Title

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Journal

Bioscience, Biotechnology, and Biochemistry

Volume 82, 2018 - Issue 6: Special Issue: Recent advances in isoprenoid studies

Published

19 Feb 2018

URL

https://doi.org/10.1080/09168451.2018.1433020

Biosynthesis and applications of prenylquinones

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Funding

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 17H03806).

Disclosure statement

The author declares that there is no conflict of interests.

Abbreviations

DHFL, dehypoxanthinylfutalosine

DHNA, 1,4-dihydroxy-2-naphthoate

DMK, demethylmenaquinone

DMAPP, dimethylallyl pyrophosphate

DXP, 1-deoxy-D-xylulose-5-phosphate

FPP, farnesyl pyrophosphate

GPP, geranyl pyrophosphate

GGPP, geranylgeranyl pyrophosphate

HGA, homogentisate

IPP, isopentenyl pyrophosphate

MEP, 2*C*-methyl-D-erythritol-4-phosphate

MK, menaquinone

MVA, mevalonate

PDS, prenyl diphosphate synthase

PHB, *p*-hydroxybenzoate

PhQ, phylloquinone

PQ, plastoquinone

RQ, rhodoquinone

UQ, ubiquinone

Abstract

Prenylquinones are isoprenoid compounds with a characteristic quinone structure and isoprenyl tail that are ubiquitous in almost all living organisms. There are four major prenylquinone classes: ubiquinone (UQ), menaquinone (MK), plastoquinone (PQ), and rhodoquinone (RQ). The quinone structure and isoprenyl tail length differ among organisms. UQ, PQ, and RQ contain benzoquinone, while MK contains naphthoquinone. UQ, MK, and RQ are involved in oxidative phosphorylation, while PQ functions in photosynthetic electron transfer. Some organisms possess two types of prenylquinones; *Escherichia coli* has UQ_8 and MK_8, and *Caenorhabditis elegans* has UQ_9 and RQ_9. Crystal structures of most of the enzymes involved in MK synthesis have been solved. Studies on the biosynthesis and functions of quinones have advanced recently, including for phylloquinone (PhQ), which has a phytyl moiety instead of an isoprenyl tail. Herein, the synthesis and applications of prenylquinones are reviewed.

Keywords: Ubiquinone, menaquinone, plastoquinone, rhodoquinone, phylloquinone

1. Introduction

Isoprenoids are compounds built from two common precursors, isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). More than 50,000 isoprenoid compounds are found in nature.[1)] Among them, isoprenylated quinones, in which the length of the isoprenoid side chain or tail varies, are widely distributed in almost all living organisms, and they function in electron transfer. Living organisms must acquire energy through oxidative phosphorylation or photosynthetic phosphorylation, and these processes require lipid molecules to transfer electrons and protons between protein complexes. Typically, ubiquinone (UQ) transfers electrons from Complex I or II to Complex III in oxidative phosphorylation, while plastoquinone

(PQ) transfers electrons from photosystem II to the cytochrome b_6f complex in photosynthesis.[2)]

The isoprenoid side chain is responsible for the lipid-soluble nature of quinones, and anchors them in membrane lipid bilayers, while the electron transfer capacity is derived from the quinone head. The quinone ring undergoes a two-step reversible oxidation/reduction between reduced and oxidized forms. This common property allows electrons and protons to shuttle between different protein complexes in biological membranes, allowing it to function as both a cofactor in enzyme reactions, and as an antioxidant.

Widely distributed (major) and more restricted (minor) quinones are present in almost all living organisms. UQ, menaquinone (MK), PQ, and rhodoquinone (RQ) are major quinones, and UQ and RQ are distributed in prokaryotes and eukaryotes, while MK is found in bacteria and archaea, and PQ is restricted to cyanobacteria and plants. Minor quinones include thermoplasmaquinone, methionaquinone, chlorobiumquinone, sulfolobusquinone, and caldariellaquinone, and are found in bacteria and archaea.[3)]

The length of the isoprenoid side chain and the type of quinone are variable (side chain length is annotated in subscript in this review). For example, bacteria such as *Bacillus subtilis* produce MK_7, *Escherichia coli* synthesize UQ_8 and MK_8, and *Synechocystis* spp. generate PQ_9. Yeasts such as *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* produce UQ_6 and UQ_{10}, respectively. Plants such as *Arabidopsis thaliana* produce UQ_9 and PQ_9, while *Nicotiana tabacum* synthesize UQ_{10} and PQ_9. Nematodes such as *Caenorhabditis elegans* produce UQ_9 and RQ_9, and higher animals such as *Mus musculus* and *Homo sapiens* make UQ_9 and UQ_{10}, respectively (Fig. 1). The types of prenylquinones in organisms are highly variable; hence they have been used for classification of microbes.[4, 5)]

The biosynthesis of prenylquinones has been extensively studied, and despite significant knowledge accumulated, some biosynthetic reactions remain poorly

understood. In this review, the biosynthesis of four major prenylquinones and phylloquinone (PhQ) is summarized in detail.

2. Isoprenoid side chains are synthesized via 2*C*-methyl-D-erythritol-4-phosphate (MEP) and mevalonate (MVA) pathways

The isoprenoid side chains of prenylquinones are synthesized by prenyl diphosphate synthase (PDS) from DMAPP, geranyl pyrophosphate (GPP), geranylgeranyl pyrophosphate (GGPP), or farnesyl pyrophosphate (FPP) by condensation of IPP. IPP and DMAPP are synthesized from either the 2*C*-methyl-D-erythritol-4-phosphate (MEP) pathway [6-8] or the mevalonate (MVA) pathway.[9] The MEP pathway is present in most prokaryotes, and the MVA pathway occurs in archaea and eukaryotes.[10] Plants and *Streptomycetes* possess both pathways.

The MVA pathway was discovered in the 1960s and consists of seven enzyme-catalyzed reactions. It performs several key functions within cells, and is an important central metabolic pathway in all higher eukaryotes. The MVA pathway of *S. cerevisiae* is shown in Fig. 2 as representative of eukaryotes. Formation of acetoacetyl-CoA from two acetyl-CoA molecules by acetyl-CoA acetyltransferase (Erg10) is followed by the synthesis of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by Erg13. In the third step, MVA is generated by reduction of HMG-CoA by HMG-CoA reductase (Hmg), the target of the famous "statin" drugs.[11] MVA is phosphorylated by Erg12 to generate phosphomevalonate, and further phosphorylated by Erg8. Finally, diphosphomevalonate is used by Erg19/Mvd1 to generate IPP or DMAPP. Idi isomerizes between IPP and DMAPP, and DMAPP and IPP are further utilized in condensation reactions for the biosynthesis of isoprenoids. The reactions of all enzymes in the MVA pathway and their three-dimensional structures have been summarized previously.[9]

The MEP pathway for the biosynthesis of IPP and DMAPP was discovered in the 1990s and consists of eight enzyme-catalyzed reactions. The MEP pathway of *E.*

coli is shown in Fig. 3. Condensation of pyruvate and D-glyceraldehyde-3-phosphate to form 1-deoxy-D-xylulose-5-phosphate (DXP) is catalyzed by Dxs (Fig. 3). The second step is the conversion of DXP to MEP by IspC, and 4-diphosphocytidyl-2*C*-methyl-D-erythritol (CDP-ME) is then generated from MEP and CTP by IspD. The fourth step is the phosphorylation of CDP-ME to generate 4-diphosphocytidyl-2*C*-methyl-D-erythritol-2-phosphate (CDP-ME2P) by IspE, and IspF subsequently removes CMP from CDP-ME2P to generate 2*C*-methyl-D-erythritol-2,4-cyclodiphosphate (MEcPP). In the sixth step, IspG catalyzes the ring opening of the cyclic pyrophosphate and C3-reductive dehydration of MEcPP to generate 4-hydroxy-3-methylbut-2-enyl diphosphate (HMB-PP). Finally, IspH generates IPP or DMAPP from HMB-PP by reduction. Idi catalyzes isomerization between IPP and DMAPP in the eighth step, and some organisms lack this enzyme. Enzymes of this MEP pathway are attractive targets for the development of drugs against infectious diseases because this pathway occurs in pathogenic prokaryotes but is absent in humans. The antimalarial drug fosmidomycin, which inhibits Dxr, is one of the best-known examples of a drug that targets the MEP pathway. Three-dimensional structures of *E. coli* Dxs, IspC, IspD, IspE, IspF, IspG, and IspH have been solved, and their precise structure-based catalytic mechanisms have been described.[6)] Further details about these biosynthetic pathways synthesizing IPP can be found in previous reviews.[6-10)]

3. Prenyl diphosphate synthase

The side chain of prenylquinone is supplied by polyprenyl diphosphate synthase (PDS) and determines the side chain length of prenylquinones (Fig. 4).[12, 13)] Numerous PDS enzymes have been analyzed,[5, 14-17)] and all consist of seven conserved regions including two DDXXD motifs involved in binding substrates such as FPP (GPP or GGPP) and IPP. PDS occurs in both homomeric and heteromeric forms. PDSs in Gram-negative bacteria are mostly homomeric, while those in Gram-positive bacteria are mostly

