33]. UV-B screening, ROS scavenging, and the regulation of the actions of auxins and abscisic acid are usually cited as the selection drivers for the emergence of flavonoids in land plants [1*], and some authors have proposed that flavonols could be central to these adaptive mechanisms [2]. The metabolic connection between kaempferol and ubiquinone invites the question as to whether ubiquinone could contribute to some of the cellular functions that have so far been attributed exclusively to flavonoids. This applies in particular to the antioxidant activity of flavonols because ubiquinone is, together with carotenoids, tocopherols, and estrogens, one of the major liposoluble scavengers of reactive oxygen species

(ROS) in eukaryotes [34–36]. Of outstanding interest here is the recent demonstration that in Arabidopsis, the level of kaempferol in lateral root primordia inversely correlates with that of ROS, which in turn controls lateral root emergence [16**]. Moreover, reverse genetics and correlation analysis between flavonol content and number of lateral roots suggested that the two other major flavonols in Arabidopsis, quercetin, and isorhamnetin, did not play a role in this regulatory mechanism [16**]. Incidentally, there is also evidence that the cleavage product from the B-ring of quercetin, 3,4-dihydroxybenzoate, does not serve as a ring precursor for ubiquinone biosynthesis in plants [19]. Inverse correlations between flavonol content and ROS accumulation have also been shown to be central to pollen viability and tube growth and abscisic acid-dependent stomatal closure [6, 8*, 15]. Even if in such instances the significance of specific flavonol species was not investigated, it is tempting to speculate that ubiquinone, via the catabolism of kaempferol, may contribute to these developmental and regulatory processes. In contrast, there is firm evidence that despite the parallel upregulation of flavonoid and ubiquinone biosynthesis in response to high-light stress, the increase in ubiquinone production in high light is independent of kaempferol catabolism [20].

One should not end this section without mentioning that mammalian cells have also been shown to readily use exogenous kaempferol as an aromatic ring precursor for ubiquinone biosynthesis [37*]. Isotopic tracer experiments demonstrated that here again, it was specifically the B-ring of kaempferol that was incorporated into ubiquinone [38]. Notably, naringenin was shown to have no significant effect on ubiquinone biosynthesis when fed to these cell cultures [37*]. These observations are strikingly similar to those made with plants, and suggest that in mammalian cells as well the incorporation of the B-ring of kaempferol into ubiquinone proceeds via the direct oxidative release of 4-HB. It is not known, however, if in mammalian cells such a cleavage is enzymatic or simply results from the spontaneous oxidation of kaempferol. More surprising perhaps is the case of the yeast Saccharomyces cerevisiae, which despite having evolved a plant-dependent saprophytic lifestyle, makes only marginal use of exogenous kaempferol for ubiquinone biosynthesis [37*].

Conclusions and future directions

Beyond the semantic consideration as to whether kaempferol and its flavonoid precursors should still be considered exclusively as specialized metabolites, the discovery that the upper branch of the core flavonoid biosynthetic pathway feeds into the assembly of a respiratory cofactor opens several new frontiers for investigations. For instance, finding out how widespread is the occurrence of the functional link between kaempferol and ubiquinone across plant lineages will help understand when this metabolic branch point evolved during plant evolution and how strong the selection pressure is for its maintenance. Moreover, because even modest changes in ubiquinone level have a major impact on ROS scavenging in plant tissues [35,39], identifying the enzymatic components that control the release of 4-HB from kaempferol —in particular kaempferol 3-O-b-glycosidase(s) and kaempferol peroxidase(s)— might provide new tools to boost ubiquinone content and oxidative stress tolerance in plant cells.

