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Review

Occurrence, biosynthesis and function of isoprenoid quinones

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ABSTRACT

Isoprenoid quinones are one of the most important groups of compounds occurring in membranes of living organisms. These compounds are composed of a hydrophilic head group and an apolar isoprenoid side chain, giving the molecules a lipid-soluble character. Isoprenoid quinones function mainly as electron and proton carriers in photosynthetic and respiratory electron transport chains and these compounds show also additional functions, such as antioxidant function. Most of naturally occurring isoprenoid quinones belong to naphthoquinones or evolutionary younger benzoquinones. Among benzoquinones, the most widespread and important are ubiquinones and plastoquinones. Menaquinones, belonging to naphthoquinones, function in respiratory and photosynthetic electron transport chains of bacteria. Phylloquinone K_1, a phytyl naphthoquinone, functions in the photosynthetic electron transport in photosystem I. Ubiquinones participate in respiratory chains of eukaryotic mitochondria and some bacteria. Plastoquinones are components of photosynthetic electron transport chains of cyanobacteria and plant chloroplasts. Biosynthetic pathway of isoprenoid quinones has been described, as well as their additional, recently recognized, diverse functions in bacterial, plant and animal metabolism.

1. Introduction

Isoprenoid quinones are membrane-bound compounds found in nearly all living organisms. The only exception presently known is some obligatory fermentative bacteria that lost the ability of synthesis of isoprenoid quinones [1] and methanogenic *Archea*, belonging to *Methanosarcinales* [2]. Isoprenoid quinones are composed of a polar head group and a hydrophobic side chain. The apolar isoprenoid side chain gives the molecules a lipid-soluble character and anchors them in membrane lipid bilayers, whereas the hydrophilic head group enables interaction with hydrophilic parts of proteins. It is generally accepted that long-chain, isoprenoid quinones localize in the hydrophobic mid-plane region of the lipid bilayer, whereas the polar head can oscillate between mid-plane and polar interphase of the membrane [3]. The quinone ring can undergo two-step reversible reduction leading to quinol form (Fig. 1). The reduced form of isoprenoid quinones is more polar and the quinol head group is thought to preferentially localize in polar, interphase region of membranes [3,4].

The ability of reversible reduction and the presence of the lipid-soluble side chain make the isoprenoid quinones ideal candidates for their function as hydrogen shuttles between different protein complexes of biological membranes. Isoprenoid quinones, which are also termed prenylquinones [5,6], function in electron transport chains as membrane-bound, mobile hydrogen carriers but some of these molecules are permanently associated with proteins and participate in electron transport within protein complexes. Such protein-bound prenylquinones, where semiquinone form is stabilized, often act as a "gates" between one and two-electron processes. The reduced forms of isoprenoid quinones have pronounced antioxidant properties and protect membranes from lipid peroxidation and deleterious effects of reactive oxygen species on membrane components. During recent years, a vast number of data concerning function of isoprenoid quinones as enzyme cofactors accumulated. These compounds were also postulated to participate in regulation of gene expression and signal transduction within cells [7].

The great majority of biological isoprenoid quinones belong to naphthoquinones or benzoquinones. The two most important groups of benzoquinones are ubiquinones and plastoquinones, differing in the pattern of ring substitution. Besides, the hydrophobic side chains of isoprenoid quinones can vary not only in the length but also in a degree of saturation, as well as in the presence of additional groups. Different groups of isoprenoid quinones occur in different taxonomic groups of organisms, making isoprenoid quinone profile a useful taxonomic tool [1].

Abbreviations: DHFL, dehypoxanthinylfutalosine; DHNA, 1,4-dihydroxy-2-naphthoate; DMK, demethylmenaquinone; DXP, 1-deoxy-D-xylulose-5-phosphate; ETF-QU, electron transfer flavoprotein:UQ oxidoreductase; FNR, ferredoxin:$NADP^+$ oxidoreductase; GGCX, γ-glutamyl carboxylase; Gla, γ-carboxyglutamate; HGA, homogentisate; K_1, phylloquinone; MK, menaquinone; MKH_2, menaquinol; MTQ, methionaquinone; MVA, mevalonate; NDH-2, type II dehydrogenase; PHB, *p*-hydroxybenzoate; PS, photosystem; PQ, plastoquinone; PQH_2, plastoquinol; QFR, quinol:fumarate oxidoreductase; ROS, reactive oxygen species; RQ, rhodoquinone; RQH_2, rhodoquinol; SQR, sulfide:quinone oxidoreductase; TPQ, thermoplasmaquinone; TQ, tocopherol quinone; TQH_2, tocopherol quinol; UQ, ubiquinone; UQH_2, ubiquinol

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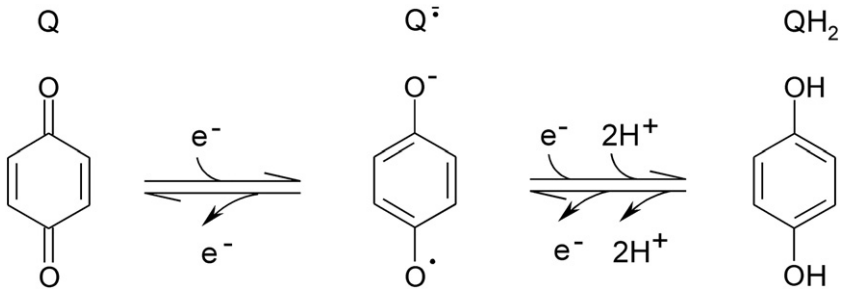

Fig. 1. Redox reactions of the quinone ring, Q—oxidized form, $Q^{\cdot -}$—charged, semiquinone radical, unstable, can be stabilized by interaction with proteins, QH_2—stable, non-charged hydroquinone form.

2. Isoprenoid naphthoquinones

2.1. Menaquinones and related compounds

2.1.1. Occurrence

Menaquinones (MK) (Fig. 2) are the most widespread microbial respiratory quinones that are evolutionary most ancient type of isoprenoid quinones [8]. These compounds can be found in many groups of *Archaea* [9] and bacteria, such as γ- δ- ε-proteobacteria, gram-positive bacteria, green sulfur bacteria, green filamentous bacteria, deinococci and flavobacteria [8,10,11]. Menaquinones have low midpoint redox potential, and their appearance in early phase of evolution can be connected with the reducing character of atmosphere before appearance of oxygenic photosynthesis and the following increase in oxygen concentration in the environment. The "transition" from naphthoquinones to other quinones, showing higher midpoint redox potential, occurred independently in a few groups of *Prokaryota* as an adaptation to aerobic metabolism. The reduced menaquinones become rapidly and noncatalytically oxidized in the presence of oxygen [11], therefore these compounds cannot efficiently operate in an atmosphere containing oxygen. It should be mentioned, that some obligatory fermentative bacteria had lost the ability to synthesize menaquinones—most of bacteria of genus *Lactobacillus* and *Streptococcus*, but genes of menaquinone biosynthetic pathway can be found in some of the species [1,12]. The isoprenoid side chain of menaquinones is most frequently composed of 6–10 prenyl units but also homologues with one to 14 prenyl units were found in some species [1]. The side chain is most often fully unsaturated, but it can be also partially or fully saturated in some organisms [1]. The length and degree of saturation of the side chain are often dependent on the growth temperature of a given species. Menaquinones contain methyl-naphthoquinone as a head group, but in some prokaryotes compounds with different modifications of the head group were identified (Fig. 2). Among the *Archea*, thermoplasmaquinone (TPQ) and methionaquinone (MTQ) occur in *Thermoplasma* [9,13]. Demethylmenaquinones (DMKs) and methylmenaquinones are often used by proteobacteria and gram-positive bacteria [1,14]. Chlorobiumquinone (1′-oxo-menaquinone-7) was found in photosynthetic green sulfur bacteria—it is only known isoprenoid naphthoquinone containing carbonyl group in the side chain [1]. Surprisingly, chlorobiumquinone was also identified as a major isoprenoid quinone in parasitic protozoan *Leischmania*

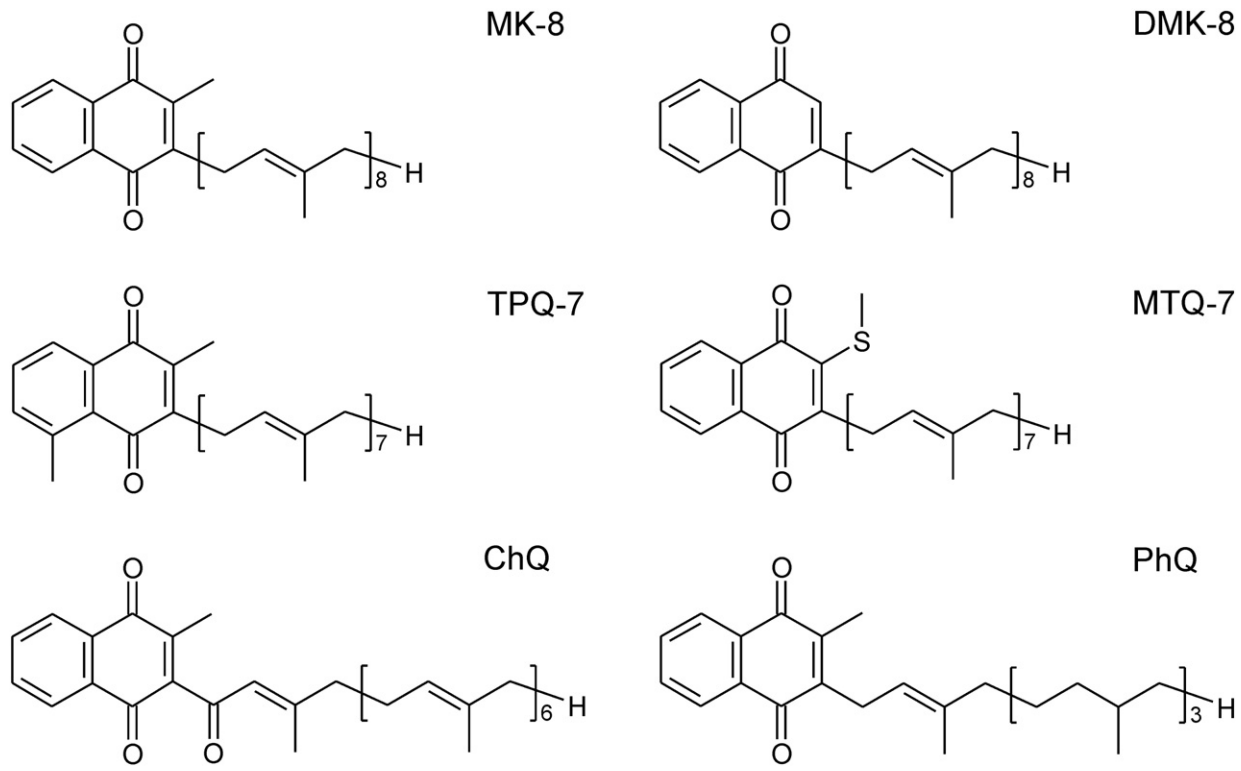

Fig. 2. Isoprenoid naphthoquinones: MK-8, menaquinone-8 and DMK-8, demethylmenaquinone-8 present in *E. coli*; TPQ-7, thermoplasmaquinone-7 and MTQ-7, methionaquinone-7 found in *Thermoplasma acidophilum*; ChQ, chlorobiumquinone (1′-oxo-menaquinone-7) occurring in *Chlorobium tepidum*, PhQ—phylloquinone.

donovani [15]. It is thought to act in plasma membrane of the parasite as a part of defense system against oxidative burst of the host. Moreover, the presence of homologues of the genes found in photosynthetic bacteria was discovered in trypanosomatids, which let to hypothesize that ancestors of *Leishman*ia could have had endosymbionts but lost it during evolution [15].