158 heteromeric.[15, 18] Eukaryotes have both heteromeric (e.g., Coq1 and SPS1) and
159 homomeric types (e.g., human PDSS1 and PDSS2).[19-21] The distribution of these PDSs
160 differs among organisms, and among different components in organisms. For example,
161 *E. coli* contains only one polyprenyl diphosphate synthase (IspB) and shares the side
162 chain of UQ and MK.[22, 23] Meanwhile, plants such as *Arabidopsis* possess three
163 different PDSs, in this case three solanesyl diphosphate synthases (SPS1, SPS2, and
164 SPS3), which are localized to different subcellular organelles (the ER, chloroplasts, and
165 mitochondria, respectively).[24, 25] Humans contain one PDS comprising two subunits,
166 PDSS1 and PDSS2,[21] similar to *S. pombe* PDS, which also consists of a heteromeric
167 complex and served as the basis for analysis of the human enzyme.[20, 21] A heteromeric
168 form of PDS was probably evolved in *S. pombe* or earlier organisms and succeeded to
169 humans. The result that artificial heteromeric PDSs between Coq1 and Dps1 or IspB
170 and Dps1 is functional[19, 26] supported an idea that heteromeric form was evolved from
171 homomeric form.
172 The three-dimensional structure of PDS has been solved, and octaprenyl
173 diphosphate synthase (IspB) from *E. coli* consists of 14 α-helices.[27] Recent
174 co-crystallization of IspB with its substrates (FPP and IPP) revealed aspartate-rich
175 motifs surrounding the binding regions of substrates, and indicated a product pocket
176 that determines the chain length. The three-dimensional structure of the heteromeric
177 heptaprenyl diphosphate synthase from *Staphylococcus aureus* was solved,[28] revealing
178 a regulatory subunit that does not resemble the catalytic subunit.
179 *E. coli ispB* is essential for growth, while *ispA* encoding FPS is not,[22]
180 presumably because *ispB* replaces the function of *ispA*.[29] Since *ispB* is required for the
181 synthesis of the side chain of both UQ and MK, *E. coli* cannot survive without both
182 quinones. Coq1 in *S. cerevisiae*[19] and Dps1 (or Dlp1) in *S. pombe* are not essential for
183 growth,[20, 30] while *C. elegans coq1* and PDSS1 (or PDSS2) in mouse are essential for
184 development.[31, 32]
185

4. Prenylquinones

Different groups of prenylquinones such as UQ, MK, PQ, and RQ (Fig. 1) are present in different taxonomic groups, and prenylquinone profiling is a useful taxonomic tool.[4] Exactly why such a wide variety of quinones are found in nature is an interesting question. The isoprenoid side chain gives these molecule their lipid-soluble character, the quinone ring defines the redox mid-potential, and organisms have evolved the optimal quinone types for survival. The redox potential (E^0) of MK is -74 mV, compared with -63 mV for RQ and +100 mV for UQ. The lower redox potential of MK and RQ explains why they are used in electron transfer systems under anaerobic conditions, while UQ is employed in aerobic conditions. Differences in the natural environment of living organisms probably affect selection of the preferred quinone type. Evolutionally, MK probably arose in archaea, while PQ and UQ evolved later in bacteria and became distributed in eukaryotes, and RQ forms evolved most recently. However, some researchers believe that PQ may have evolved first in cyanobacteria, and was then distributed to other organisms, because the pathway for UQ biosynthesis is similar to that of PQ, and PQ has the simplest structure among prenylquniones.[33]

Some organisms possess two types of quinones, such as *E. coli* that synthesizes UQ_8 and MK_8, and *C. elegans* that has UQ_9 and RQ_9. Possessing different types of quinones may be beneficial for adapting to changing environmental conditions. In *E. coli*, the level of UQ_8 is 4–5 times higher than that of MK_8 and demethyl menaquinone $(DMK)_8$ when growing under aerobic conditions, whereas UQ is three times less abundant than MKs under anaerobic conditions. In *Euglena gracilis*, RQ_9 is present at a similar concentration to UQ_9 under aerobic conditions, but is more abundant under anaerobic culture conditions. In *C. elegans*, UQ_9 is 3.56-fold more abundant than RQ_9, indicating a preference for aerobic growth, although anaerobic growth also occurs.[34]

The significance of the length of the side chain of prenylquinones remains contentious, and only UQ has been thoroughly investigated. The side chain of UQ is

214 determined by the supplied prenyl diphosphate synthesized by PDS.[12] Genetically
215 engineered *S. cerevisiae* produce UQ_5 to UQ_{10} and grow well, but the native form (UQ_6
216 in this case) is preferred for better growth.[13] *E. coli* producing UQ_6 to UQ_{10} also grow
217 well, but a longer side chain is preferable for better growth.[22] *C. elegans clk-1* mutant,
218 which lacks the penultimate enzyme (Coq7) in UQ synthesis, lives longer than wild
219 type. When engineering *E. coli* producing UQ_6 to UQ_{10} were used as diet, they reverse
220 the longevity of this mutant, but the effect is different.[35] *C. elegans* prefers longer UQs
221 such as UQ_8 to UQ_{10}, and the preference for a certain length may reflect the affinity for
222 binding proteins or the membrane lipid composition. Why plants prefer the isoprene
223 unit 9 form in PQs, while animals prefer the isoprene unit 4 form in MKs (or PQs) is
224 also interesting.
225 A variety of scarcer prenylquinones other than those widely distributed in
226 nature have been identified. Thermoplasmaquinone and methionaquinone are found in
227 *Thermoplasma* spp. and *Hydrogenobacter thermophilus*, respectively.[36, 37]
228 Chlorobiumquinone, containing oxygenized isoprenoid in MK, is found in the
229 photosynthetic bacterium *Chlorobium limicola* and in *Leishmania* parasitic
230 protozoans.[38] Sulfolobusquinone, caldariellaquinone, and benzodithiophenoquinone,
231 containing sulfur in an additional heterocyclic ring, are found in *Sulfolobales*, an order
232 of thermophilic and aerobic archaebacteria.[39] Sulfomenaquinone, containing sulfur in
233 the end of the side chain, is found in *Mycobacterium tuberculosis*,[40] and a saturated
234 isoprenoid in UQ is found in Fungi.[41] There are a few known organisms, such as
235 obligatory fermentative bacteria, that lack prenylquinones.[4]
236
237 **5. Ubiquinone (coenzyme Q)**
238 Ubiquinone (UQ; 2,3-dimethoxy-5-methyl-6-polyprenyl-1,4-benzoquinone) is an
239 essential cofactor in oxidative phosphorylation, present in all eukaryotes and alpha-,
240 beta-, and gamma-proteobacteria.[4] UQ was discovered by F. Crane in 1957, and the
241 structure was determined by K. Folkers the following year.[42] UQ functions in many

242 physiological processes including sulfide oxidation,[43, 44] first discovered in fission yeast
243 and later in humans, as well as regulation of the mitochondrial permeability transition
244 pore, and the translocation of protons and Ca^{2+} across biological membranes in
245 eukaryotes.[45] UQ is the only lipid-soluble antioxidant produced in humans, and it is
246 present in almost all membranes, ranging from mitochondrial membranes, Golgi, ER,
247 and plasma membranes, to very low density lipoproteins. UQ_{10} production decreases
248 with aging in humans, as does the antioxidant capability of cells.[46] In humans,
249 the heart, liver, and kidney have higher UQ_{10} levels than other organs.[47]

250 In model organisms such as *E. coli*, *S. cerevisiae*, and *S. pombe*, UQ
251 deficiency is not lethal, but causes growth defects on minimum medium, and a
252 heightened sensitivity to oxidative stress.[17] In *C. elegans*,[31] UQ deficiency leads to
253 gamma-aminobutyric acid (GABA) neuron degeneration, and in *Drosophila*
254 *melanogaster*,[48] it can cause mitochondrial stress and neuronal apoptosis. In
255 *Arabidopsis*, UQ is necessary for seed development.[49] In humans, UQ_{10} deficiency has
256 been implicated in various diseases involving muscle and neural development, with the
257 severity of the disease correlated with the acuteness of the UQ_{10} shortfall.[50]

258 The biosynthetic pathway of UQ has been reviewed previously,[17, 51-55] but
259 important progress has been made in recent years. Biosynthesis of UQ has received
260 greatest attention in *E. coli* and *S. cerevisiae*, serving as representative prokaryotes and
261 eukaryotes, respectively (Fig. 4). Some variation in UQ biosynthetic enzymes is
262 observed in prokaryotes and eukaryotes; in particular, decarboxylation and C1
263 hydroxylation enzymes are not defined in eukaryotes, and likely to be different from
264 prokaryotic enzymes.[51]

265 In *E. coli*, PHB is first condensed with *trans*-polyprenyl diphosphate by
266 UbiA,[56] and the ring structure is then modified. The decarboxylation step is catalyzed
267 by UbiD with the assistance of UbiX, which generates the prenylated FMN cofactor for
268 UbiD.[57] UbiX functions as a flavin prenyltransferase. The ring is further hydroxylated
269 by UbiI,[58] *O*-methylated by UbiG,[59] hydroxylated by UbiH, *C*-methylated by UbiE,[60]

hydroxylated by UbiF,[61] then *O*-methylated by UbiG. It is reported that *ubiK* and *ubiJ* are required for efficient biosynthesis of UQ in *E. coli*.[62] Hydroxylation and ring formation are reportedly catalyzed by enzymes encoded by *ubiM* and *ubiL* in *Rhodospirillum*.[33] The *ubiZ* gene product is predicted to be involved in UQ synthesis in *Acinetobacter junii*, based on genomic analysis of 254 human gut microbes.[63] However, verification of these genes in the biosynthesis of UQ awaits further evidence. An attempt to produce a higher amount of UQ by genetic engineering was first succeeded in *E. coli* by expressing *ubiA, ubiB, ubiC, ubiG, ubiH* and *ispB* [64]

In *S. cerevisiae*, PHB and *para*-amino benzoic acid (pABA) are used for UQ synthesis. PHB is synthesized from 4-hydroxybenzaldehyde by Hfd1 in *S. cerevisiae*.[24] A conserved homolog of Hfd1 is found in humans, but it is still not clear how many steps are required to form 4-hydroxybenzaldehyde from tyrosine.[65] pABA was originally identified as a precursor of ring formation in *S. cerevisiae*, and we observed that it is also used in *S. pombe* (unpublished). The first ring is prenylated by Coq2,[66] modified via hydroxylation by Coq6,[67] followed by *O*-methylation by Coq3.[59] The enzymes responsible for decarboxylation and hydroxylation remain unclear. The ring is then modified further via *C*-methylation by Coq5,[68] a final hydroxylation by Coq7,[69] and *O*-methylation by Coq3. The genes involved in biosynthesis in eukaryotes are well conserved among yeasts, plants, and humans,[70] although there is some variation among species. Even between the two model yeasts *S. cerevisiae* and *S. pombe*, components of PDS are different.[19] There are at least four genes (*COQ4*, *COQ8*, *COQ9*, and *COQ11*) responsible for the synthesis of UQ, but their functions are not known. The function of Coq4 is clearly conserved in humans and plants.[70] Conservation of Coq9 in higher eukaryotes is not so obvious, but interestingly, a homolog is also found in some prokaryotes.[33] Coq11 is associated with the UQ synthetic enzyme complex named CoQ synthome, and is required for UQ synthesis in *S. cerevisiae.*[71] Coq11 is also required for efficient UQ synthesis in *S. pombe* (unpublished). A deamination step is required for the synthesis of UQ from pABA, and the involvement of Coq9 or Coq6 has been

298 proposed.[72, 73] The UbiD and UbiX homologs Pad1 and Fdc1 found in yeasts are not
299 involved in UQ synthesis, but are required for ferulic acid synthesis.[74] How
300 decarboxylation takes place during ring formation in eukaryotes is a long-standing
301 question in UQ synthesis.