Learning about the subcellular localization of these enzymes is also important because the prenylation and further modifications of 4-HB for ubiquinone biosynthesis take place in mitochondria [40–43], while kaempferol is synthesized in the cytosol and its glycosyl conjugates are stored primarily in the vacuole [44–46]. The identification of a b-glucosidase that frees the C-3 hydroxyl position of flavonols in the apoplast [28] and of peroxidases acting on kaempferol in the vacuole and in plastids [47,48] suggest that kaempferol glycosides, kaempferol, and 4-HB are subjected to a complex intracellular —and possibly intercellular— trafficking. Each of the cognate transport steps thus represents potential bottlenecks in the supply of 4-HB for ubiquinone biosynthesis. Furthermore, plant tissues readily glycosylate 4-HB and here again store the resulting conjugates in the vacuole, where they appear to be unavailable for ubiquinone biosynthesis [26]. Therefore, it seems likely that plants have evolved mechanisms — e.g. channeling, carrier proteins— to protect 4-HB prior to its import in mitochondria. Last, the availability of Arabidopsis mutants and silenced transgenics that have marked defects in ubiquinone accumulation, but a priori intact flavonol metabolism (e.g. Refs. [19,49,50]), should help answer the intriguing question as to whether ubiquinone contributes to ROS scavenging and signaling in lateral root emergence, pollen development, and stomatal aperture.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. * Davies KM, Jibran R, Zhou Y, Albert NW, Brummell DA, Jordan BR, Bowman JL, Schwinn KE: The evolution of flavonoid biosynthesis: a bryophyte perspective. Front Plant Sci 2020, 11:7.

An excellent introduction to flavonoid functions in plants. This article also provides a historical perspective on the main hypotheses for the emergence of different groups of flavonoids throughout plant lineages.

2. Brunetti C, Sebastiani F, Tattini M: Review: ABA, flavonols, and the evolvability of land plants. Plant Sci 2019, 280:448–454.

3. Harvaux M, Kloppstech K: The protective functions of carotenoid and flavonoid pigments against excess visible radiation at chilling temperature investigated in Arabidopsis npq and tt mutants. Planta 2001, 213:953–966.

4. Li J, Ou-Lee TM, Raba R, Amundson RG, Last RL: Arabidopsis flavonoid mutants are hypersensitive to UV-B irradiation. Plant Cell 1993, 5:171 –179.

5. Gayomba SR, Muday GK: Flavonols regulate root hair development by modulating accumulation of reactive oxygen species in the root epidermis. Development 2020, 147. dev185819.

6. Watkins JM, Chapman JM, Muday GK: Abscisic acid-induced reactive oxygen species are modulated by flavonols to control stomata aperture. Plant Physiol 2017, 175:1807–1825.

7. Sugimoto K, Zager JJ, Aubin BS, Lange BM, Howe GA: Flavonoid deficiency disrupts redox homeostasis and terpenoid biosynthesis in glandular trichomes of tomato. Plant Physiol 2021, https://doi.org/10.1093/plphys/kiab488. Epub ahead of print.

8. * Muhlemann JK, Younts TLB, Muday GK: Flavonols control pollen tube growth and integrity by regulating ROS homeostasis during high-temperature stress. Proc Natl Acad Sci USA 2018, 115:E11188–E11197.

Compelling evidence that a decrease in flavonol content resulting from a loss of function of flavanone-3-hydroxylase in tomato results in an increase in ROS level and a parallel decrease in pollen tube growth and integrity. Note that because loss of flavanone-3-hydroxylase impacts the accumulation of quercetin and kaempferol, defects in pollen viability and development could result from a decrease in either or both of these flavonols.

9. Brown DE, Rashotte AM, Murphy AS, Normanly J, Tague BW, Peer WA, Taiz L, Muday GK: Flavonoids act as negative regulators of auxin transport in vivo in arabidopsis. Plant Physiol 2001, 126:524–535.

10. Buer CS, Kordbacheh F, Truong TT, Hocart CH, Djordjevic MA: Alteration of flavonoid accumulation patterns in transparent testa mutants disturbs auxin transport, gravity responses, and imparts long-term effects on root and shoot architecture. Planta 2013, 238:171–189.

11. Teale WD, Pasternak T, Dal Bosco C, Dovzhenko A, Kratzat K, Bildl W, Schwörer M, Falk T, Ruperti B, Schaefer JV, Shahriari M, Pilgermayer L, Li X, Lübben F, Plückthun A, Schulte U, Palme K: Flavonol-mediated stabilization of PIN efflux complexes regulates polar auxin transport. EMBO J 2021, 40, e104416.

12. Kellenberger RT, Byers KJRP, De Brito Francisco RM, Staedler YM, LaFountain AM, Schönenberger J, Schiestl FP, Schlüter PM: Emergence of a floral colour polymorphism by pollinator-mediated overdominance. Nat Commun 2019, 10:63.