2.1.2. Biosynthesis

During biosynthesis of menaquinones and other isoprenoid quinones, the head group precursor and the isoprenoid side chain are synthesized separately. Then both counterparts are condensed by an enzyme belonging to prenyltransferase family and the resulting product undergoes further modifications. The primary precursors for the isoprenoid chain are dimethylallyl diphosphate and isopentenyl diphosphate. There are two distinct and independent biosynthetic pathways leading to these precursors: mevalonate (MVA) and 1-deoxy-D-xylulose-5-phosphate (DXP) pathways and the presence of these pathways in different taxonomic groups is a complex issue [16]. *Archaea* are thought to take advantage of the MVA pathway. In known genomes of species belonging to this group, there are homologues of genes encoding enzymes of this pathway, whereas there are no homologues of the DXP pathway genes. On the other hand, great majority of bacteria use DXP pathway, but there are exceptions. *Myxococcus fulvus* and *Chloroflexus aurantiacus* use MVA pathway, while *Streptomycetes* possess both pathways and in some obligate parasitic bacteria, like *Rickettsia prowazekii* or *Mycoplasma genitalium,* there are no genes for isopentenyl diphosphate synthesis [16]. All the animals and fungi, studied up to date, take advantage of the MVA pathway, while higher plants use both of them: DXP pathway proceeds in plastids, whereas enzymes of the MVA pathway are found in cytosolic compartment. Thus, higher plants use the DXP pathway during biosynthesis of prenyl chains of phylloquinone, plastoquinone, tocopherolquinone, as well as chlorophyll and tocopherol, whereas MVA pathway is used for ubiquinone synthesis [17]. There is also a variety of the pathways in algae and *Protista*, e.g. *Euglena gracilis* uses only MVA pathway, *Chlamydomonas reinhardtii* – only DXP pathway, while the rhodophyte *Cyanidium caldarum* – both [16]. This complicated pattern is thought to be a result of horizontal gene transfer and endosymbiotic origin of organelles. The isoprenoid side chain is formed from precursors through series of condensation reactions carried out by a specific prenyl diphosphate synthase.

In the menaquinone biosynthetic pathway, 1,4-dihydroxy-2-naphthoate (DHNA), the precursor of the head group, is derived from chorismate formed via shikimate pathway. There are known two pathways of MK biosynthesis (Fig. 3A and B). In the first pathway, enzymes encoded by *men* genes and the recently identified thioesterase [18] are involved in MK formation. The enzymes engaged in DHNA biosynthesis are: MenF—isochorismate synthase, MenD—2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase, MenH—SHCHC synthase, MenC—*o*-succinyl benzoate synthase, MenE—*o*-succinylbenzoic acid-CoA synthase, MenB—1,4-dihydroxy-2-naphthoyl-CoA synthase and DHNA-CoA thioesterase [18]. Until recently, MenH was thought to hydrolyze DHNA-CoA but it was shown that this enzyme lacks thioesterase activity and to catalyze in fact earlier step in the pathway [19] (Fig. 3A). The condensation reaction is catalyzed by DHNA prenyltransferase. The number of prenyl units in the attached isoprenoid side chain is determined by the length of isoprenoid diphosphate and may differ among species (e.g. *E.coli*—mainly MK-8, *Bacillus firmus*—MK-7, *Geobacter metallireducens*—MK-8 [10,20]). After condensation, the naphthoate group is modified by methylation. The majority of enzymes involved in MK synthesis are soluble [21]. Recently, the second pathway has been discovered [22]. The studies on this pathway began with the observation, that some microorganisms, such as *Helicobacter pylori, Campylobacter jejuni, Streptomyces coelicolor* or *Thermus thermophilus* are able to synthesize MK even though they do not have orthologues of certain *men* genes. After extensive studies including bioinformatic analysis, mutagenesis, radioisotope labeling and genetic engineering, the alternative, so called "futalosine pathway" has been identified (Fig. 3B) [22]. In this pathway, four enzymes are engaged in DHNA biosynthesis: MqnA catalyzes condensation of chorismate, inosine and C2 unit (probably derived from phosphoenolpyruvate) leading to futalosine, MqnB—futalosine hydrolase splits off hypoxanthine forming dehypoxanthinylfutalosine (DHFL), MqnC cyclize DHFL and MqnD cleavages cyclic DHFL to release DHNA [23]. The following steps are thought to be the same as in the other pathway [23].

2.1.3. Function

The best known function of MKs is participation in prokaryotic respiratory and photosynthetic electron transport chains [8,10,24]. As far as *Prokaryota* are concerned, the peculiar character of their metabolism is the high flexibility and diversity of energy generating systems, which is due to numerous types of proteins participating in these processes. Prokaryotic organisms are able to perform anoxygenic and oxygenic photosynthesis, as well as chemosynthesis where oxidation of sulfide, CNS^-, ammonium, hydrogen or Fe(II) takes place. In the process of respiration, *Prokaryota* can use oxygen as a terminal electron acceptor, but many species take advantage of other compounds, like nitrite, nitrate, sulfate, sulfite, thiosulfate, polisulfide, elemental sulfur, fumarate, Fe (III), metal oxoanions, selenate and others (for the review concerning flexibility of bacterial respiration see [25]). The example of bacterium displaying pronounced flexibility of respiration is *Shewanella oneidensis*, facultative anaerobic γ-proteobacterium, which is able to use: fumarate, nitrate, nitrite, sulfide, thiosulfide, elemental sulfur, selenite, tellurite, Fe(III), Mn(IV), Mn(III), Cr(VI) and U(VI) as terminal electron acceptors [26,27]. The above mentioned electron transport chains of the respiratory pathways are very complex—they can be branched, with electron influx into specific branches strictly regulated, depending on environmental conditions, or they can be simple and are composed of only two proteins and MK [25,28–30]. Most of these pathways involve MKs, as lipid-soluble, diffusing molecules transferring electrons and protons between protein complexes [25]. Exceptionally, directly interacting proteins have been postulated, as in the case of hydrogenase and polysulfide reductase of *Wolinella succinogenes*, where participation of bound MK was postulated [31]. Some bacteria lost their electron transport chains, but for many species exogenously supplied heme and MK enhance the culture growth, which was postulated to be an effect of partial reconstitution of the membrane electron transfer [32,33].

The detailed description of prokaryotic respiratory chains is beyond the scope of this review, but some examples of enzymes that are able to reduce/oxidise MK/MKH_2 will be described. It is worth mentioning, that many of these enzymes are able to generate proton gradient, which is crucial for energy conserving processes. There are two mechanisms of ΔpH generation: pumping of protons across the membranes and the so called redox loop mechanism, where reduction of one substrate, accompanied by proton(s) binding, occurs on one side of the membrane, whereas oxidation of the other substrate, accompanied by proton(s) release, occurs on the opposite site, while electrons are transferred through the protein [34].

Many bacteria contain multisubunit NADH:MK oxidoreductases that are able to pump protons across the membrane. These complexes are analogical to mitochondrial complex I, so they are called NDH-1 type dehydrogenases. They usually contain 13–14 subunits and some of them are thought to have additional enzymatic activities. These proteins are still poorly known. The other group, very widespread among bacteria, is NDH-2 (type II) dehydrogenases. These enzymes are considerably smaller than NDH-1, contain a flavin cofactor and do not show proton pumping activity [35].

In strictly anaerobic, sulfate reducing archeon *Archaeoglobus fulgidus*, $F_{420}H_2$:quinone oxidoreductase was identified, that is thought

to be a functional equivalent of NADH:quinone oxidoreductase [36]. This enzyme acts as an initial enzyme in the membrane electron transfer system and is a multisubunit complex which, similarly to bacterial NDH-1 and mitochondrial complex I, may be composed of three subcomplexes. Moreover, the significant homology between archaebacterial enzyme subunits and those of bacterial NDH-1 and complex I has been found [36]. This is an interesting example of biochemical unity of the living organisms.

Substrates like malate, pyruvate and glycerolo-3-phosphate can be also oxidized with simultaneous MK reduction [25,37].

The most thoroughly examined group of bacterial respiratory enzymes are succinate:quinone oxidoreductases that are analogues of mitochondrial complex II. Three dimensional structures of *E. coli* succinate:quinone oxidoreductase and *W. succinogenes* quinol:fumarate oxidoreductase have been resolved [38]. The corresponding enzymes from many bacteria, both gram-negative and -positive, have been purified and examined up to date [39–43].

Succinate:quinone oxidoreductases belong to a large family, including both eukaryotic and prokaryotic enzymes, and share the common structure. Despite extensive studies, there is no general

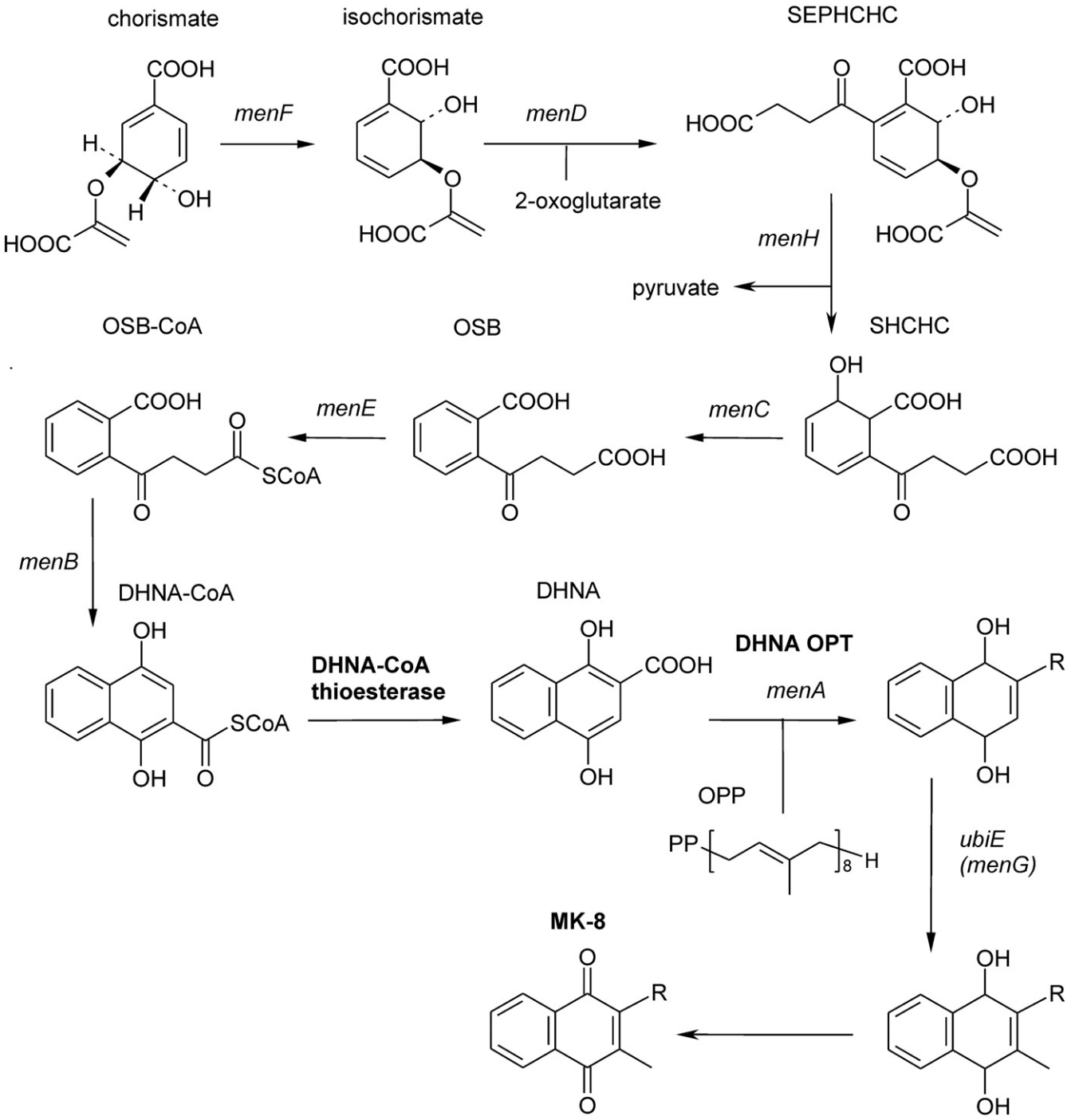

Fig. 3. A. The biosynthetic pathway of menaquinone-8. DHNA, 1,4-dihydroxy-2-naphthoate; DHNA OPT, DHNA octaprenyltransferase; R, octaprenyl side chain; OSB, *o*-succinylbenzoate; SEPHCHC, 2-succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylic acid; SHCHC, (1*R*,6*R*)-2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylic acid. B. The alternative pathway of DHNA (1,4-dihydroxy-2-naphoate) biosynthesis. DHFL, dehypoxanthinylfutalosine.