302 In addition to the three-dimensional structure described previously,[51] the
303 structure of Coq3 was recently solved.[75] Coq3 forms a typical Class I *S*-adenosyl
304 methionine methyltransferase (SAM-MTase) fold. Coq3 is a membrane-binding protein
305 specifically binding to liposomes containing phosphatidylglycerol (PG), cardiolipin
306 (CL), or diphosphatidylglycerol (DPPG). The three-dimensional structures of Coq7 and
307 Coq11 are yet to be reported.

308 How UQ is transported has been a long-standing question. By searching for
309 the binding protein using UQ, three UQ-binding proteins, Coq10, saposin, and
310 voltage-dependent anion channel (VDAC1), were identified.[76, 77] Coq10 is localized to
311 mitochondria in eukaryotes, and homologs are found in prokaryotes. Lack of Coq10
312 results in respiration deficiency in yeasts.[76, 78] Coq10 itself is not required for the
313 biosynthesis of UQ, but it is thought to be required for efficient operation of electron
314 transfer systems. The binding site of Coq10 for UQ_{10} was determined by
315 affinity-purified Coq10 using a UQ analog in *S. pombe*.[77] Saposin is another protein
316 that binds UQ, but it is only found in mammals. Among different types, saposin B was
317 shown to bind UQ as well as tocopherol.[79] VDAC1, located in the mitochondrial outer
318 membrane of *S. cerevisiae*, is another UQ-binding protein.[80] The role of VDAC1 in
319 Ca^{2+}-induced mitochondrial permeability is affected by binding to UQ, but whether this
320 function is conserved in other organisms is not known.

321 The unique fission yeast *Schizosaccharomyces japonicus* produces 200-fold
322 less UQ_{10} than *S. pombe*.[81] This fission yeast acquires energy through fermentation and
323 has abandoned respiration. How this yeast survives in its natural environment with such
324 a small amount of UQ_{10} is interesting and worthy of study.
325

6. Menaquinones

Menaquinone (MK; 2-methyl-3-polyprenyl-1,4-naphthoquinone) is found in bacteria, and is the sole quinone in anaerobically growing bacteria.[82, 83] MK was discovered in 1939 by E. A. Doisy.[84] MKs are found in archaea and bacteria such as γ-, δ-, and ε-proteobacteria, Gram-positive bacteria, green sulfur bacteria, green filamentous bacteria, and flavobacteria. As MKs have a low midpoint redox potential, they are believed to have appeared early in evolution before UQ, since they function in a reducing atmosphere as was present before the increase in oxygen concentration following the arrival of photosynthetic organisms.

MKs occur in different forms, with the number of isoprene units varying between 4 and 13. Some bacteria such as *E. coli* possess both UQ_8 and MK_8, and the relative amounts of each depend on oxygen levels; while UQ levels are higher under aerobic conditions, MK_8 is more abundant under anaerobic conditions. Neither MK nor UQ is essential for survival in *E. coli*, but at least one of these prenylquinones is needed.[22] The side chain of MK is usually fully unsaturated, but it can be also be partially or fully saturated in some organisms.[85]

Two pathways are known for the synthesis of MK. The classical pathway involves nine steps catalyzed by MenF, MenD, MenH, MenC, MenE, MenB, MenI, MenA, and MenG (Fig. 6).[86] The biosynthesis of MK in *E. coli* starts from the conversion of chorismate to isochorismate by MenF, and succination is then catalyzed by MenD. In the third step, 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate (SHCHC) is synthesized by MenH, and *O*-succinylbenzoate (OSB) is then synthesized from SHCHC by MenC. In the fifth step, CoA is adducted to OSB by MenE, and MenB then cyclizes OSB-CoA to form DHNA-CoA. In the seventh step, MenI synthesizes naphthoate,[87] which is prenylated by MenA, and the product is methylated by MenG (UbiE) in the final step. Prenylation takes place during the later stages via MenA, in contrast with the synthesis of UQ in which it occurs earlier via UbiA (Fig. 5). The methylation enzyme (MenG) for MK is homologous to UbiE functioning in UQ

354 synthesis in *E. coli*. MenJ works as a reductase of the side chain in *Mycobacterium*
355 *tuberculosis*.[88] Further methylation of MK is observed in some bacterium such as
356 *Shewanella oneidensis*.[89]
357 The novel pathway for MK synthesis was first discovered in *Streptomyces coelicolor*
358 and subsequently in *Helicobacter pylori* and *Thermus thermophilus*.[90, 91] Six enzymes
359 are engaged in 1,4-dihydroxy-6-naphthoate biosynthesis. MqnA converts chorismate to
360 3-[(1-carboxyvinyl)oxy]benzoic acid, which is condensed with SAM by MqnE, leading
361 to aminofutalosine (AFL). MqnE is a radical SAM enzyme that catalyzes the addition of
362 the adenosyl radical to the double bond of 3-[(1-carboxyvinyl)oxy]benzoic acid.
363 Deamination of AFL is catalyzed by a specific deaminase for which no common gene
364 name has been assigned.[92] MqnB (futalosine hydrolase) then removes hypoxanthine,
365 forming dehypoxanthinylfutalosine (DHFL).[93] MqnC cyclizes DHFL, and MqnD
366 cleaves the cyclic 1,4-dihydroxy-6-naphthoate to release 1,4-dihydroxy-6-naphthoate
367 (Fig. 7). In *H. pylori*, MqnB directly converts aminodeoxyfutalosine into DHFL,[94]
368 indicating an alternative way in the futalosine pathway.
369 The novel genes *mqnP*, *mqnL*, and *mqnN* were predicted to encode enzymes
370 involved in MK synthesis in *Helicobacter cinaedi* following genomic analysis of 254
371 human gut microbes.[63] MqnP is predicted to be involved in prenylation of
372 1,4-dihydroxy-6-naphthoate, and MqnL and MqnN are likely involved in
373 decarboxylation. Comparing gene clusters can be useful for predicting biosynthetic
374 genes such as those orchestrating the synthesis of MK. However, biochemical analysis
375 is essential for confirming any predictions, and analysis of this futalosine pathway
376 leading to MK is still under investigation.
377 The three-dimensional structures of MK biosynthetic enzymes MenC from *E.*
378 *coli* [95] and *Thermosynechococcus elongatus*,[96] and MenB,[97] MenD,[98] MenE,[99]
379 MenF,[100] MenH,[101] and MenI[102] from *E. coli*, have been determined (Fig. 8). The
380 structure of MenC is similar to that of other members of the enolase superfamily.[95] The
381 structure of MenB, a crotonase superfamily member, was solved in complex with a

substrate analog, revealing an intramolecular Claisen condensation reaction mechanism.[97] MenD is highly dependent on thiamine diphosphate for its structural stability.[98] MenE requires a conserved arginine for binding the OSB carboxylate, and catalyzes CoA ligation via an acyl-adenylate intermediate.[99] Structural and biochemical analyses of MenF revealed Lys190 as the base that activates a water molecule for nucleophilic attack at the chorismate C2 carbon.[100] MenH has an α/β-hydrolase fold with a catalytic triad comprising Ser86, His232, and Asp210.[101] MenI (YdiI) belongs to the hotdog fold enzyme superfamily.[102] The three-dimensional structures of MqnA[103] and MqnD, and AFL deaminase (Nis0429) functioning in the futalosine-mediated MK pathway, have been solved.[92] The structure of MqnA (DUF178) from *Deinococcus radiodurans* was originally solved as a domain of unknown function before being identified as MqnA.[103] The structure of MqnD from *Thermus thermophilus* HB8 comprises two alpha/beta domains, a large domain, and a small domain.[104] The three-dimensional structure of MqnB from *H. pylori* has a Rossmann fold.[93] The structures of AFL deaminase (Nis0429) from *Nitratiruptor* sp. and Dr0824 from *D. radiodurans* reveal that Ser145 interacts with the carboxylate moiety of the substrate.[92]

7. Phylloquinones (PhQs, vitamin K_1)

Phylloquinone (VK_1; 2-methyl-3-phytyl-1,4-naphthoquinone) functions as an essential photosynthetic electron transporter in photosystem I, and was discovered by H. C. P. Dam in 1934 as a vitamin.[105] Higher amounts are found in green leafy vegetables because it is directly involved in photosynthesis. Humans rely on PhQ uptake from vegetables as a precursor for the synthesis of MK_4. PhQ is thought to be converted to MK_4 by UBIAD in humans. Experiments performed on rodents showed that at least some of their tissues are able to convert PhQ to MK_4. UBIAD mediates the conversion of PhQ into MK_4, probably by cleaving the side chain of PhQ to generate 2-methyl-1,4-naphthoquinone (menadione; VK_3), then prenylating it with GGPP to form MK_4.[106]

The biosynthetic pathway of PhQ in cyanobacteria and plants is thought to resemble the MK pathway.[2, 107] Four genes, *menF*, *menD*, *menC*, and *menH*, involved in PhQ biosynthesis in *Arabidopsis*, are fused at a single locus named *PHYLLO*.[108] The structure of the MenI ortholog AtDHNAT1 (DHNA-CoA thioesterase) has been solved.[109] *O*-succinylbenzoyl-coenzyme A (OSB-CoA) ligase (a MenE ortholog) encoded by *aae14* is essential for PhQ synthesis.[110] A MenG ortholog was identified as the methyltransferase catalyzing the last step of PhQ synthesis in *Arabidopsis*,[111] and a MenB homolog has been identified in the *Arabidopsis* genome sequence. MenB, MenI, and MenG orthologs localize to the peroxisome,[112] while PHYLLO, comprising MenF, MenD, MenC, and MenH orthologs, is localized to chloroplasts.[108] Carboxy-1,4-naphthoquinone phytyltransferase (a MenA ortholog) is involved in PhQ synthesis chloroplasts.[113] The phytyl moiety of PhQ is synthesized either by reduction of GGPP in *de novo* synthesis, or via the salvage pathway. Recent analysis of *Arabidopsis vte6* encoding phytyl phosphate kinase revealed that it performs an essential role in PhQ synthesis.[114] The entire biosynthetic pathway of PhQ in plants is still under investigation.