13. Yang Z, Li N, Kitano T, Li P, Spindel JE, Wang L, Bai G, Xiao Y, McCouch SR, Ishihara A, Zhang J, Yang X, Chen Z, Wei J, Ge H, Jander G, Yan J: Genetic mapping identifies a rice naringenin O-glucosyltransferase that influences insect resistance. Plant J 2021, 106:1401–1413.

14. Murata K, Kitano T, Yoshimoto R, Takata R, Ube N, Ueno K, Ueno M, Yabuta Y, Teraishi M, Holland CK, Jander G, Okumoto Y, Mori N, Ishihara A: Natural variation in the expression and catalytic activity of a naringenin 7-O-methyltransferase influences antifungal defenses in diverse rice cultivars. Plant J 2020, 101:1103–1117.

15. Watkins JM, Hechler PJ, Muday GK: Ethylene-induced flavonol accumulation in guard cells suppresses reactive oxygen species and moderates stomatal aperture. Plant Physiol 2014, 164:1707–1717.

16. ** Chapman JM, Muday GK: Flavonols modulate lateral root emergence by scavenging reactive oxygen species in Arabidopsis thaliana. J Biol Chem 2021, 296:100222.

An elegant combination of reverse genetics, chemical complementations, and confocal microscopy experiments pinpoints kaempferol as a negative regulator of lateral root emergence via ROS scavenging. The authors mention the possibility that downstream metabolites of kaempferol could contribute to such a mechanism.

17. Maloney GS, DiNapoli KT, Muday GK: The anthocyanin reduced tomato mutant demonstrates the role of flavonols in tomato lateral root and root hair development. Plant Physiol 2014, 166:614–631.

18. Silva-Navas J, Moreno-Risueno MA, Manzano C, Téllez- Robledo B, Navarro-Neila S, Carrasco V, Pollmann S, Gallego FJ, Del Pozo JC: Flavonols mediate root phototropism and growth through regulation of proliferation-to-differentiation transition. Plant Cell 2016, 28:1372–1387.

19. Block A, Widhalm JR, Fatihi A, Cahoon RE, Wamboldt Y, Elowsky C, Mackenzie SA, Cahoon EB, Chapple C, Dudareva N, Basset GJ: The origin and biosynthesis of the benzenoid moiety of ubiquinone (coenzyme Q) in arabidopsis. Plant Cell 2014, 26:1938–1948.

20. Soubeyrand E, Kelly M, Keene SA, Bernert AC, Latimer S, Johnson TS, Elowsky C, Colquhoun TA, Block AK, Basset GJ: Arabidopsis 4-COUMAROYL-COA LIGASE 8 contributes to the biosynthesis of the benzenoid ring of coenzyme Q in peroxisomes. Biochem J 2019, 476:3521–3532.

21. ** Soubeyrand E, Johnson TS, Latimer S, Block A, Kim J, Colquhoun TA, Butelli E, Martin C, Wilson MA, Basset GJ: The peroxidative cleavage of kaempferol contributes to the biosynthesis of the benzenoid moiety of ubiquinone in plants. Plant Cell 2018, 30:2910–2921.

Gene network modeling, reverse genetics, heavy isotope feeding assays, and enzyme assays established that the peroxidative cleavage of the B-ring of kaempferol in Arabidopsis generates 4-hydroxybenzoate and that the latter is incorporated into ubiquinone. Ubiquinone quantification in a tomato flavanone-3-hydroxylase mutant and flavonol-accumulating tomato fruits indicated that flavonol and ubiquinone metabolisms are linked in this species as well. The study also proposes a mechanistic model for the attack of kaempferol by heme-dependent peroxidases.

22. Fernández-Del-Río L, Clarke CF, Coenzyme Q: Biosynthesis: An update on the origins of the benzenoid ring and discovery of new ring precursors. Metabolites 2021, 11:385.

23. Saito K, Yonekura-Sakakibara K, Nakabayashi R, Higashi Y, Yamazaki M, Tohge T, Fernie AR: The flavonoid biosynthetic pathway in Arabidopsis: structural and genetic diversity. Plant Physiol Biochem 2013, 72:21 –34.