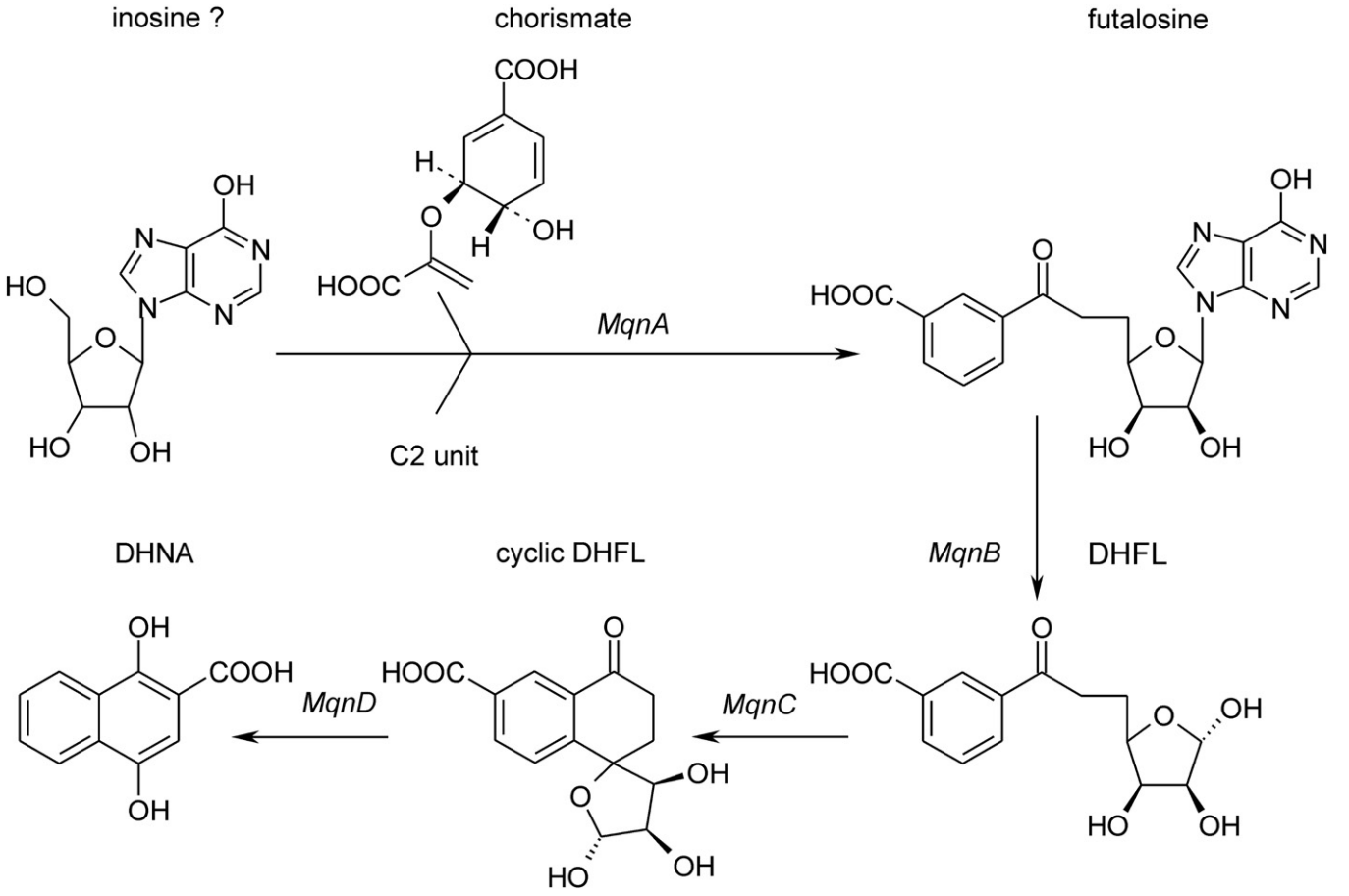

Fig. 3 (*continued*).

agreement concerning the sites of quinone oxidation and reduction in some types of these enzymes [40]. *In vitro*, succinate:quinone oxidoreductases can catalyze oxidation of succinate to fumarate coupled with the reduction of quinone, as well as reduction of fumarate coupled with quinol oxidation. Direction of these reactions depends on the conditions and substrates applied. *In vivo*, the activity of dehydrogenases has to be strictly controlled.

In bacterial aerobic respiration, succinate:quinone oxidoreductases catalyze succinate oxidation, similarly as in the mitochondrial electron transport chain. However, in case of MK reduction, the low redox potential of MK makes this process endergonic in contrast to exergonic reduction of UQ [41]. Therefore, oxidation of succinate coupled with the reduction of MK requires providing of energy. It was shown that in the examined gram-positive aerobic bacteria, such as *Bacillus subtilis* or *Bacillus licheniformis* having only MK, energization of cellular membrane is necessary for succinate:menaquinone oxidoreductase activity [41,43]. Therefore, it was proposed that menaquinone reduction by this enzyme is proton driven.

In anaerobic bacteria displaying fumarate respiration, fumarate serves as a terminal electron acceptor, while formate and hydrogen are used for electron donation into the chain [38]. These bacteria possess quinol:fumarate oxidoreductases. An example of such bacteria is rumen ε-proteobacterium *W. succinogenes* which grows considerably faster anaerobically on fumarate and nitrate than in the presence of oxygen [37]. As menaquinol:fumarate reduction is exergonic, it was supposed that bacterial quinol:fumarate reductase is able to generate proton gradient due to redox loop mechanism [41].

Finally, there are facultative anaerobic bacteria that can switch between these two modes. In *E. coli,* two separate enzymes are present, one expressed under aerobic conditions, oxidizing succinate and reducing ubiquinone, and the second, expressed under anaerobic conditions, which reduces fumarate and uses MKH_2 as an electron donor. Different expression profiles of these enzymes and types of isoprenoid quinones used in respiration assure separation of succinate oxidation and fumarate reduction [44].

Interestingly, many of the enzymes participating in bacterial respiratory chains share general structure. The examples of such enzymes are: hydrogenase, formate dehydrogenase, nitrate reductase and thiosulfate reductase [45]. Among them, hydrogenase and formate dehydrogenase are enzymes introducing electrons into the chain, while nitrate reductase catalyzes reduction of a terminal electron acceptor. Formate dehydrogenase oxidizes formate to carbon dioxide and generates pH gradient by redox loop mechanism. The hydrophilic part of the enzyme, where formate oxidation takes place, is orientated towards periplasm, whereas the MK binding site is present in an integral membrane subunit, near the cytoplasmic side of the membrane [46]. Hydrogenase catalyzes hydrogen oxidation coupled with MK reduction and builds up proton gradient through redox loop. The hydrogenase's HydA subunit contains Ni/Fe catalytic center, HydB subunit contains three FeS clusters and HydC subunit contains two hemes *b* [28]. Membrane-bound nitrate reductase (Nir), expressed under anaerobic and microaerobic conditions catalyzes reduction of nitrate to nitrite coupled with oxidation of MKH_2 and generates proton gradient [47]. *E. coli* Nir is expressed under high nitrate concentration and can use both MKH_2 and ubiquinol (UQH_2) as electron donors [48,49].

Enzymes similar in structure to nitrate reductase, were postulated to participate in sulfate and selenate reduction in some bacteria [45,50]. The structure of quinol oxidizing polysulfite reductase from *T. thermophilus* has been recently resolved [51].

The other important proteins interacting with MK/MKH_2 are cytochrome *bc* complexes [52,53].

The large group of oxidases can be divided into two families: heme:copper oxidases and cytochrome *bd* oxidases. Among the first group of oxidases, there are enzymes that catalyze quinol oxidation coupled with the reduction of a terminal acceptor [54]. Cytochrome *bd* oxidases transfer electrons from quinols to a terminal acceptor and generate gradient by redox loop mechanism [55]. These enzymes are widely distributed among bacteria [54]. Many bacteria, among them *Corynebacterium glutamicum* and some mycobacteria, have both heme:copper oxidase(s) and cytochrome *bd* oxidase, so their respiratory chain is branched [29,54].

The other important family of proteins is NapC/NirT family. These are membrane-bound tetra- or pentaheme c-type cytochromes, occurring in cell membranes of gram-negative bacteria, catalyzing quinol oxidation coupled with reduction of periplasmic proteins, which are different types of reductases. In *W. succinogenes*, the membrane-bound NrfH reduces NrfA—periplasmic complex of nitrite reductase [56]. In *E. coli*, NapC is thought to participate in electron transfer to NapA-NapB—periplasmic complex of nitrate reductase [48]. The CymA protein from *S. oneidensis* is assumed to be directly reduced by quinols and then it transfers electrons to a wide range of reductases [57].

It was recently discovered, that cell free supernatants from *S. oneidensis* culture reduced carbon tetrachloride to chloroform and Fe(III) to Fe(II) ions and the reducing agent in this process was identified to be MK-1. This indicates that the bacteria produce and release the short-chain, soluble MK [58].

In proteobacteria, that besides MKs are also able to synthesize ubiquinones (UQs), the relative proportion of these isoprenoid quinones depends on the metabolism type – strictly aerobic bacteria have UQs, strictly anaerobic – MKs [10]. Facultatively anaerobic proteobacteria, like *E. coli,* synthesize both UQ and MK [10,59]. Relative amounts of these isoprenoid quinones vary depending on the oxygen level. In *E. coli* growing under aerobic conditions, UQ level is 4–5 times higher than that of MK and DMK, whereas under anaerobic conditions UQ amount is three times lower than that of both menaquinones [59,60]. Since the midpoint redox potential of MKs is lower than that of UQs, the former isoprenoid quinones are more suitable for respiratory chains with the lower-potential electron acceptors [8,10]. In *E. coli* mutants lacking one of the isoprenoid quinones, the other can functionally replace the missing one, but this is not the case for all the respiratory pathways because of substrate preferences of certain dehydrogenases [59].