8. Plastoquinones

Plastoquinone (PQ; 2,3-dimethyl-1,4-benzoquinone), discovered in 1946,[115] functions in the electron transport chain of oxygenic photosynthesis, and plays an indispensable role in plant growth and development. PQ is found in cyanobacteria and plants. PQ_9 is distributed widely among organisms, while PQ_8 is found in maize. In the biosynthesis of PQ in plants, tyrosine is converted to *p*-hydroxyphenylpyruvate (PHPP) by tyrosine aminotransferase (TAT).[2] Homogentisate (HGA) is then synthesized from HPP by *p*-hydroxyphenylpyruvate dioxygenase (Fig. 9). The prenyl tail is synthesized independently from the head group by SPS1, and IPP for prenyl tail synthesis is supplied by the MEP pathway in chloroplasts. Condensation of HGA with the prenyl tail is catalyzed by homogentisate solanesyl transferase (HST).[116] Finally, a methylation

reaction is catalyzed by methyl transferase (Vte3).[117] The *vte* genes are required for vitamin E synthesis and perform some functions in PQ synthesis. The lipid-associated protein Fibrillin5 (FBN5), required for PQ synthesis, interacts with SPS1 and SPS2.[118] Overexpression of SPS1 in *Arabidopsis* resulted in enhanced phototolerance.[119]

Similar to UQ, the biosynthesis of PQ differs in eukaryotes and prokaryotes. Chorismate lyase generates PHB in the synthesis of PQ in the cyanobacterium *Synechocystis*.[120] PHB is prenylated by Slr0926, and decarboxylated by Slr1099 and Sll0936, then oxygenized and methylated to make PQ (Fig. 9).

There are other forms of PQ with shorter side chains such as PQ_3 and PQ_4, as well as analogs such as PQ-B, and PQ-C, which differ in the modification pattern of their side chains.[115] PQ-C contains hydroxyl group in the prenyl chain and PQ-B is a fatty acid ester form of PQ-C.[115]

9. Rhodoquinones

Rhodoquinone (RQ; 2-methoxy-3-Amino-5-methyl-6-polyprenyl-1,4-benzoquinone) was discovered in the bacterium *Rhodospirillum rubrum* in 1965, and subsequently in other organisms such as *Rhodoferax fermentansi*,[121] *E. gracilis*,[122] *C. elegans*,[33] planaria, parasitic helminths, snails, mussels, lungworms, and oysters. Anaerobically and aerobically grown *E. gracilis* cells contain similar total amounts of RQ and UQ, but RQ constitutes 43% and 28% of the pool under anaerobic and aerobic conditions, respectively.[122] Helminth parasites can use fumarate as a terminal electron acceptor in the respiratory chain since they possess RQ-fumarate oxidoreductase. *C. elegans* produce both UQ_9 and RQ_9, and the relative amounts are thought to be of relevance to lifespan.[123] *Rhodoplanes serenus* produces UQ_{10} and RQ_{10}.[124] As these examples demonstrate, organisms possessing RQ also have UQ, and UQ was shown to be required for the biosynthesis of RQ in *R. rubrum*. A novel gene named *rquA* was found in *R. rubrum* that is required only for RQ synthesis but not UQ synthesis.[125] The biosynthesis of RQ is still not fully understood.

10. Applications of prenylquinones

UQ_{10} (coenzyme Q_{10}) is popular as a food supplement and sold worldwide in both reduced and oxidized forms. The demand for skin care cosmetics and public awareness of the importance of antioxidants such as UQ_{10} has increased, and UQ_{10} is also used therapeutically in Alzheimer's, Huntington's, Parkinson's, and cardiovascular diseases.[47] As UQ_{10} is naturally produced in humans, and available from foods such as meat and fish, side effects are very rare. Taking statins to reduce the amount of cholesterol also lowers UQ_{10} levels, and so taking both simultaneously is recommended.[47] The UQ_{10} commercial market is large, and UQ_{10} is purified from yeast or photosynthetic bacteria. Several native producers of UQ_{10} have been investigated to optimize UQ_{10} production. *S. pombe*, *Sporidiobolus johnsonii*, *Rhodobacter sphaeroides*, and *Agrobacterium tumefaciens* reportedly produce 1.0, 10.5, 8.7, and 4.5 mg/g dry cell weight (DCW), respectively.[126] However, because these amounts were measured by different groups using different methods, direct comparison is necessary to assess the efficiency of UQ_{10} production by these microorganisms. Attempts to produce UQ_{10} in rice and tobacco have proven successful,[127, 128] and regulation of genetically modified organisms (GMOs) hampers the commercial production of UQ_{10} in rice.

MK is also sold as a food supplement in the form of MK_4 or MK_7. MK_7 is from *B. subtilis*, and MK_4 is produced in animals. The Japanese food Natto, fermented by *B. subtilis*, contains MK_7, and increases bone mineral density and reduces bone fractures. Humans do not biosynthesize MK, but it is utilized for blood coagulation, bone metabolism, and cell-cycle regulation. The major sources of MK in humans are the diet and gut flora. As MK is only synthesized in bacteria, inhibitors of MK synthesis are useful for inhibiting the growth of harmful bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). Using this concept, analogs of each reaction step were synthesized and shown to be efficient inhibitors such as 7-methoxy naphthalene

493 derivatives, methyl 4-oxo-4-phenylbut-2-enoate, and lysocin E of MenA,[129] MenB,[130]
494 and MenE, respectively.[131]

495 PhQ (VK_1) is used as a vitamin supplement since mammals are not able to
496 synthesize it, and must obtain it from their diet. PhQ is as a cofactor for coagulation
497 factors II, VII, IX, and X, required for the formation of anticoagulant factors protein C
498 and S, and for bone protein formation. PhQ is commonly used to treat warfarin toxicity.

499 PQ itself is not a commercially useful product, but derivatives such as
500 plastoquinonyl-decyl-triphenylphophonium (SkQ1) and its methylated derivative SkQ3
501 are under consideration for usage as antioxidants. Mitochondrial-targeted SkQ1 is
502 currently under clinical trial for glaucoma treatment and prevention of dry eye.[132]

503 RQ is only found in a limited number of organisms that are not used for food,
504 and applications for RQ have not been reported.

505

506 **11. Concluding remarks**

507 There are a wide variety of prenylquinones in nature, but their synthesis is not fully
508 understood. In this review, the biosynthesis of prenylquinones was summarized, with
509 emphasis on UQ, MK, PhQ, PQ, and RQ. Extensive studies have uncovered in detail
510 MEP and MVA biosynthetic pathways that lead to the synthesis of IPP and DMAPP.
511 Enzymes condensing IPP with DMAPP to produce polyprenyl diphosphate have been
512 particularly well studied. While the synthesis of the isoprenoid side chain is relatively
513 well characterized, many aspects of the modification of prenylquinones remain obscure.
514 UQ synthesis in bacteria is quite well defined, but our knowledge of UQ synthesis in
515 eukaryotes is incomplete. Classical MK synthesis is mostly understood, but the novel
516 MK pathway mediated by futalosine is vague in comparison. Many three-dimensional
517 structures related to UQ and MK synthesis have been solved, but some reactions in PhQ
518 synthesis remain undefined. Furthermore, exactly how RQ is synthesized after UQ
519 remains to be solved. Bioinformatics and genomics approaches are proving useful for
520 predicting the biosynthetic pathways of these prenylquinones, but details of such work

fall beyond the scope of this review. Nevertheless, this summary of recent progress on the biosynthesis of prenylquinones should prove useful, and will likely accelerate the characterization of unknown reactions and enzymes.

Acknowledgments

I thank Dr. T. Kaino for checking this manuscript.

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Figure legends

Figure 1. Distribution of four major prenylquinones in different organisms

Ubiquinone (UQ) is present in almost all living organisms from bacteria to higher eukaryotes. Menaquinone (MK) is distributed in bacteria and archaea, and therefore considered the oldest type of prenylquinone, first synthesized in primitive living organisms. Plastoquinone (PQ) occurs in cyanobacteria, and was presumably subsequently transferred to plants. Rhodoquinone (RQ) is the most recently evolved quinone, and is synthesized from UQ.

Figure 2. The mevalonate (MVA) pathway in *Saccharomyces cerevisiae*

The MVA pathway consists of seven enzyme-catalyzed reactions. The first step is the formation of acetoacetyl-CoA from two acetyl-CoA molecules by Erg10 (acetyl-CoA acetyl transferase). Subsequently, Erg13 (HMG-CoA synthase), Hmg1/Hmg2 (HMG-CoA reductase), Erg12 (mevalonate kinase), Erg8 (phosphomevalonate kinase), and Erg19 (diphosphomevalonate decarboxylase) lead to the production of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). Idi1 isomerizes between IPP and DMAPP.

Figure 3. The 2*C*-methyl-D-erythritol-4-phosphate (MEP) pathway in *Escherichia coli*

The MEP pathway consists of eight enzyme-catalyzed reactions. The first step is the condensation of pyruvate and glyceraldehyde-3-phosphate to form 1-deoxy-D-xylulose-5-phosphate by Dxs (DXP synthase). Subsequent steps catalyzed by IspC (DXP reductoisomerase), IspD (MEP cytidyltransferase), IspE (CDP-ME kinase), IspF (MECDP synthase), IspG (4-hydroxy-3-methylbut-2-enyl diphosphate synthase), and IspH (4-hydroxy-3-methylbut-2-enyl diphosphate reductase) lead to the production of IPP and DMAPP.