24. Dastmalchi M: Elusive partners: a review of the auxiliary proteins guiding metabolic flux in flavonoid biosynthesis. Plant J 2021, 108:314–329.

25. Sugiyama R, Li R, Kuwahara A, Nakabayashi R, Sotta N, Mori T, Ito T, Ohkama-Ohtsu N, Fujiwara T, Saito K, Nakano RT, Bednarek P, Hirai MY: Retrograde sulfur flow from glucosinolates to cysteine in Arabidopsis thaliana. Proc Natl Acad Sci U S A 2021, 118. e2017890118.

26. Soubeyrand E, Latimer S, Bernert AC, Keene SA, Johnson TS, Shin D, Block AK, Colquhoun TA, Schäffner AR, Kim J, Basset GJ: 3-O-glycosylation of kaempferol restricts the supply of the benzenoid precursor of ubiquinone (Coenzyme Q) in Arabidopsis thaliana. Phytochemistry 2021, 186:112738.

27. Yonekura-Sakakibara K, Tohge T, Matsuda F, Nakabayashi R, Takayama H, Niida R, Watanabe-Takahashi A, Inoue E, Saito K: Comprehensive flavonol profiling and transcriptome coexpression analysis leading to decoding gene-metabolite correlations in Arabidopsis. Plant Cell 2008, 20:2160–2176.

28. Roepke J, Gordon HOW, Neil KJA, Gidda S, Mullen RT, Freixas Coutin JA, Bray-Stone D, Bozzo GG: An apoplastic b-glucosidase is essential for the degradation of flavonol 3-O-b-Glucoside-7-O-a-Rhamnosides in arabidopsis. Plant Cell Physiol 2017, 58:1030–1047.

29. Baba SA, Vishwakarma RA, Ashraf N: Functional characterization of CsBGlu12, a b-glucosidase from crocus sativus, provides insights into its role in abiotic stress through accumulation of antioxidant flavonols. J Biol Chem 2017, 292: 4700 –4713.

30. Wolf L, Rizzini L, Stracke R, Ulm R, Rensing SA: The molecular and physiological responses of Physcomitrella patens to ultraviolet-B radiation. Plant Physiol 2010, 153:1123–1134.

31. Goiris K, Muylaert K, Voorspoels S, Noten B, De Paepe D, E Baart GJ, De Cooman L: Detection of flavonoids in microalgae from different evolutionary lineages. J Phycol 2014, 50:483–492.

32. Yonekura-Sakakibara K, Higashi Y, Nakabayashi R: The origin and evolution of plant flavonoid metabolism. Front Plant Sci 2019, 10:943.

33. Clayton WA, Albert NW, Thrimawithana AH, McGhie TK, Deroles SC, Schwinn KE, Warren BA, McLachlan ARG, Bowman JL, Jordan BR, Davies KM: UVR8-mediated induction of flavonoid biosynthesis for UVB tolerance is conserved between the liverwort Marchantia polymorpha and flowering plants. Plant J 2018, 96:503–517.

34. Bentinger M, Brismar K, Dallner G: The antioxidant role of coenzyme Q. Mitochondrion 2007, 7(Suppl):S41–S50.

35. Dutta A, Chan SH, Pauli NT, Raina R: Hypersensitive response-like lesions 1 codes for AtPPT1 and regulates accumulation of ROS and defense against bacterial pathogen Pseudomonas syringae in Arabidopsis thaliana. Antioxidants Redox Signal 2015, 22:785–796.

36. Kemmerer ZA, Robinson KP, Schmitz JM, Manicki M, Paulson BR, Jochem A, Hutchins PD, Coon JJ, Pagliarini DJ: UbiB proteins regulate cellular CoQ distribution in Saccharomyces cerevisiae. Nat Commun 2021, 12:4769.