Dependence of the quinone used on oxygen concentration has been also reported in *Archaea* [13] In facultative anaerobic, thermophilic archaeon *Thermoplasma acidophilum*, three isprenoid naphthoquinones, differing in midpoint redox potentials were found: MK-7, TPQ-7 and MTK-7. Under anaerobic conditions TPQ-7 constituted 97% of the total quinone pool, whereas under aerobic conditions all the three quinones were present, each at about one third of the total pool [13].

Menaquinones participate also in bacterial photosynthesis. MKs are found both in photosystem II (PSII)-type reaction centers (RC) of purple bacteria and green filamentous bacteria [61]. These compounds also occur in PSI-type reaction centers of green sulfur bacteria and heliobacteria [61]. Many purple bacteria species make use of UQs for photosynthesis, but there are also some species taking advantage of MKs. In the case of *Halorhodospira halophila*, belonging to γ-proteobacteria, MK-8 functions in the photosynthetic electron transfer chain, while UQ-8 probably functions in the respiratory chain only [11]. Green filamentous bacteria utilize mainly MK-10 in their photosynthetic and respiratory electron transport chains [62]. Green sulfur bacteria contain PSI-type of RC and MK-7 at A_1 site [63]. Despite similarity of RC of green sulfur bacteria to PSI, until now there is no evidence that MK acts as an intermediate in electron transfer between A_0 and FeS centers. This conclusion is based on the observation that electron transfer in their RC, lacking MK, was not impaired. Functioning of MK-9, present at A_1 site of RC of *Heliobacterium chlorum*, as an obligatory intermediate in the electron transfer was also questioned [64,65].

An interesting observation is that MK-4 was found in PSI of certain cyanobacteria (*Gloeobacter violaceus*, *Synechococcus* PCC 7002) diatoms and primitive red alga *C. caldarum* [66–68].

Menaquinones were identified in relatively high amounts also in chlorosomes of green photosynthetic bacteria [69–71]. Chlorosomes of green sulfur bacterium *Chlorobium tepidum* contain mostly chlorobiumquinone, and smaller amounts of MK-7 [69]. It was found that most of *C. tepidum* chlorobiumquinone is localized in chlorosomes. It was observed that chlorosomes of obligatory anaerobic green sulfur bacteria exhibited high fluorescence, which rapidly decreased under aerobic conditions [69]. This observation was supposed to be connected with the presence of chlorobiumquinone that was postulated to sense redox state and inhibit electron transfer to the RC under aerobic conditions to avoid a possible oxidative stress [69].

Besides the function of MK in electron transfer, its participation in cellular signaling of *Klebsiella pneumoniae* was found, where MK participates in regulation of nitrogen fixation. It was shown that NifL protein, acting as a corepressor in the regulation of expression of nitrogen fixation genes, can be reduced by MKH_2 under anaerobic conditions, which is followed by NifL sequestration on the cellular membrane [72].

The unique sulfated derivative of MK-9(H_2), with sulfate group attached to the end of the isoprenoid chain, was recently discovered on cell surface of *Mycobacterium tuberculosis* [73]. It was shown to act as negative regulator of virulence in the mouse model and it was suggested to participate in host–pathogen interactions [73].

2.2. Phylloquinone

2.2.1. Occurrence

Phylloquinone (vitamin K_1) is synthesized by cyanobacteria, algae and higher plants, i.e. all the photosynthetic organisms able to perform oxygenic photosynthesis [6,74]. Its structure differs from menaquinones by the presence of the phytol side chain (Fig. 2). In leaves, phylloquinone is found mainly in chloroplasts [75–77], where the majority of this isoprenoid quinone is specifically bound to PSI [78,79]. In plastoglobules, which are the plastidic site for storage of excess lipophilic compounds, vitamin K_1 was found only in trace amounts [80,81], although higher values of about 50% of total phylloquinone outside PSI have been also reported [82,83]. Low amounts of vitamin K_1 are also present in the chloroplast envelope [84], where it is synthesized. The presence of phylloquinone in plasma membrane isolated from maize has also been reported [85]. Phylloquinone occurs in higher plants mainly in leaves, where it is found predominantly in the oxidized form, while in other organs, like in fruits, roots and bulbs, it was found only in trace amounts and exclusively in the oxidized form [86,87].

Phylloquinone is also present in mammals, which require it for blood clotting and other reactions. However, mammals are not able to synthesize vitamin K_1 and have to obtain it with food.

2.2.2. Biosynthesis

Phylloquinone biosynthesis is limited to organisms carrying oxygenic photosynthesis. The biosynthetic pathway is analogical to that of MK. The difference is that prenyltransferase catalyzing the condensation step uses phytyl diphosphate as a substrate, which is synthesized via DXP pathway in higher plants and cyanobacteria [17,82,88]. The principle reactions of phylloquinone biosynthesis in plants occur in the inner membrane of chloroplast envelope [89]. Experiments performed on an *Arabidopsis* mutant with the impaired phylloquinone biosynthesis showed involvement of protein product of nuclear gene *PHYLLO*, sharing homology with four individual eubacterial genes *menF*, *menD*, *menC* and *menH*, encoding enzymes

catalyzing respective reactions of menaquinones and phylloquinone biosynthetic pathways in eubacteria and cyanobacteria, respectively [83]. The four *men* genes occur separately in red algae, but in the diatom *Thallassiosira pseudonana,* one gene sharing homology with four *men* genes has been also found, but the order of homological regions is different. This fact suggests that genes involved in phylloquinone biosynthesis are derived from prokaryotic endosymbionts and fusion of these genes was evolutionarily profitable. The *PHYLLO* protein of higher plants, in contrast to green and red algae, is not able to catalyze the synthesis of isochorismate, because it lacks chorismate binding domain. In *Arabidopsis,* there are two other genes with homology to *menF* gene catalyzing this reaction. Isochorismate synthesis is also a part of salicylic acid biosynthesis, so it was postulated, that splitting of the gene was beneficial, because it enabled regulation of this reaction independently of phylloquinone biosynthesis. It was suggested that phylloquinone biosynthetic enzymes form large complex making possible channeling of the biosynthetic intermediates [83].

We have searched for homologues of *E. coli* 1,4-dihydroxy-naphthoate octaprenyltransferase in GenBank microbial protein sequences databases (http://www.ncbi.nlm.nih.gov) using BLAST algorithm available on NCBI. Surprisingly, we found less homologues than we expected due to common MK occurrence in bacteria and archaebacteria. In some groups of gram-positive bacteria such as *Lactobacillus, Lactococcus, Streptococcus, Clostridium* only a few homologues were found. Lack of homologues in these bacteria can be explained by loss of the ability of MK synthesis. These bacteria, living in nutrient-rich environments obtain their energy from fermentation and this led in a consequence to progressive loss of genes necessary for respiration [12]. Generally, loss of genes was also often observed in some groups of obligatory parasitic bacteria [16].

2.2.3. Function

The role of phylloquinone as an electron transfer cofactor in PSI is well known and documented [61]. Within PSI there are two phylloquinone molecules, each in one of two-electron transfer branches. The experiments using time-resolved spectrophotometric measurements [90], as well as experiments performed on site-directed mutants of reaction center polypeptides (PsaA and PsaB) with the modifications near phylloquinone binding sites [91], showed that in PS I both branches are active, but the kinetics of electron transfer is different. Phylloquinone associated with PsaB protein is re-oxidized with the half-time of 15–30 ns, while the second molecule associated with PsaA protein—with the half-time of 150–300 ns [91]. Experiments performed on *C. reinhardtii* and *A. thaliana* mutants with impaired phylloquinone biosynthesis [82,92] showed that it was functionally replaced, but electron transfer rate was slower than that in the wild types. The *Chlamydomonas* mutant had impaired an early step of phylloquinone biosynthesis, therefore it lacked any naphthoquinones and it was found that phylloquinone in PSI was replaced by plastoquinone. In this case, the electron transfer between A_1 and FeS centers was slowed down more than 40-fold. The *Arabidopsis* mutant had impaired the last step of phylloquinone biosynthesis, therefore it accumulated phytyl-1,4-naphthoquinone, which could be detected in A_1 site and in a consequence the electron transfer was two times slower. Both mutants were able to grow at low light, but displayed increased sensitivity to high light. Although total PQ was not affected in the *Chlamydomonas* mutant, the size of free PQ-pool was reduced by 20–30% and PSII level was decreased [92]. In the *Arabidopsis* mutant, PSII quantum yield decreased in high light, anthocyanin accumulation was enhanced and xanthophyll cycle activated [82].

The detection of phylloquinone in the plant plasma memebrane led to speculations concerning other functions of this prenylquinone [85]. The occurrence of phylloquinone-mediated electron transport chains in plant plasma membranes, analogical to mammal membrane redox systems, where UQ is engaged, has been postulated [85]. Phylloquinol oxidase activity has been detected in plasma membranes of soybean [93]. There are also data showing NAD(P)H:quinone oxidoreductase activity in the plasma membrane [85]. Moreover, several redox enzymes, as well as b-type cytochromes were found in the membrane preparations [85]. The postulated roles of phylloquinone in membrane redox systems are both antioxidant and prooxidant functions. Phylloquinone could be involved in ROS generation in response to pathogen attack or stress. It is known that ROS can be signal transducers in plants, so the role of membrane electron transfer chains in signaling cannot be excluded [85].

Although mammals are not able to synthesize isoprenoid naphthoquinones, these compounds are indispensable for their metabolism and have to be supplied with food or obtained from symbiotic bacteria living in intestine [94]. Therefore, isoprenoid naphthoquinones were treated as vitamins: phylloquinone was named vitamin K_1, menaquinone—vitamin K_2 and menadione, a synthetic compound lacking the side chain, vitamin K_3. It was shown that although phylloquinone is a major dietary form of vitamin K, MK-4 can be found in humans and rodents and its concentration exceeds that of phylloquinone in most of their tissues [95]. Experiments performed on rodents showed that at least some of their tissues are able to convert phylloquinone to MK-4 [95]. The best known role of vitamin K is functioning as a cofactor for γ-glutamyl carboxylase (GGCX), an enzyme responsible for posttranslational modification of some proteins [94]. GGCX requires the reduced forms of vitamin K—phylloquinol or MKH_2. In the reaction catalyzed by GGCX, the isoprenoid quinols are converted to 2,3-epoxides and have to be recycled back to the reduced forms, which is catalyzed by vitamin K epoxide reductase and vitamin K reductase. This interconversion of vitamin K is called the K cycle [94]. GGCX carboxylates specific glutamate residues, converting them into γ-carboxyglutamate (Gla). The Gla residues form calcium binding sites, which is essential for activity of Gla-containing proteins that were called vitamin K-dependent proteins. The best known examples of these proteins are coagulation factors II, VII, IX and X, that are responsible for proper blood clotting [96,97]. The other known group of Gla-containing proteins is those involved in regulation of bone metabolism and growth, such as osteocalcin, that regulates bone mineralization, matrix Gla protein (MGP) and protein S [97]. The role of MGP in preventing calcification of vessel walls was also shown [98]. There are also other K-dependent proteins known, but their role is unclear [94]. Besides the contribution in γ-carboxylation, vitamin K is supposed to have additional effects attributed mainly to MK-4 [97,99]. It has been recently shown that MK-4 is bound by steroid and xenobiotic receptor (SXR)/pregnane X receptor (PXR) that is responsible for signaling pathway leading to induction of expression of Msx2, an osteoblastogenic factor [100,101]. A difference between phylloquinone and MK-4 uptake, metabolism and utilization *in vitro* was shown [102]. Participation of vitamin K in signal transduction and regulation of gene expression requires further study [103]. Vitamin K is also supposed to be important for proper metabolism of sphingolipids in brain [104]. The ability of vitamin K to inhibit growth and induce apoptosis of some cancer cell lines has been reported [105,106]. It was also shown that vitamin K is an antiapoptotic factor in some neuronal cell cultures [107] and it modulates certain cytokines, such as osteoprotegrin and interleukin-6 [99].