Figure 4. Biosynthetic pathway of the isoprenoid tail of prenylquinones

1029 Polyprenyl diphosphate synthase synthesizes *trans*-polyprenyl diphosphate of a certain
1030 length. *S. cerevisiae* Coq1 (hexaprenyl diphosphate synthase) forms products from six
1031 isoprene units, *E. coli* IspB (octaprenyl diphosphate synthase) synthesizes products with
1032 eight isoprene units, *Arabidopsi*s SPS1, SPS2, and SPS3 (solanesyl diphosphate
1033 synthase) generate products with nine isoprene units, and human and
1034 *Schizosaccharomyces pombe* decaprenyl diphosphate synthase (DPS; a heteromer of
1035 PDSS1 and PDSS2 or Dps1 and Dlp1, respectively) catalyzes the formation of products
1036 with ten isoprene units. *S. cerevisiae* Coq2 (PHB-hexaprenyl diphosphate transferase),
1037 *E. coli* UbiA (PHB-octaprenyl diphosphate transferase), and human COQ2
1038 (PHB-decaprenyl diphosphate transferase) or *S. pombe* Ppt1 (Coq2; PHB-decaprenyl
1039 diphosphate transferase) condense *p*-hydroxybenzoate (PHB) with *trans*-polyprenyl
1040 diphosphate to form UQ_6, UQ_8, and UQ_{10}, respectively. MenA prenylates DHNA, and
1041 homogentisate solanesyl transferase (HST) prenylates homogentisate (HGA). DPP,
1042 decaprenyl diphosphate; HexPP, hexaprenyl diphosphate; NPP, nonaprenyl
1043 diphosphate; OPP, octaprenyl diphosphate.
1044
1045 Figure 5. Overview of the proposed UQ biosynthetic pathway
1046 The UQ biosynthetic pathways of *E. coli* and *S. cerevisiae* are shown. In *E. coli*, PHB is
1047 first condensed with *trans*-polyprenyl diphosphate, and the ring structure is then
1048 modified. Decarboxylation catalyzed by UbiD (3-octaprenyl-4-hydroxybenzoate
1049 decarboxylase) and UbiX (flavin prenyl transferase) follows. The ring is further
1050 hydroxylated by UbiI (2-octaprenylphenol hydroxylase), *O*-methylated by UbiG
1051 (2-octaprenyl-6-hydroxy phenol methylase), hydroxylated by UbiH
1052 (2-octaprenyl-6-methoxyphenol hydroxylase), *C*-methylated by UbiE
1053 (2-octaprenyl-6-methoxy-1,4-benzoquinone methylase), hydroxylated by UbiF
1054 (2-octaprenyl-3-methyl-6-methoxy-1,4-benzoquinone oxygenase), and *O*-methylated by
1055 UbiG (3-demethylubiquinone 3-methyltransferase). In *S. cerevisiae*, para-amino
1056 benzoic acid (pABA) and PHB are used for UQ synthesis. The first ring is modified via

hydroxylation by Coq6 (PHB-2-hexaprenyl hydroxylase), followed by *O*-methylation by Coq3 (2-hexaprenyl-6-hydroxy phenol methyltransferase). After decarboxylation and hydroxylation steps, the ring is further modified via *C*-methylation by Coq5 (2-hexaprenyl-6-methoxy-1,4-benzoquinone methyltransferase), a final hydroxylation by Coq7 (2-hexaprenyl-3-methyl-6-methoxy-1,4-benzoquinone oxygenase), and *O*-methylation by Coq3. *H. sapiens* contains similar enzymes with *S. cerevisiae* except PDSS1 an PDSS2.[70)]

Figure 6. Menaquinone biosynthesis in *E. coli*

The biosynthesis of menaquinone in *E. coli* starts from the conversion of chorismate to isochorismate by MenF. Subsequently, MK is synthesized by MenD (succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexadiene-1-carboxylate synthase), MenH (2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase), MenC (*O*-succinylbenzoate synthase), MenE (*O*-succinylbenzoic acid-CoA ligase), MenB (naphthoate synthase), MenI (DHNA-CoA thioesterase), MenA (1,4-dihydroxy-2-naphthoate octaprenyltransferase), and MenG (UbiE). *MenJ functions as a reductase of the side chain in *Mycobacterium tuberculosis*.

Figure 7. Novel pathway of menaquinone synthesis via futalosine

A novel menaquinone biosynthesis pathway was originally discovered in *Streptomyces coelicolor*, in which 1,4-dihydroxy-6-naphthoate is synthesized by MqnA (chorismate dehydratase), MqnD (1,4-dihydroxy-6-naphthoate synthase), MqnE (aminofutalosine synthase), AFL deaminase, MqnB (futalosine hydrolase), and MqnC (dehypoxanthine futalosine cyclase). MK synthesis from 1,4-dihydroxy-6-naphthoate is still not clearly understood, but a prenylation step catalyzed by MqnP has been proposed.

Figure 8. Crystal structures of menaquinone biosynthetic enzymes

(A) MenF from *E. coli* (PDB ID: 2EUA). (B) MenC from *E. coli* (PDB ID: 1FHU). (C) MenB from *E. coli* (PDB ID: 3T89). (D) MenD from *E. coli* (PDB ID: 3HWX). (F) MenE from *E. coli* (PDB ID: 5C5H). (G) MenH from *E. coli* (PDB ID: 4GDM). (H) MenI from *E. coli* (PDB ID: 4K4B). (I) MqnA from *Deinococcus radiodurans* (PDB ID: 216E). (J) MqnD from *Thermus thermophilus* HBB (PDB ID: 3A3U). (K) MqnB from *Helicobacter pylori* (PDB ID: 4BMX).

Figure 9. The biosynthesis of plastoquinone

In plants, tyrosine is converted to *p*-hydroxyphenylpyruvate (PHPP) by TAT (tyrosine amino transferase), and the product is oxidized to HGA by HPPD (*p*-hydroxyphenylpyruvate dioxygenase). HGA is prenylated by HST (homogentisate prenyltransferase), and methylated by VTE3 (MSBQ methyltransferase) to yield PQ. In *Synechocystis*, PHB is used as a quinone backbone, and after prenylation of PHB by Slr0926, decarboxylation, oxidation, and methylation take place.

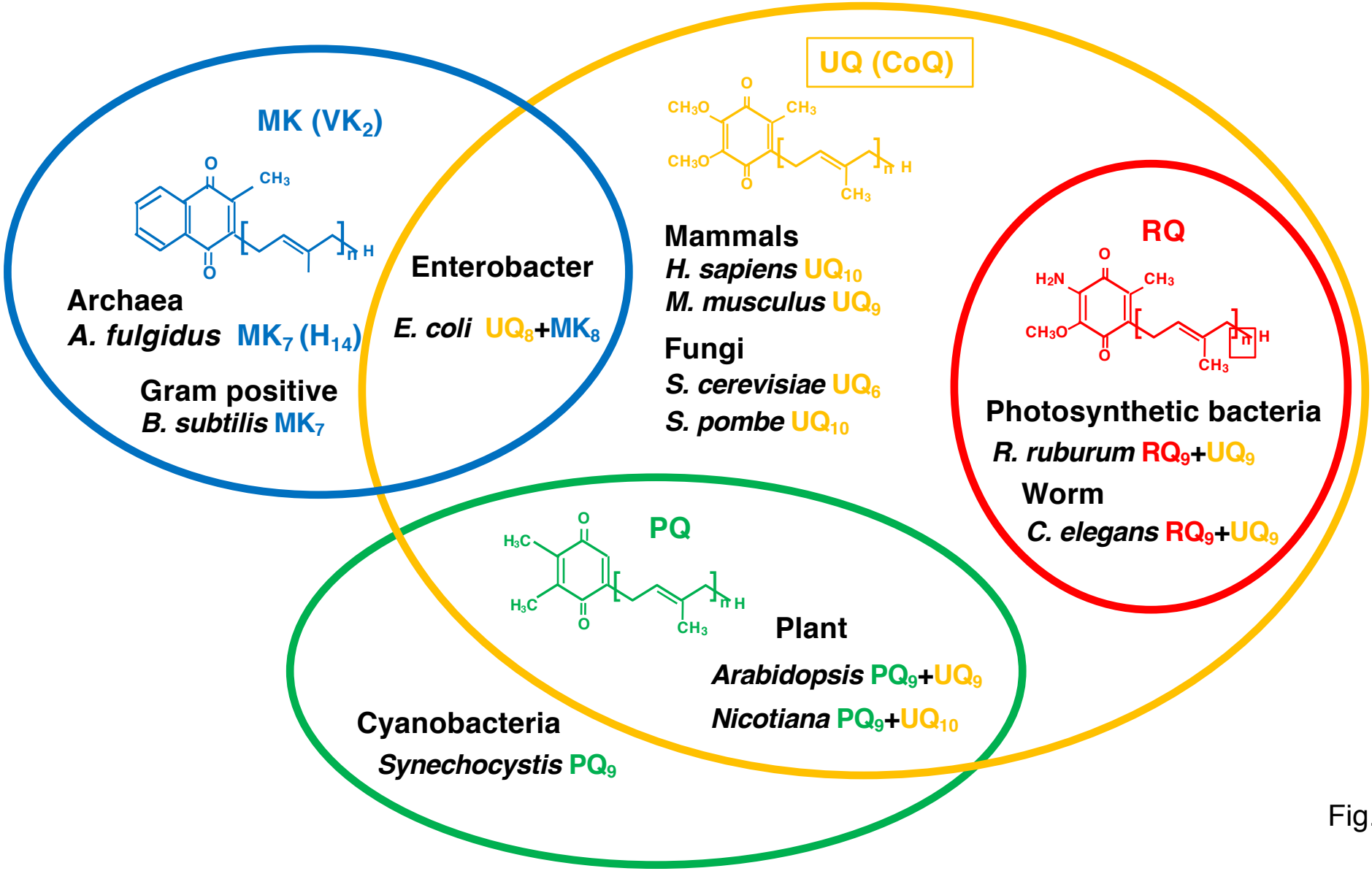
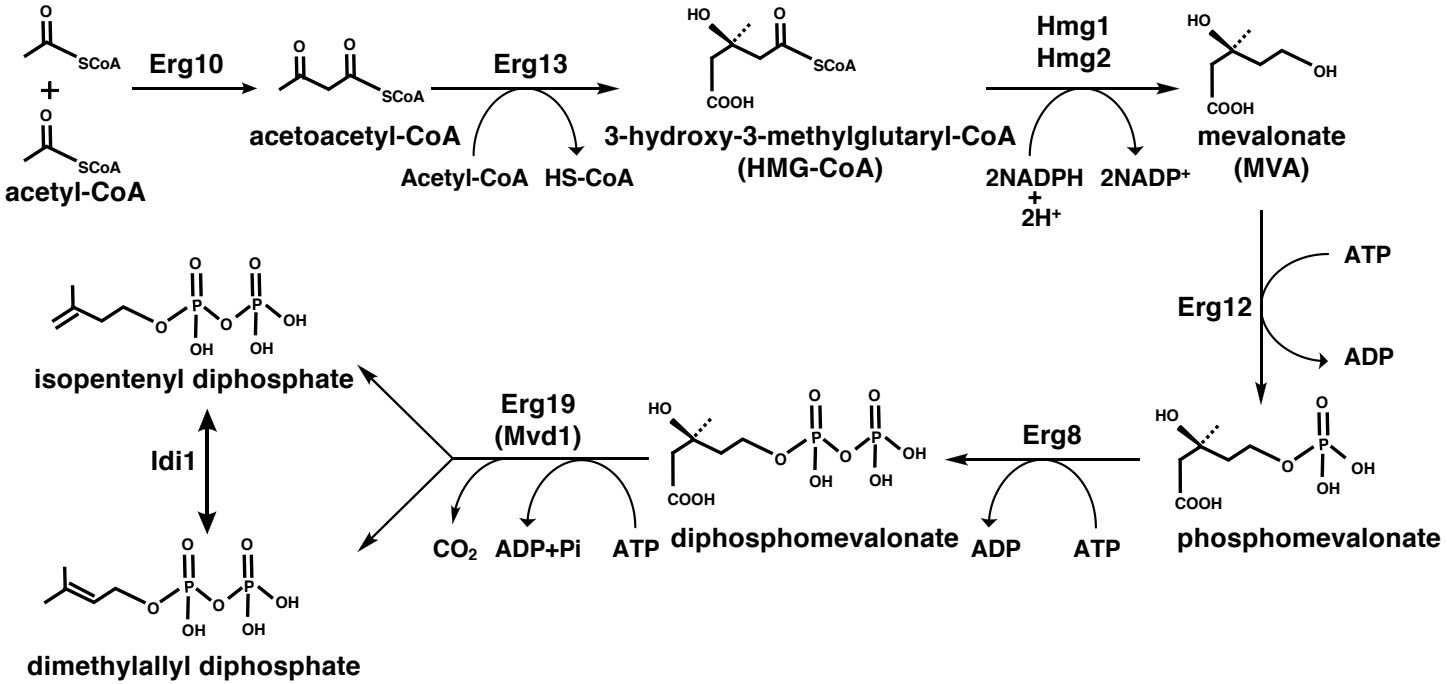