37. * Fernández-Del-Río L, Nag A, Gutiérrez Casado E, Ariza J, Awad AM, Joseph AI, Kwon O, Verdin E, de Cabo R, Schneider C, Torres JZ, Burón MI, Clarke CF, Villalba JM: Kaempferol increases levels of coenzyme Q in kidney cells and serves as a biosynthetic ring precursor. Free Radic Biol Med 2017, 110:176–187.
Feeding experiments established that mouse and human kidney cells use kaempferol as an aromatic ring precursor for ubiquinone biosynthesis. By testing various flavonoids, the study identifies some of the structural determinants that are crucial for the incorporation of kaempferol into ubiquinone.

38. Fernández-Del-Río L, Soubeyrand E, Basset GJ, Clarke CF: Metabolism of the flavonol kaempferol in kidney cells liberates the B-ring to enter coenzyme Q biosynthesis. Molecules 2020, 25:2955.

39. Ohara K, Kokado Y, Yamamoto H, Sato F, Yazaki K: Engineering of ubiquinone biosynthesis using the yeast coq2 gene confers oxidative stress tolerance in transgenic tobacco. Plant J 2004, 40:734–743.

40. Avelange-Macherel MH, Joyard J: Cloning and functional expression of AtCOQ3, the Arabidopsis homologue of the yeast COQ3 gene, encoding a methyltransferase from plant mitochondria involved in ubiquinone biosynthesis. Plant J 1998, 14:203–213.

41. Okada K, Ohara K, Yazaki K, Nozaki K, Uchida N, Kawamukai M, Nojiri H, Yamane H: The AtPPT1 gene encoding 4-hydroxybenzoate polyprenyl diphosphate transferase in ubiquinone biosynthesis is required for embryo development in Arabidopsis thaliana. Plant Mol Biol 2004, 55:567–577.

42. Ohara K, Yamamoto K, Hamamoto M, Sasaki K, Yazaki K: Functional characterization of OsPPT1, which encodes p-hydroxybenzoate polyprenyltransferase involved in ubiquinone biosynthesis in Oryza sativa. Plant Cell Physiol 2006, 47: 581 –590.

43. Liu M, Chen X, Wang M, Lu S: SmPPT, a 4-hydroxybenzoate polyprenyl diphosphate transferase gene involved in ubiquinone biosynthesis, confers salt tolerance in Salvia miltiorrhiza. Plant Cell Rep 2019, 38:1527–1540.

44. Agati G, Galardi C, Gravano E, Romani A, Tattini M: Flavonoid distribution in tissues of Phillyrea latifolia L. leaves as estimated by microspectrofluorometry and multispectral fluorescence microimaging. Photochem Photobiol 2002, 76: 350 –360.

45. Tattini M, Galardi C, Pinelli P, Massai R, Remorini D, Agati G: Differential accumulation of flavonoids and hydroxycinnamates in leaves of Ligustrum vulgare under excess light and drought stress. New Phytol 2004, 163:547–561.

46. Zhao J, Dixon RA: The 'ins' and 'outs' of flavonoid transport. Trends Plant Sci 2010, 15:72 –80.

47. Ferreres F, Figueiredo R, Bettencourt S, Carqueijeiro I, Oliveira J, Gil-Izquierdo A, Pereira DM, Valentão P, Andrade PB, Duarte P, Barceló AR, Sottomayor M: Identification of phenolic compounds in isolated vacuoles of the medicinal plant Catharanthus roseus and their interaction with vacuolar class III peroxidase: an H_2O_2 affair? J Exp Bot 2011, 62: 2841 –2854.

48. Takahama U: Hydrogen peroxide-dependent oxidation of flavonols by intact spinach chloroplasts. Plant Physiol 1984, 74: 852 –855.

49. Ducluzeau AL, Wamboldt Y, Elowsky CG, Mackenzie SA, Schuurink RC, Basset GJ: Gene network reconstruction identifies the authentic trans-prenyl diphosphate synthase that makes the solanesyl moiety of ubiquinone-9 in Arabidopsis. Plant J 2012, 69:366–375.

50. Latimer S, Keene SA, Stutts LR, Berger A, Bernert AC, Soubeyrand E, Wright J, Clarke CF, Block AK, Colquhoun TA, Elowsky C, Christensen A, Wilson MA, Basset GJ: A dedicated flavin-dependent monooxygenase catalyzes the hydroxylation of demethoxyubiquinone into ubiquinone (coenzyme Q) in Arabidopsis. J Biol Chem 2021, 297:101283.