A review covering current state of knowledge on vitamin K in humans has been recently published [108].

3. Isoprenoid quinones of sulfolobales

3.1. Occurrence

Isoprenoid quinones with an additional heterocyclic ring containing sulfur were discovered in *Sulfolobales*, the thermophilic and aerobic archaebacteria (Fig. 4). Until now, three quinones of this type

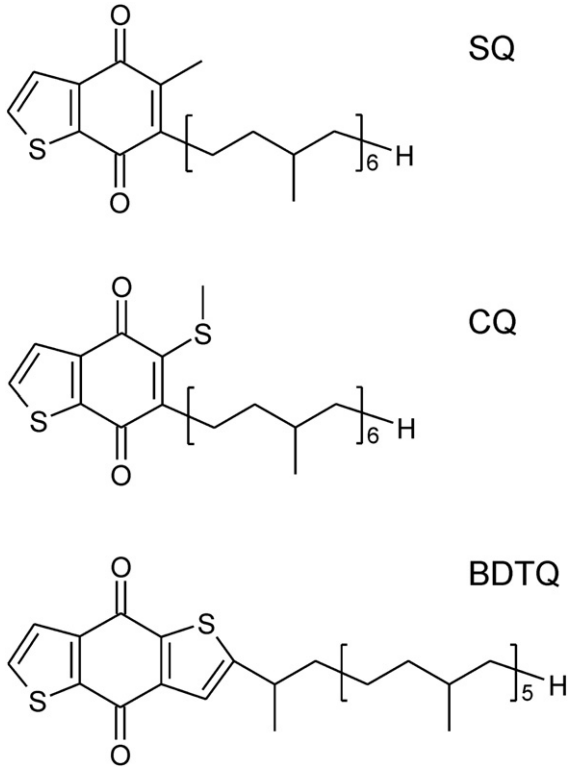

Fig. 4. Isoprenoid quinones of *Sulfolobales*: SQ, sulfolobusquinone; CQ, caldariellaquinone; BDTQ, benzodithiophenoquinone.

are known: caldariellaquinone, sulfolobusquinone and benzodithiophenoquinone [1,9]. These isoprenoid quinones show higher midpoint redox potential than the corresponding naphthoquinones and are supposed to appear later than MKs during evolution, in the course of adaptation to aerobic conditions [11].

3.2. Biosynthesis

The biosynthesis of these compounds is poorly known. Radiolabeling experiments showed that the isoprenoid side chain is synthesized via MVA pathway and that tyrosine is a precursor of the benzothiophene ring of caldariellaquinone [109,110].

3.3. Function

The isoprenoid sulfoquinones of *Sulfolobales* participate in electron transfer during chemosynthetic oxidation of sulfur compounds and aerobic respiratory chain. The first enzyme, coupling oxidation of a sulfur compound with the reduction of caldariellaquinone, was discovered in *Acidians ambivalens* [111]. The membrane-bound enzyme, thiosulfate:quinone oxidoreductase (TQO), oxidizes thiosulfate to tetrathionate and contains non-covalently bound sulfoquinones [111].

4. Isoprenoid benzoquinones

4.1. Ubiquinones

4.1.1. Occurrence

Ubiquinones (UQs) are evolutionarily "younger" than MKs and probably appeared during the evolution of proteobacteria. In the kingdom of *Eubacteria,* UQs are found only in α- β- and γ-proteobacteria, while other groups have MKs [1,8,10]. UQs are also present in eukaryotic organisms, which is in line with the theory of endosymbiosis, according to which proteobacteria were ancestors of mitochondria. Although UQs were discovered during studies of mitochondria, it was shown later that all the endomembranes of animal cells contain these isoprenoid quinones. UQs were found in endoplasmic reticulum, Golgi apparatus, lysosomes, peroxisomes, nuclear envelope and plasma membrane [112–114]. The number of isoprenoid units in the prenyl side chain often varies among species. Some organisms have more than one type of UQ, but usually there is one most abundant homologue. Most mammals, including humans, have mainly UQ-10 and small amounts of UQ-9, whereas UQ-9 prevails in rodents [115]. In invertebrates, UQ-8 to UQ-10 were identified [115]. The homologues found in fungi were UQ-6 to UQ-10 [115]. UQ-10 occurs in *Schisosaccharomyces pombe*, while UQ-8 and UQ-6 dominate in *E. coli*, and *Saccharomyces cerevisiae*, respectively [7,116]. In bacteria, UQ-8, UQ-9 or UQ-10 is usually the major components, while UQ-1 to UQ-7 homologues could be also found in minor amounts [1]. Mitochondria of higher plants contain UQ-10 or UQ-9, while those of lower plants might have also UQ-7 and UQ-8 [117]. In *Capsicum* fruits, an exceptional UQ-11 homologue was found besides the shorter homologues [117].

4.1.2. Biosynthesis

The biosynthetic pathways of UQ (Fig. 5) in *E. coli* and *S. cerevisiae,* as well as in higher eukaryotes have been widely studied [7,10,118–122]. The pathways of *E. coli* and *S. cerevisiae* differ in some details. Presently, not all the biosynthetic steps in yeast are known, but the general route of UQ biosynthesis is common for pro- and eukaryota.

The precursor of the head group of UQ, *p*-hydroxybenzoate (PHB), can be formed from chorismate via the shikimate pathway in *E. coli*. PHB is synthesized both by shikimate pathway and from tyrosine in *S. cerevisiae* [121], whereas in higher eukaryotes it is derived from tyrosine or sometimes from phenyloalanine. Condensation of PHB with prenyl side chain is catalyzed by PHB prenyltransferase that is critical for UQ biosynthesis. PHB prenyltransferases are specific for the head group but usually have broad substrate specificity for the polyprenyl side chain transferred [118]. After the condensation reaction, the aromatic ring undergoes several modifications. The order of these reactions varies between prokaryotes and eukaryotes. Instead of decarboxylation, hydroxylation and *O*-methylation in *E. coli* (Fig. 5), hydroxylation, *O*-metylation and decarboxylation in *S. cerevisiae* take place. Next biosynthetic steps are common for both organisms [118]. The length of the isoprenoid side chain of UQs is determined by a specific prenyl diphosphate synthase. Most of these enzymes are homodimers, while some heteromeric enzymes were also found [7]. Comparing the structure of different synthases, it was found that the most significant site for the determination of the length was the 5th position from the first of two aspartate-rich regions in these enzymes [7]. Moreover, it was found that the formation of a dimer is essential for determination of the length in *E. coli* [7].

In contrast to MK biosynthesis, UQ-biosynthetic enzymes are localized mostly in membranes. It is supposed that eukaryotic enzymes participating in last steps of UQ biosynthesis are located on the matrix side of the inner mitochondrial membrane and specific redistribution of UQ to other membranes is required [119,123]. The studies concerning intracellular UQ transport were performed, but this issue is still poorly examined [123,124].

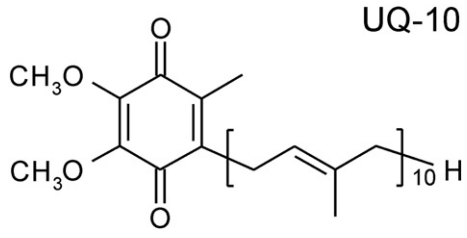

Fig. 5. UQ-10, occurring in bacteria, yeasts, plants and mammals.

Even though UQ is synthesized in humans, it is used as a diet supplement (coenzyme Q) and in cosmetic industry. This requires chemical biological synthesis on a large scale. There are several organisms used or tested for macro-scale of UQ-10 bioproduction. Many of them are microbes that naturally produce UQ-10, e.g. *Rhodobacter sphaeroides*, *Agrobacterium tumefaciens*, *Paracoccus denitrificans, Cryptococcus laurentii, Sphingomonas sp*. The first three bacteria have already been used for industrial UQ production [125,126]. The widely used technique to enhance UQ productivity is chemical mutagenesis, as well as metabolic engineering [126]. In this respect, also yeast species, such as *S. cerevisiae* and UQ-10-containing *S. pombe*, are of interest [122]. Genetic engineering has also been applied to force organisms naturally producing UQs with a shorter isoprenoid side chain, such as *E. coli* and rice, to synthesize UQ-10 [116,126]. Because of pharmaceutical applications, UQ-10 bioavailability, uptake and distribution in humans were also widely studied [127].

We have searched for homologues of PHB octaprenyltransferase of *E. coli* in GenBank databases of microbial protein sequences using BLAST algorithm. Homologues in α- β- γ-proteobacteria were found, but some of them were also present in δ subgroup which does not synthesize UQs. Moreover, PHB prenyltransferase homologues were found in gram-positive bacteria containing menaquinones, flavobacteria, green sulfur bacteria, spirochetes, chlamydia, cyanobacteria and even in *Archea* kingdom. Some of these organisms lack UQs [1,24], but the role of PHB prenyltransferase homologues remains unknown.

4.1.3. Function

UQs (Fig. 6) are the best known and most thoroughly examined group among all isoprenoid quinones because of their function as obligatory cofactors in the aerobic respiratory electron transport chain, acting as electron and proton carriers [3]. In the mammalian, mitochondrial electron transport chain, UQ transfers electrons from complexes I and II to complex III in the inner mitochondrial membrane. Complex I, still not fully examined, is a multisubunit enzyme with NADH:UQ oxidoreductase activity, containing FMN and FeS clusters [3,128,129]. Complex II (succinate dehydrogenase), containing FAD, FeS clusters and heme *b*, couples oxidation of succinate to fumarate with the reduction of UQ. Complex III (cytochrome bc_1), being an oligomeric dimer containing hemes (b_H and b_L) and FeS clusters, functions as ubiquinol:cytochrome *c* oxidoreductase and links redox reactions with proton translocation across the membrane in the Q-cycle. It was shown that UQ is required for complex III stability [130]. The most recognized model of UQ functioning assumes