MK (VK_2)
Archaea
A. fulgidus MK_7 (H_{14})
Gram positive
B. subtilis MK_7
Enterobacter
E. coli UQ_8+MK_8
UQ (CoQ)
Mammals
H. sapiens UQ_{10}
M. musculus UQ_9
Fungi
S. cerevisiae UQ_6
S. pombe UQ_{10}
RQ
Photosynthetic bacteria
R. ruburum RQ_9+UQ_9
Worm
C. elegans RQ_9+UQ_9
PQ
Plant
Arabidopsis PQ_9+UQ_9
Nicotiana PQ_9+UQ_{10}
Cyanobacteria
Synechocystis PQ_9

Fig. 1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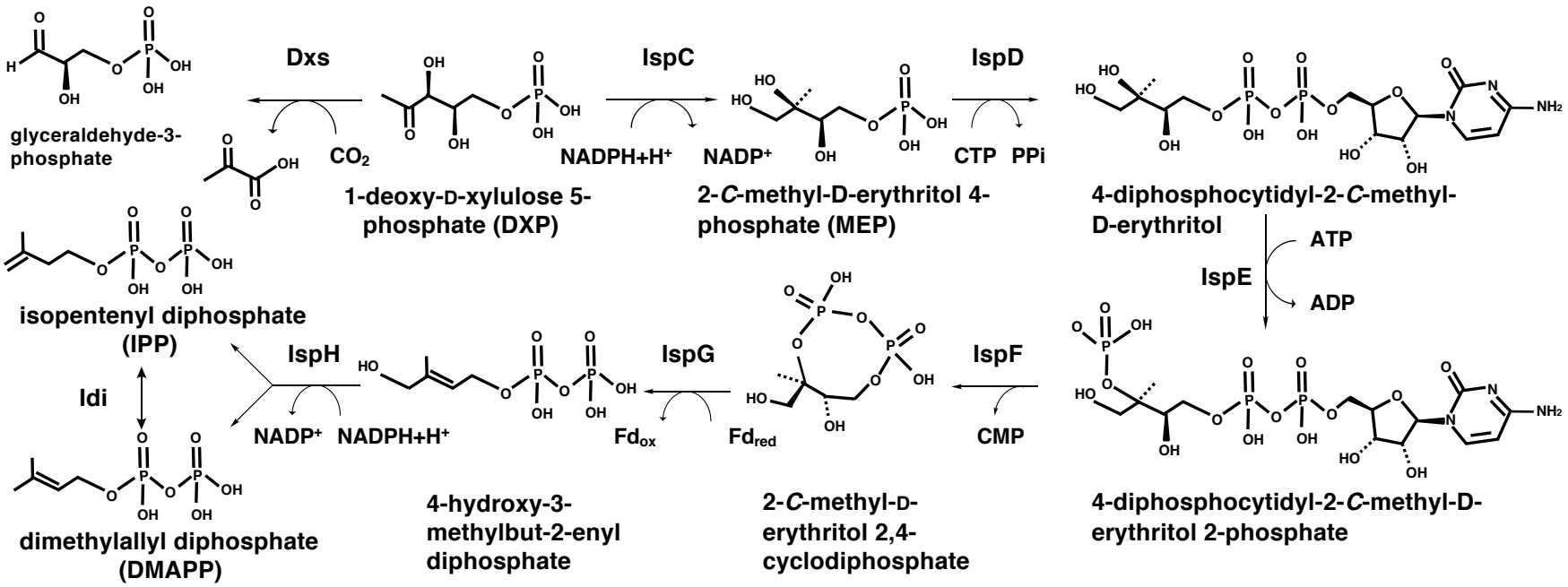
Hmg2
2NADPH
+
2H+
2NADP+
mevalonate
(MVA)
ATP
Erg12
ADP
phosphomevalonate
Erg8
ADP
ATP
diphosphomevalonate
Erg19
(Mvd1)
CO2
ADP+Pi
ATP
Idi1
isopentenyl diphosphate
dimethylallyl diphosphate

Fig. 2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NADP+
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IspD
CTP
PPi
4-diphosphocytidyl-2-C-methyl-D-erythritol
IspE
ATP
ADP
4-diphosphocytidyl-2-C-methyl-D-erythritol 2-phosphate
IspF
CMP
2-C-methyl-D-erythritol 2,4-cyclodiphosphate
IspG
Fdox
Fdred
4-hydroxy-3-methylbut-2-enyl diphosphate
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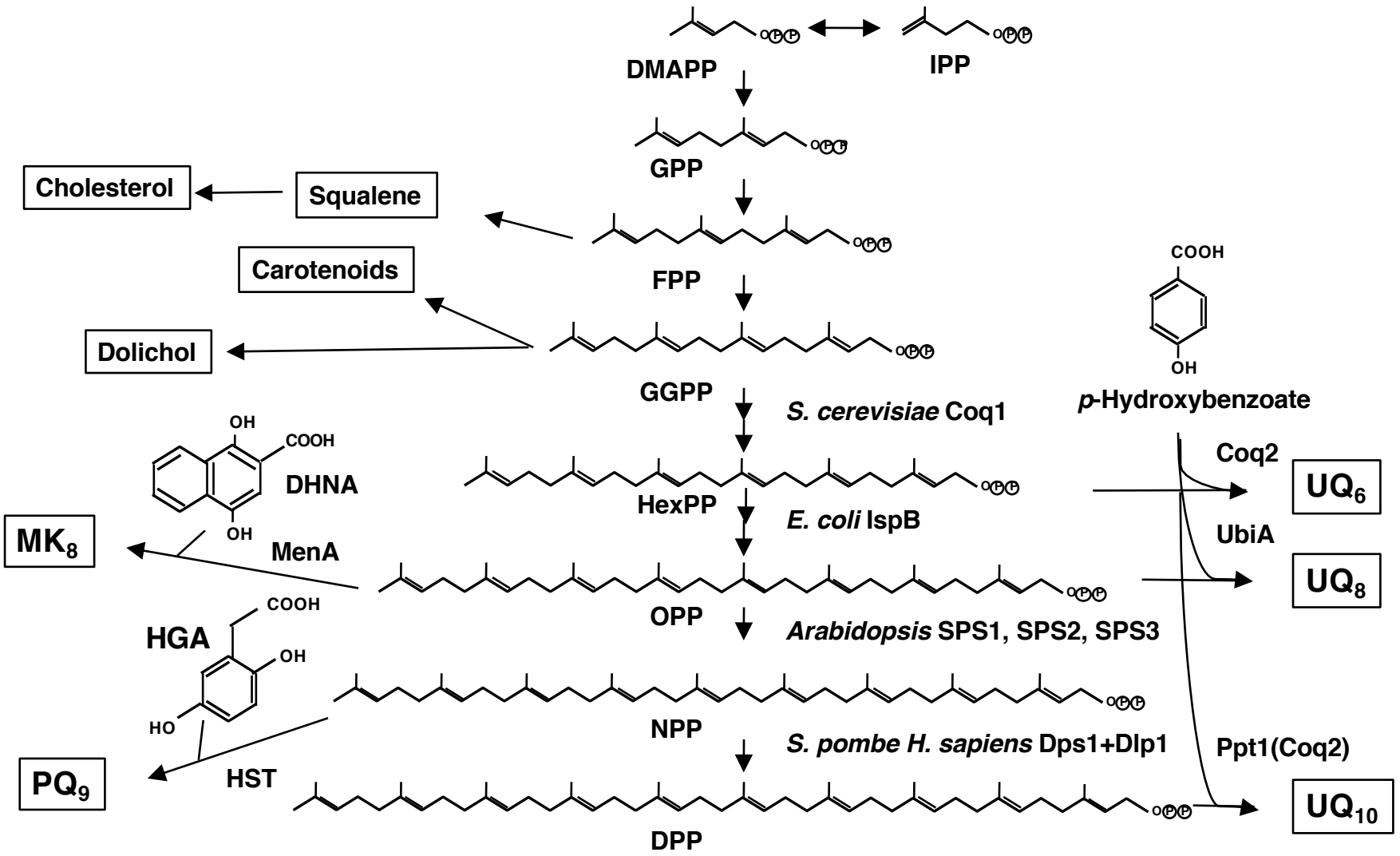
NADPH+H+
Idi
isopentenyl diphosphate (IPP)
dimethylallyl diphosphate (DMAPP)

Fig. 3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OH
Coq2
UQ6
HexPP
E. coli IspB
UbiA
UQ8
DHNA
MK8
MenA
OPP
Arabidopsis SPS1, SPS2, SPS3
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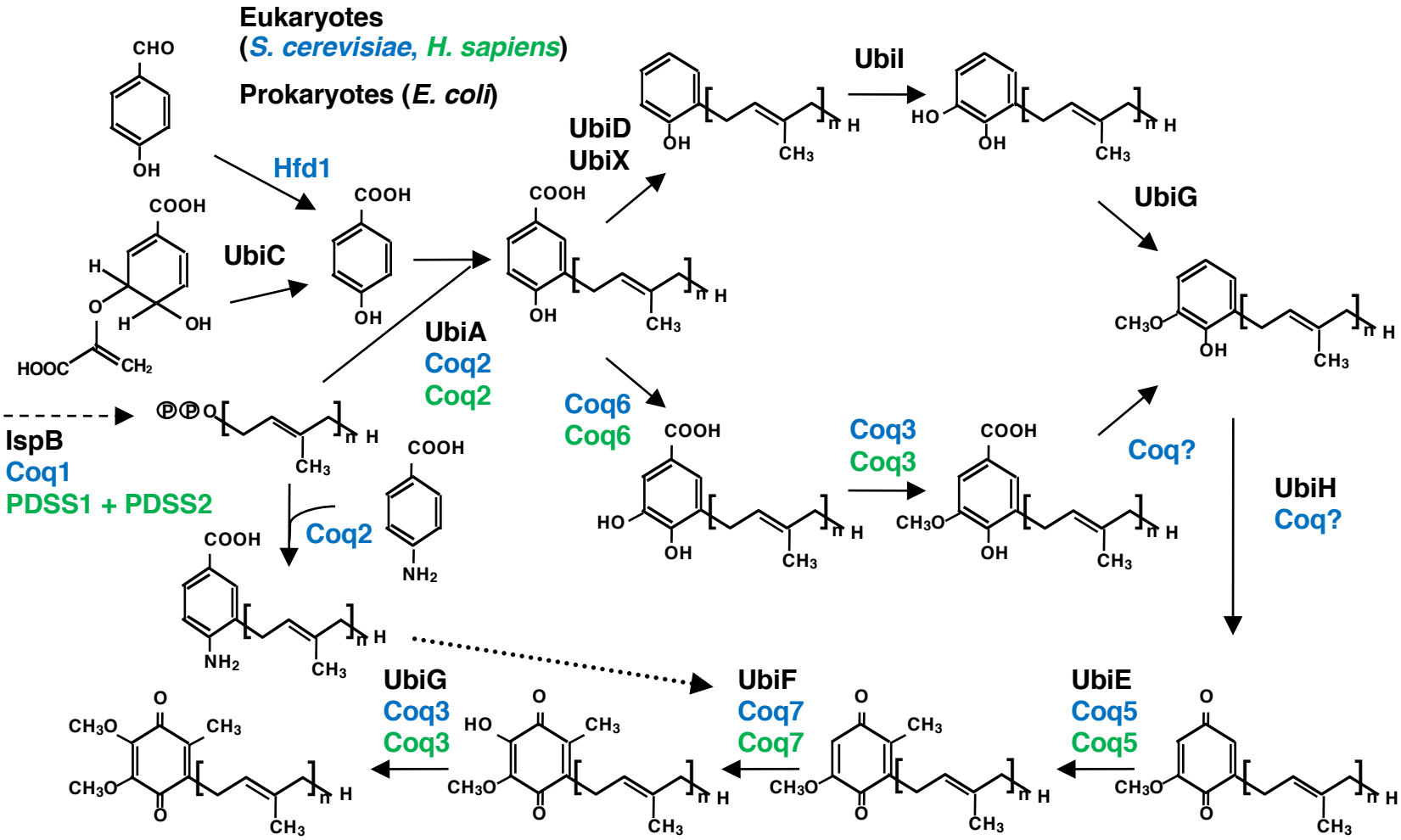
NPP
S. pombe H. sapiens Dps1+Dlp1
Ppt1(Coq2)
PQ9
HST
UQ10
DPP

Fig.4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(S. cerevisiae, H. sapiens)
Prokaryotes (E. coli)
Hfd1
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Coq2
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UbiI
UbiG
Coq6
Coq6
Coq3
Coq3
Coq?
UbiH
Coq?
IspB
Coq1
PDSS1 + PDSS2
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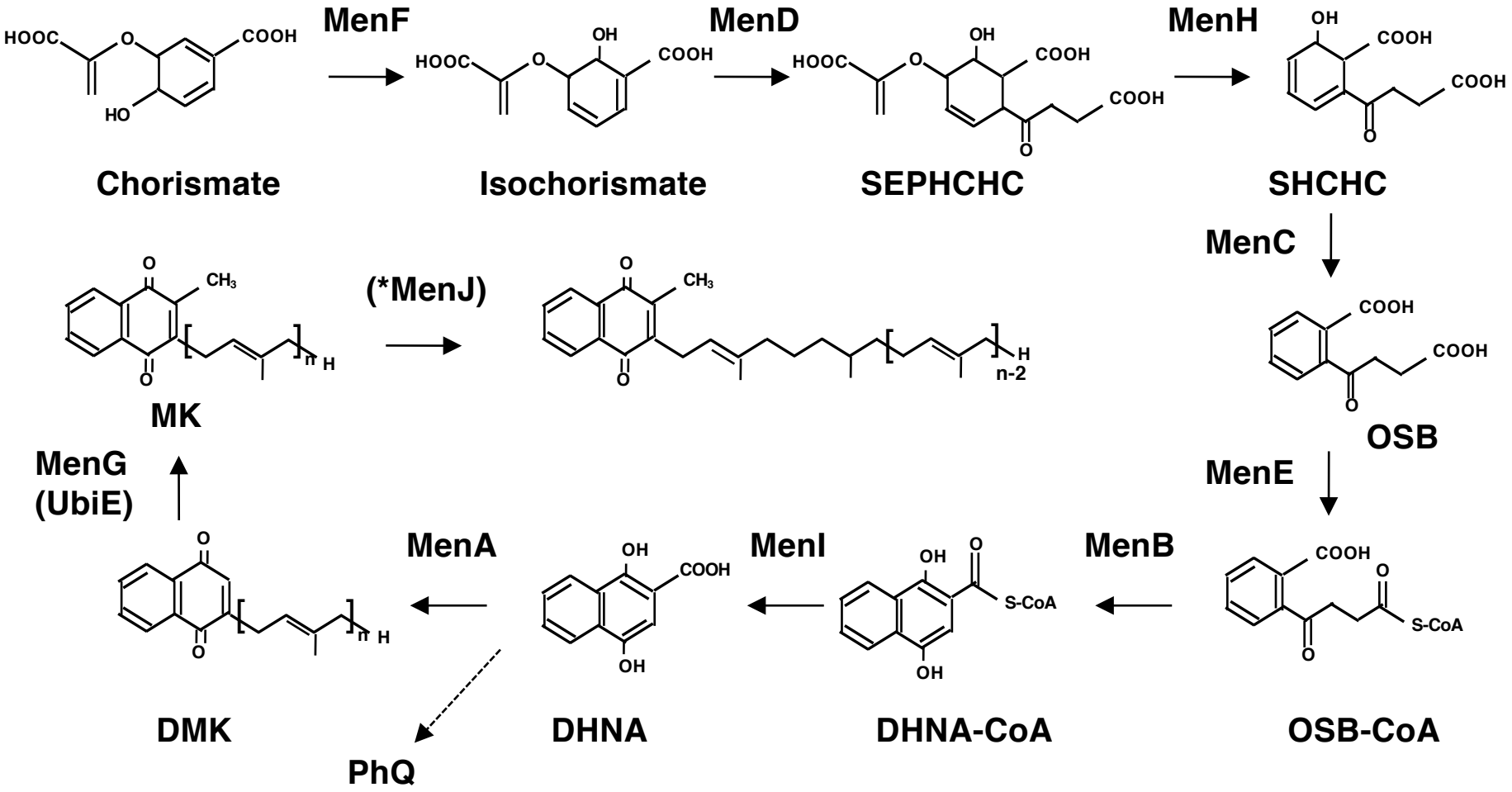
UQ
DMQ

Fig.5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SHCHC
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MenE
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MenI
DHNA
MenA
DMK
PhQ
MenG
(UbiE)
MK
(*MenJ)
n-2