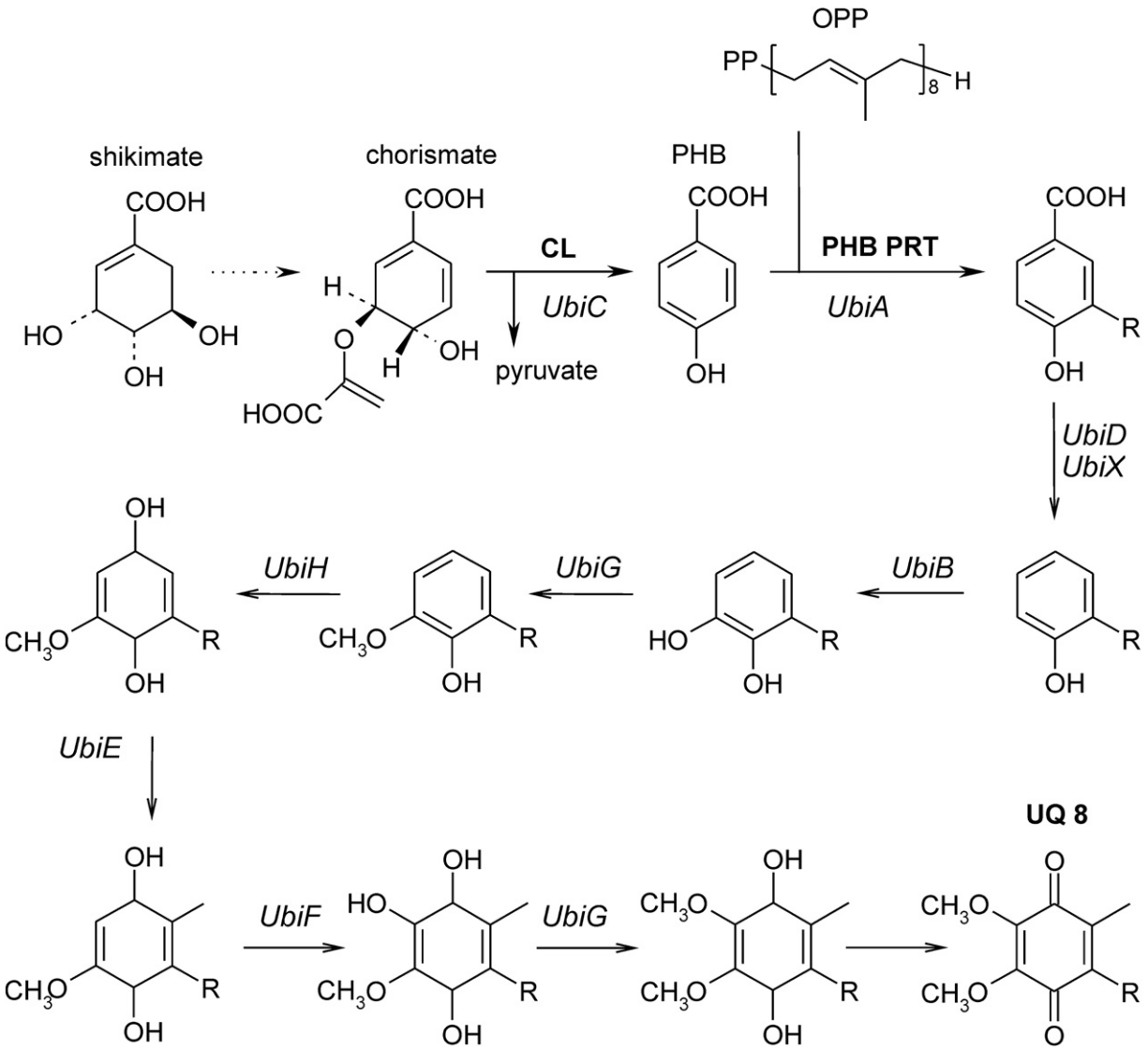

Fig. 6. Ubiquinone-8 biosynthesis in *Escherichia coli*. CL, chorismate lyase; OPP, octaprenyl diphosphate; PHB, *p*-hydroxybenzoate (in animals and plants derived from tyrosine); PHB PRT, *p*-hydroxybenzoate octaprenyltransferase; R, octaprenyl side chain.

existence of homogenous UQ/UQH_2 pool freely diffusing in the inner mitochondrial membrane and transferring reducing equivalents between randomly dispersed complexes but recently, occurrence of super-complexes where substrate channeling could take place, was postulated [129]. It has been assumed for a long time that the shape of the UQ molecule is nearly linear and the molecule is located in the hydrophobic mid-plane region of the lipid bilayer, with the polar head group oscillating between the mid-plane and the polar membrane interphase, allowing interaction of the head group of UQ with redox centers in the mitochondrial complexes [3]. However, in the molecular modeling experiments, the folded conformation of the UQ side chain was found for both the redox forms [3]. Such a conformation would explain several previous observations [3].

Recently, mitochondrial UQ-binding protein, called COQ10, was identified in *S. cerevisiae* and *S. pombe* [131–133]. The experiments performed on *coq10* null mutants showed that the observed phenotype is similar to those of mutants with the impaired UQ biosynthesis. The mutants displayed deficiency in respiration, increased sensitivity to H_2O_2, requirement for antioxidants for proper growth, and high levels of H_2S production [131,132]. Surprisingly, UQ level in these mutants was nearly the same as that in the wild type, suggesting that COQ10 does not participate in UQ biosynthesis. On the other hand, the enhanced UQ level, obtained by overexpression of UQ-biosynthetic genes or growing yeasts on UQ-10 containing medium, complemented lack of COQ10 [131,132]. The *coq10* homologues are widespread in bacteria and eukaryotes. It was shown that the human orthologue can functionally compensate for the absence of COQ10 in the examined yeast species [131,132]. However, the exact function of COQ10 remains unclear.

Besides the three mentioned complexes found in mitochondria and bacteria, there are other specialized enzymes able to reduce/oxidise UQ/UQH_2 in plants, fungi, *Protista* and many bacteria. Therefore, the electron transfer chain can be branched [134]. The example of such enzymes are bacterial, fungal and plant, cyanide insensitive, alternative oxidases, catalyzing aerobic oxidation of UQH_2. These enzymes are supposed to enhance UQ turnover when the energy state of the cell is high, but their function still remains rather poorly known [3]. Among the enzymes reducing UQ, a very abundant group are type II dehydrogenases (NDH-2) which function as NAD(P)H:UQ oxidoreductases [134,135]. Eukaryotic NDH-2 enzymes were found on both sides of the inner mitochondrial membrane, whereas the bacterial enzymes are found on the cytoplasmic side. In *S. cerevisiae*, lacking complex I, NDH-2 dehydrogenases are the main electron entry pathways into the chain [129]. The other known enzymes that are able to reduce UQ are glycerol-3′-phosphate (G3P) dehydrogenase, electron transfer flavoprotein-ubiquinone oxidoreductase (ETF–QU) and dihydroorotate dehydrogenase [3,134]. G3P dehydrogenase found in mammalian, insect and yeast mitochondria forms metabolic shuttle for cytosol-derived reducing equivalents. FAD containing ETF-QU, present in mammalian and plant mitochondria, mediates electron transfer from a variety of different dehydrogenases, including those involved in fatty acid oxidation or amino acid catabolism, to UQ. The flavoprotein and dihydroorote dehydrogenase catalyze oxidation of dihydroorotate to orotate, the fourth step in pyrimidine biosynthesis.

There are several other bacterial enzymes participating in different redox reactions that are able to reduce UQ. In *E. coli,* FAD-dependent D-lactate dehydrogenase, oxidizing lactate to pyruvate was found, as well as glucose dehydrogenase, oxidizing glucose to D-gluconate, the latter containing pyrroloquinoline quinone and UQ at active sites [136–138]. The ability of proline dehydrogenase from *E. coli* to reduce UQ has been postulated [139]. In an acetic acid bacterium, *Gluconobacter suboxydans,* quinoprotein alcohol dehydrogenase involved in UQ reduction has been found [140].

In photosynthesis of purple bacteria (*Rhodospirillum rubrum* and *Rhodobacter capsulatus*), UQs are found at two quinone binding sites Q_A and Q_B within PS II-type reaction center. UQ is reduced at the Q_B site and then oxidized by cytochrome bc_1, which enables generation of both proton motive force and reducing power due to reverse electron flow [61,141].

UQs are also reduced by enzymes involved in photosynthetic and chemosynthetic electron chains where reduced inorganic compounds serve as an electron source. It was shown that UQs, and MKs in organisms using these types of prenylquinones, are cofactors of sulfide:quinone oxidoreductases (SQR), the enzymes that are obligatory for photo- and chemolithoautotrophic bacteria growing on sulfide [142,143]. SQRs are single-peptide, membrane-bound flavoproteins belonging to glutathione reductase family. Wide distribution of SQRs in prokaryotes leads to the conclusion that these proteins were acquired early in evolution [143,144]. Moreover, SQR activity has been also shown in eukaryotes, e.g. yeast *S. pombe* and certain invertebrates like lungworm *Aenicola marina* [145,146]. The homologues of *sqr* genes were found also in fungi, insects and mammals [147]. Therefore, participation of SQRs in detoxification of sulfide or indirect connection to sulfide signaling has been proposed [148]. The widespread bacterial NapC/NrfH/NirT/TorC family of tetra- and pentaheme quinol reductases includes cytochrome c_{m552}, the membrane-bound enzyme that transfers electrons from hydroxylamine oxidoreductase, an enzyme of NH_4^+ oxidation pathway, to UQ in *Nitrosomonas* species [149]. The other members of this protein family are found in facultative anaerobic bacteria and participate in electron transfer from membrane quinol pool to a range of periplasmic terminal reductases using electron acceptors other than O_2, i.e. nitrite, nitrate, fumarate, dimethyl sulfoxide, or metal ions such as Fe^{3+} [25]. In the case of UQ it was shown that it acts as redox mediator in nitrate respiration in proteobacteria [10,59,60].

The other UQ reducing enzymes are Na^+-translocating NADH:UQ oxidoreductases found in genus *Vibrio* and some other species like *Azotobacter vinelandii*. These enzymes generate a redox-driven transmembrane electrochemical Na^+ gradient, ejecting sodium ions into periplasmic space [150,151]. This sodium potential plays a role in solute import, flagellar rotation and even can be used for bioenergetic processes [152].

In bacteria the reduced UQs and MKs are electron donors for enzymatic systems responsible for the formation of disulfide bonds [153]. The system, widely studied in *E. coli*, introduces disulfide bonds into proteins exported from the cell. It consists of two proteins: membrane-bound DsbB and periplasmic DsbA. Determination of the crystal structure of DsbA–DsbB–UQ complex led to a deeper understanding of the mechanism of disulfide bond formation [154]. DsbA has disulfide bond at its active site, which is reduced after introducing disulfide bond to a target protein and needs to be reoxidized. DsbB, containing two important disulfide bonds is able to oxidize DsbA. The role of UQ is to reoxidize DsbB reduced after restoring DsbA activity, which enables the catalytic turnover [155].

Because of participation in electron transfer chains, UQs can act as redox-sensors and can be involved in the regulation of gene expression [10]. The best known example is Arc two-component signal transduction system present in *E. coli* [156,157]. This system modulates expression of numerous operons in response to redox conditions of growth and consists of ArcB, which is membrane-bound sensor kinase, and ArcA, a response regulator. UQ was shown to inhibit autophosphorylation of ArcB through oxidation of two redox active cysteinyl residues that participate in intramolecular disulfide bond formation [158]. Recently, MK was also postulated to be connected with the Arc mediated regulation [159]. The second, less known, two-component system postulated to be UQ-dependent is Reg system in purple bacteria [160–162]. Although Reg system proteins are not homological with Arc proteins, the overall mode of action is similar [162]. Reg system participates in the regulation of whole metabolism. It influences expression of proteins required for photosynthesis, carbon and nitrogen fixation and hydrogen utilization

and consists of membrane-bound sensor kinase RegB and response regulator RegA [160]. It was shown that exogenous UQ was capable of inhibiting RegB autophosphorylation [161]. Additionally, the sensor kinases BvgS and EvgS from *Bordetella pertussis* and *E. coli*, respectively, also exhibited decreased autophosphorylation in the presence of UQ *in vitro* [163]. The role of UQ in the regulation of gene expression in eukaryotes has been examined [164].