Fig.6

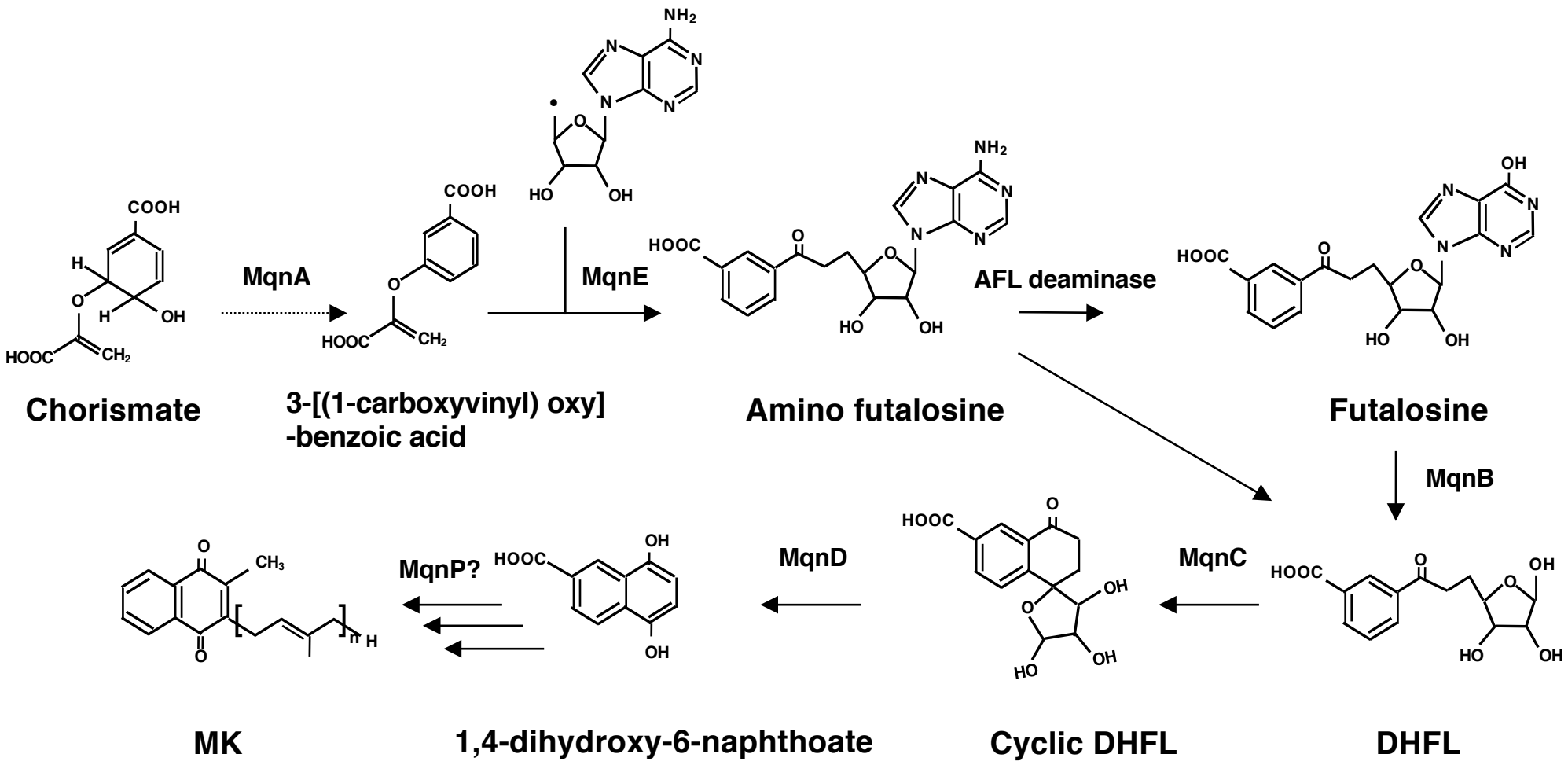
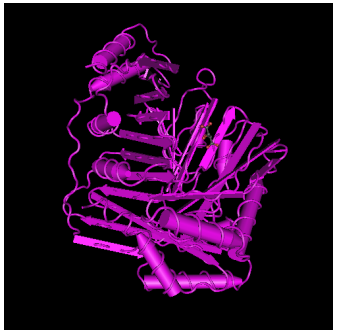
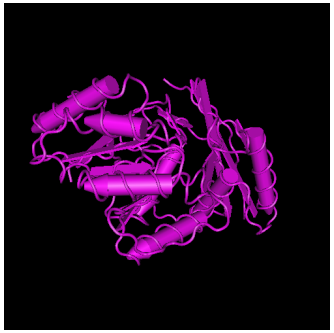

MqnA
MqnE
AFL deaminase
MqnB
MqnC
MqnD
MqnP?
Chorismate
3-[(1-carboxyvinyl) oxy]
-benzoic acid
Amino futalosine
Futalosine
DHFL
Cyclic DHFL
1,4-dihydroxy-6-naphthoate
MK

Fig.7

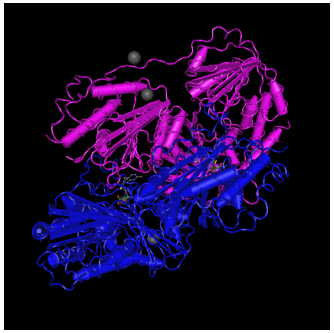


MenF

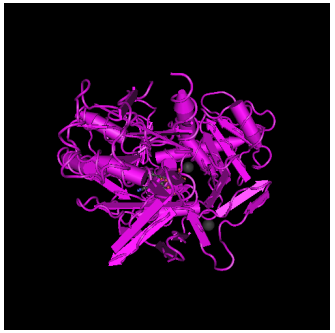


MenC

MenB



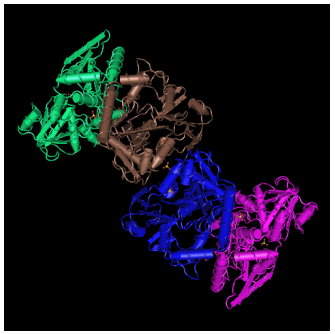
MenD



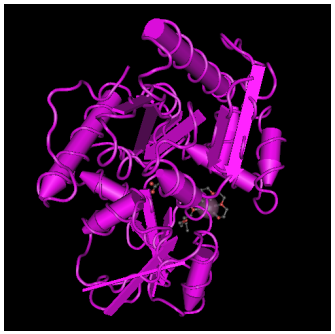
MenE

MenH

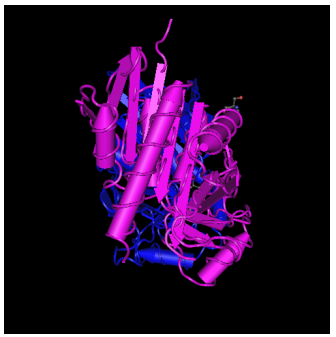
MenI



MqnA



MqnD



MqnB

Fig.8

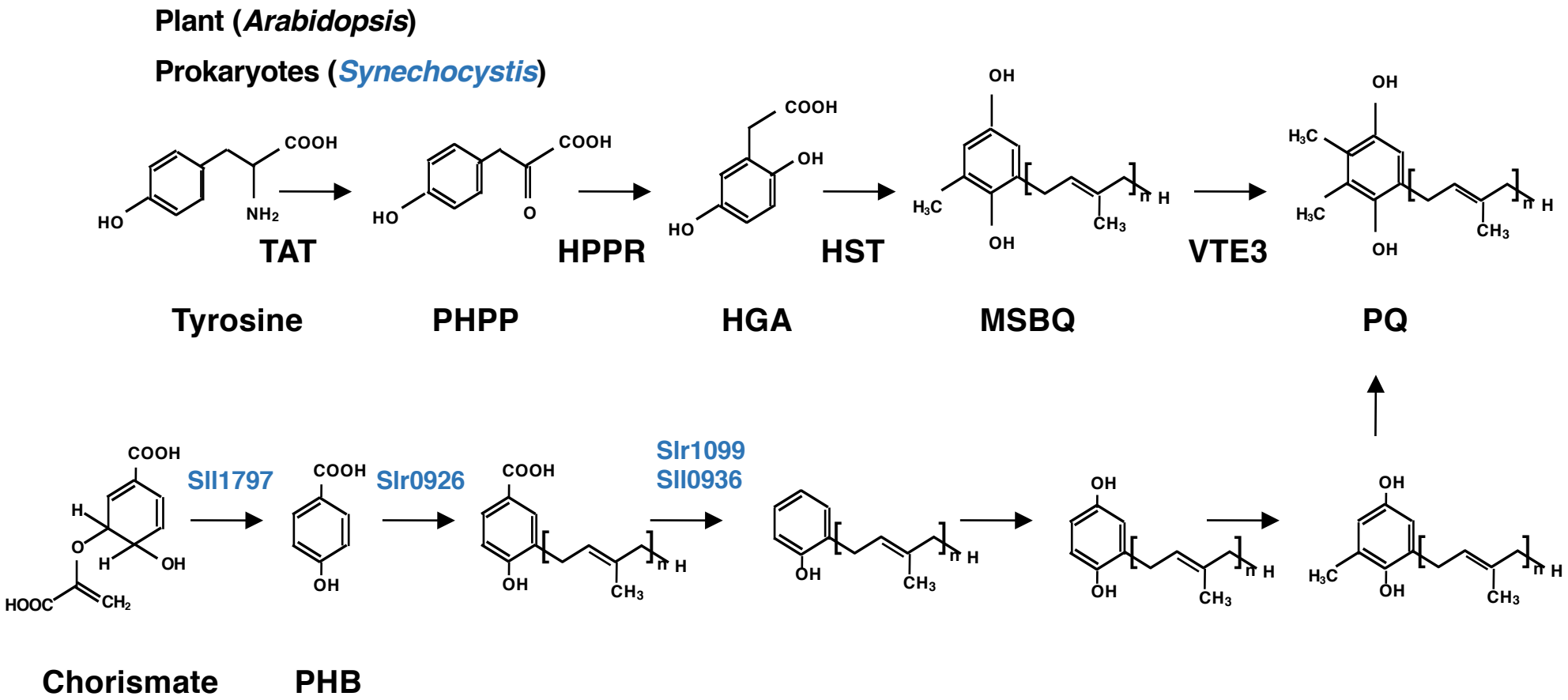

Plant (*Arabidopsis*)
Prokaryotes (*Synechocystis*)
TAT
HPPR
HST
VTE3
Tyrosine
PHPP
HGA
MSBQ
PQ
Sll1797
Slr0926
Slr1099
Sll0936
Chorismate
PHB

Fig.9