Other postulated functions of UQs are regulation of mitochondrial permeability transition pores [165] and mitochondrial uncoupling proteins [166,167]. UQ action as a proton transferring redox factor in acidification of lysosomes has been proposed [168]. Recently, during structure determination of insects Takeout1 protein it was discovered, that the protein expressed heterologously in *E. coli* contained UQ [169].

Participation of isoprenoid quinones in pro- and antioxidant processes is known for a long time [113,170]. The prooxidant action is displayed mostly by semiquinone radicals formed as intermediates in UQ redox reactions. Respiratory enzymes, such as complexes I and III, biding semiquinone forms are the main source of reactive oxygen species (ROS) in cells [3,113]. In case of complex III, the mechanism of ROS generation at quinone binding sites was confirmed, whereas superoxide formation in complex I is still poorly known [3,170]. The superoxide formation through the autooxidation of ubisemiquinone is enhanced when the influx of electrons into chain at UQ-pool exceeds the efflux [170]. The antioxidant action of the UQ redox couple is mostly due to the reduced form [112,113,171,172], although antioxidant function of UQ was also shown, for example its ability to react with superoxide anion [170,172,173]. Hydrophobic properties of the UQ couple make it possible to localize in the interior of membranes, where its main antioxidant function is the inhibition of lipid peroxidation [113,174]. The direct action of UQH_2 is to prevent initiation and propagation of the peroxidation reaction, by lipid radical scavenging. UQH_2 is able to scavenge perferryl radicals, which are initiators of lipid peroxidation and lipid peroxyl radicals responsible for the propagation phase. Moreover, the neutral ubisemiquinone radical reacts with lipid carbon-centered radicals. UQH_2 also regenerates α-tocopherol, another important cellular lipophilic antioxidant [113]. As a result of radical scavenging reactions of α-tocopherol, α-tocopheroxyl radical is formed. This radical is reduced to α-tocopherol by UQH_2 or ascorbate [113]. UQH_2 due to its hydrophobic properties regenerates α-tocopherol more efficiently than ascorbate [113]. UQ participation in scavenging of reactive nitrogen species has been also shown, while the reduced forms of UQ can promote peroxynitrite formation [170,175]. It is worth noting that the widespread occurrence of UQ in membranes is accompanied by the widespread occurrence of enzymes able to reduce UQ. This makes it possible to maintain the pool of UQH_2 in spite of its radical-based oxidation. There are several extramitochondrial enzymes suggested to participate in UQ reduction in mammalian cells: cytosolic NADPH-dependent reductase [176], NAD(P)H:quinone reductase 1 (DT-diaphorase) [177], NADH-cytochrome b_5 reductase, NADH-cytochrome P450 reductase [178], lipoamide dehydrogenase, glutathione reductase and thioredoxin reductase [179].

Antioxidant action of UQH_2 is not limited only to cellular membranes. This compound is also present in blood plasma, where it binds to three forms of lipoproteins: VLDL, LDL and HDL, therefore it protects lipoprotein lipids from oxidation [113,180]. This is also probably related to antiatherogenic effect of UQ [114]. The redox state of the UQ-pool is suggested to be also involved in cellular signaling. It was shown that UQH_2 regulates the release of ceramide from sphingomyelin, by non-competitive inhibition of neutral sphingomyelinase, thus UQH_2 prevents activation of ceramide signaling pathway leading to apoptosis [178].

The importance of UQ for human health is partially related to its antioxidant properties, but there are processes where UQ seems to act differently. It was shown that exogenously applied UQ, modulates amount of β2-integrins on the surface of blood monocytes [181] or stimulates the immune response [182]. It was shown that lowering of UQ levels is related to aging, neuro- and muscle degenerative diseases, some cardiovascular diseases, diabetes and cancers. The detailed description of these issues can be found in other reviews [183–188].

4.2. Rhodoquinone

4.2.1. Occurrence

Rhodoquinone (RQ), the UQ derivative with amino group substituting one of UQ methoxy groups (Fig. 7), was discovered in purple bacterium *R. rubrum* [189]. RQ has significantly lower redox potential than that of UQ. It was shown that RQ is common in *Rhodospirillaceae* family and in some species it is a major isoprenoid quinone [190]. RQ was also found in chemoorganotrophic, aerobic bacterium *Brachymonas denitrificans* [191]. Among eukaryotic organisms, RQ occurs in *E. gracilis* and in some facultatively anaerobic invertebrates: *Caenorhabditis elegans*, parasitic helminths, snails, mussels, lungworms and oysters [192].

4.2.2. Biosynthesis

The biosynthesis of RQ is still poorly known. It was shown that UQ is a required intermediate for the biosynthesis of RQ in *R. rubrum*, but in *C. elegans clk-1* mutant, accumulating demethoxy-UQ, RQ was also found [193,194].

4.2.3. Function

Participation of RQ in the electron transport chain was studied in the above mentioned eukaryotic organisms that are able to survive during hypoxic or temporarily anoxic conditions [192]. It was shown that these organisms can use fumarate as a terminal electron acceptor in the respiratory chain due to the presence of RQH_2:fumarate oxidoreductase (QFR). During this reaction, fumarate is reduced to succinate under anaerobic conditions. In these organisms, the mitochondrial complex II shows a reverse activity where it oxidizes succinate. In invertebrates possessing both complex II and QFR, complex II makes use of UQ as a cofactor, while QFR uses RQ, which makes it possible to distinguish and regulate fumarate/succinate redox reactions. It was shown that the RQ/UQ ratio depends on oxygen availability and correlates with the activity of fumarate reduction *in vivo* [192]. A similar effect was observed in *E. gracilis* that is able to perform unique wax ester fermentation, involving fumarate reduction as one of the steps. Anaerobically and aerobically grown *E. gracilis* cells showed similar total RQ and UQ amounts, but RQ constituted 43% and 28% of the pool under anaerobic and aerobic conditions, respectively [195].

The RQH_2:fumarate oxidoreductase activity was found also in the purple photosynthetic bacterium *Rhodoferax fermentas* [196]. The sequence comparisons indicate that the enzymes displaying RQH_2:fumarate oxidoreductase activity show low homology with bacterial MKH_2:fumarate oxidoreductases. Moreover, the data suggest that RQH_2:fumarate oxidoreductase of bacteria and invertebrates evolved independently from pro- and eukaryotic succinate:UQ oxidoreductases, respectively [196].

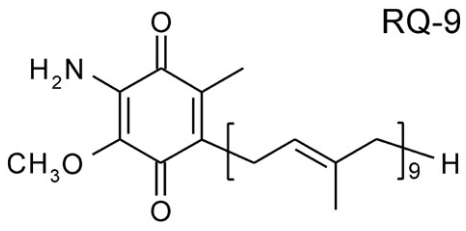

Fig. 7. RQ-9, occurring in bacteria, *Euglena*, *Caenorhabditis elegans* and worms.

4.3. Plastoquinones

4.3.1. Occurrence

Plastoquinone (PQ) (Fig. 8) was "invented" by cyanobacteria in the evolution and it is the key isoprenoid quinone in the oxygenic photosynthesis of cyanobacteria and all plants, where it shuttles electrons between membrane protein complexes and protons across the membrane [61]. It was discovered by Kofler in 1946 and rediscovered by Crane in 1959 [197]. Within chloroplast, besides thylakoids, PQ is found in plastoglobuli, which are the storage site of this compound, as well as in the inner chloroplast envelope, where its synthesis proceeds. PQ was found not only in photosynthetic plant organs, but also in minor amounts in all the other examined organs, like roots, bulbs, flowers, fruits, etiolated leaves, etc. [5,6,81].

PQ usually contains nonaprenyl isoprenoid side chain (PQ-9, PQ-A), although homologues with a shorter side chain were also reported in some plant species in minor amounts: PQ-8 in maize and *Ficus elastica*, PQ-4 in horse-chestnut and PQ-3 in spinach [197]. There was also the report on the occurrence of demethylplastoquinones: 3-demethylplastoquinone-9 and 3-demethylplastoquinone-8 in *Iris hollandica* bulbs [198]. In the past, also other forms of PQ, like PQ-C and PQ-B, were identified in many plant species [199]. Both these forms are PQ-9 derivatives and each represents a group of at least 6 isomers. PQ-C contains one hydroxyl group in the prenyl side chain and PQ-B is the fatty acid ester of PQ-C. Among fatty acids identified in PQ-B, myristic, palmitic and linolenic acids were the most abundant [200]. However, the exact structure of the individual isomers of both of these PQs remains to be determined. It is also neither known if these compounds are synthesized *de novo* or are degradation products of PQ-A, nor if both of these PQ's have any specific function. It is known that PQ-C accumulates in older leaves [201] and PQ-C-like compounds are formed from PQ-9 during scavenging reaction of singlet oxygen [202]. This could indicate that PQ-C is a non-enzymatic product of PQ-9 oxidation of no special function. On the other hand, it was demonstrated that both PQ-C and PQ-B show some activity in substituting PQ-9 as electron acceptors of PSII [200].

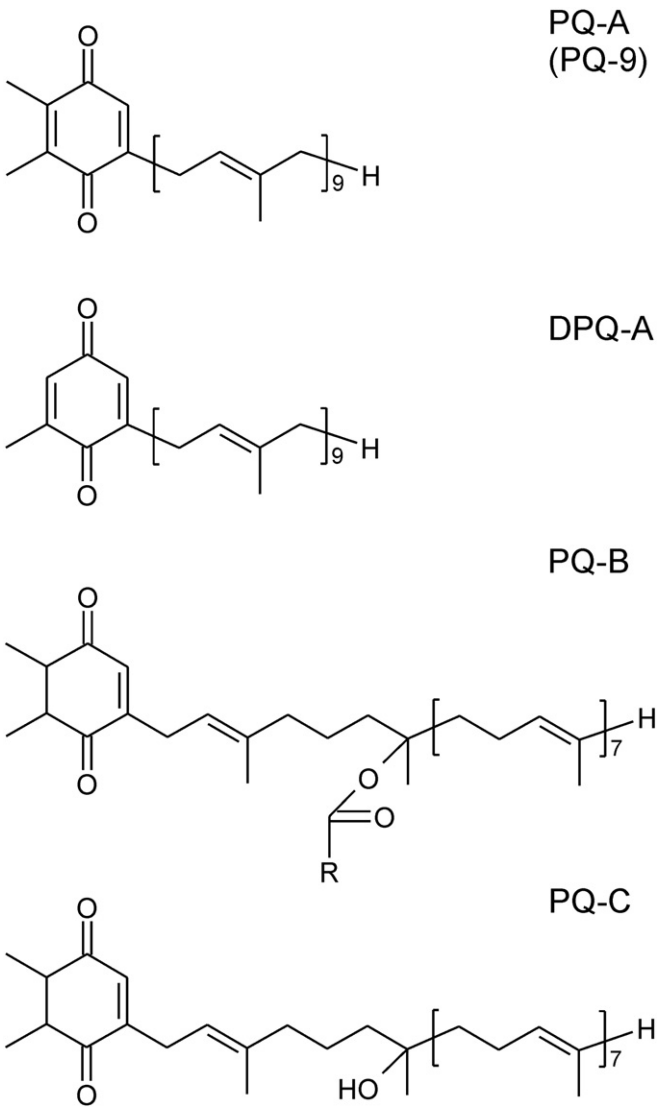

Fig. 8. Plastoquinones: PQ-A, plastoquinone-9 (PQ-9); DPQ-9, demethyplastoquinone-9; PQ-B, plastoquinone-B; PQ-C, plastoquinone-C.

4.3.2. Biosynthesis

In the plastoquinone biosynthetic pathway (Fig. 9) the head group precursor homogentisate (HGA) is derived from tyrosine and the prenyl side chain is formed in the DXP pathway [88]. Condensation of the head group and solanesyl diphosphate is catalyzed by homogentisate solanesyl transferase. Prenylation of HGA with phytol and geranylgeranyl diphosphate is also an important step in the biosynthesis of tocopherols and tocotrienols, respectively [203]. After condensation, methylation reaction takes place giving the final product. The condensation reaction is supposed to proceed in the inner chloroplast membrane [204] although endoplasmic reticulum–golgi membranes were also suggested to be the site of this reaction in spinach [205].

The above described biosynthetic pathway of PQ occurs in higher plants and algae but there are indications that in cyanobacteria the pathway is different. The *Synechocystis* sp. PCC 6803 mutant, lacking *p*-hydroxyphenylpyruvate dioxygenase, cannot form tocopherols but is able to synthesize PQ [206]. The corresponding *Arabidopsis* mutant lacks both tocopherols and PQ. This suggests that HGA is not required for PQ biosynthesis in cyanobacteria, whereas in higher plants it is necessary intermediate. Moreover, in genomes of many cyanobacteria no close homologues of HGA prenyltransferase have been found. It indicates that another biosynthetic pathway of PQ occurs in cyanobacteria. This issue requires further study.

4.3.3. Function

A firmly protein-bound PQ molecule at the Q_A site of PSII is a one-electron carrier, transferring electrons between pheophytin and another loosely bound PQ molecule at the Q_B site. After two-electron reduction and proton uptake, the formed PQH_2 molecule dissociates from the Q_B pocket and enters the mobile PQ-pool in the thylakoid membrane. Re-oxidation of PQH_2, coupled with transmembrane proton translocation proceeds at the cytochrome b_6f complex. The results of experiments on redox reactions of cytochrome b_{559} in the presence of PQs, indicated the existence of a third PQ-binding site in PSII, named Q_c [207]. This site has been recently identified in the crystal structure of the cyanobacterial PSII [208].

PQ is also involved in the cytochrome b_6f-dependent Q-cycle, similar to that operating in mitochondria. In thylakoid membranes of cyanobacteria, PQ participates both in the photosynthetic and respiratory electron transport chain [209]. In thylakoids of higher plants and algae, also other proteins interacting with PQ were identified. In the cyclic electron transport, PQ is reduced probably by ferredoxin:$NADP^+$ oxidoreductase (FNR) [210] and/or a hypothetical ferredoxin:quinone oxidoreductase (FQR). During the light-independent chlororespiration process, PQ enzymatically oxidizes NAD(P)H and transfers electrons to oxygen with the involvement of oxidases. The postulated PQ-reducing enzymes engaged in this process are NDH and NDH-2 dehydrogenases, encoded by *ndh* genes [211]. The suggested enzymes to oxidize PQH_2 were plastid terminal oxidase (PTOX), peroxidase that oxidizes PQH_2 using hydrogen

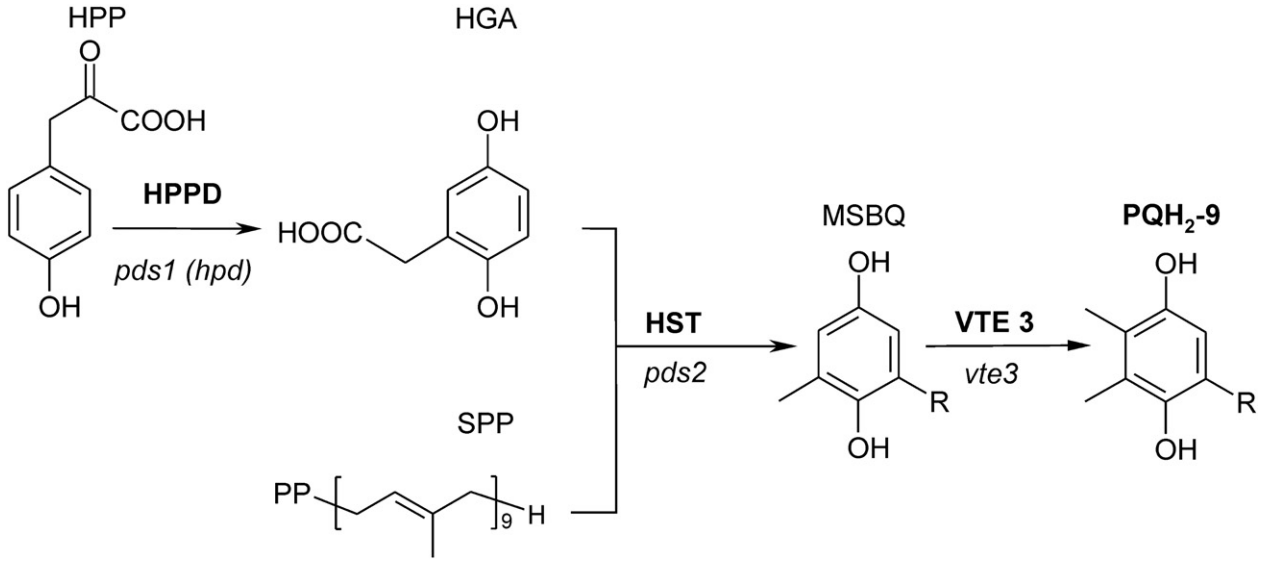

Fig. 9. Plastoquinone biosynthesis in plants. HGA, homogentisate; HPP, *p*-hydroxyphenylpyruvate (synthesized from tyrosine); HPPD, *p*-hydroxyphenylpyruvate dioxygenase; HST, homogentisate solanesyl transferase; MSBQ, 2-methyl-6-solanesyl-1,4-benzoquinol; R, solanesyl side chain; SPP, solanesyl diphosphate; VTE3, MPBQ/MSBQ methyl transferase.

peroxide and the low-potential form of cytochrome b_{559} of PSII [211,212].

PQ molecules to fulfill the function of long-range electron shuttle between PSII and cytochrome b_6f complexes in thylakoid membranes and proton pump across the membrane must show high lateral and transversal mobility. Taking into account that the length of the PQ molecule in the linear conformation corresponds approximately to the thickness of the membrane, diffusion of PQ will be most efficient within the fluid, hydrophobic mid-plane region of the membrane with the hydrophobic side chain arranged parallel to the membrane surface [213]. However, the head group of PQ must show tendency to penetrate the membrane interphase region where the PQ-binding sites at the protein complexes are situated. The head group of PQH_2, formed after PQ reduction by PSII, is more polar than that of PQ, and it is supposed to occupy more polar membrane regions. Nevertheless, it must cross the membrane to reach the oxidation site at the cytochrome b_6f complex. Based on the results of experiment performed in several model systems [214–217], it was suggested that the oxidized and reduced PQ molecules form a charge–transfer complex that facilitates penetration of hydrophobic membrane interior by PQH_2 molecules. It was shown in these studies that the formation of the charge–transfer complex increases PQH_2 solubility in hydrophobic solvents, as well as decreases the content of PQH_2 at the interphase region of monogalactosyldiacylglycerol monolayer [215,216]. A tendency to occupy different membrane regions by the oxidized and reduced forms of PQ was found in anisotropy studies of diphenylhexatriene [218], the fluorescent probe that monitors membrane lipid order.

Besides the function in the photosynthetic electron transport, also other functions of PQ were demonstrated. PQH_2 shows pronounced antioxidant activity, similar to those of tocopherols and the reduced UQ. It has been demonstrated in many experiments, performed both *in vitro* and *in vivo*, that PQH_2 inhibits membrane lipid peroxidation, is an efficient superoxide and singlet oxygen scavenger [202,219–223]. Strong accumulation of PQH_2 during acclimation to high light conditions in *Arabidopsis* has been interpreted as a defense response against oxidative stress [224]. Recently, function of PQ in heat stress reaction has been shown [225]. The decrease in size of the photoactive PQ-pool and a change in the proportions of oxidized and reduced PQ in older leaves of barley seedlings under heat treatment were observed. It was suggested that a thermoinduced change of the redox state of the PQ-pool and a redistribution of plastoquinone molecules between photoactive and non-photoactive pools are the mechanisms that reflect and regulate the response of the photosynthetic apparatus under heat stress conditions [225].

PQ has been identified also as a cofactor participating in desaturation of phytoene in carotenoid biosynthesis [226,227]. In the so called, *poly-cis* carotenoid biosynthetic pathway found nearly in all cyanobacteria, *Chlorobium* and photosynthetic eukaryotes, two closely related desaturases are involved (phytoene desaturase and ζ-carotene desaturase). During this reaction, PQ is the hydrogen acceptor, while PTOX was found to be the PQH_2 oxidant [228].

It is postulated that the redox state of the PQ-pool plays a role of the major redox sensor in chloroplasts that initiates many physiological responses to changes in the environment, especially those related to quality and intensity of light. It was shown that the redox state of the PQ-pool regulates phosphorylation of antenna complexes LHCII by activation of cytochrome b_6f complex-dependent protein kinase [229].

The role of the redox state of PQ-pool in the regulation of photosynthetic gene expression was established in experiments, where photosystems were selectively excited with light of different wavelengths or specific inhibitors of the photosynthetic electron transport chain were applied. The use of light selectively exciting PSII results in reduction of the PQ-pool, whereas light preferentially exciting PSI, enhanced oxidation of the pool. Specific inhibitors also change the PQ to PQH_2 ratio: 3-(3′,4′-dichlorophenyl)-1,1-dimethylurea (DCMU) blocks PQ reduction by PSII, while 2,5-dibromo-3-methyl-6-isopropyl-*p*-benzoquinone (DBMIB) blocks PQH_2 oxidation by cytochrome b_6f complex. This kind of experiments showed that oxidation of the PQ-pool induced expression of the *psbA* gene encoding D1 peptide of PS II core and repress expression of *psaAB* encoding peptides PsaA and PsaB occurring in the PSI core, which leads to enhanced synthesis of PSII. On the other hand, reduction of the PQ-pool induced expression of the gene *psaAB*, which increased the level of PSI [230]. These data led the authors to the conclusion that some genes were retained in chloroplast genome because they were directly regulated by the redox state of PQ/PQH_2 couple. Nevertheless, the redox state of the PQ-pool regulates also the expression of nuclear-encoded genes for ascorbate peroxidase (APX1 and APX2) [231–234] superoxide dismutase [235], carotenoid biosynthesis [236] and others.

In several experiments performed recently, cDNA microarray technique was applied to monitor the influence of the redox state of

the PQ-pool on expression of thousands of genes [237–239]. The results showed that light stress influenced the expression of *lhcb* genes coding for LHCII, which is one of the acclimation mechanisms. However, these results were questioned by others. It seems that the contribution of the redox state of the PQ-pool in the regulation of the synthesis of chloroplast proteins is a complex response, working at the longer time scale that might be also related to posttranscriptional regulation. Moreover, also other chloroplast redox systems, like glutathione or ferredoxin–thioredoxin system, might be engaged in the regulatory processes.

4.4. Tocopherolquinones

4.4.1. Occurrence

α-Tocopherol quinone (α-TQ, Fig. 10), the most widespread among TQs, has been known for years as a minor constituent of all oxygenic photosynthetic organisms that are able to perform biosynthesis of α-tocopherol. It has been identified in green plant tissue from various plant species and taxonomic groups, usually at a proportion between 1 and 2 moles per 100 moles of chlorophyll [74,76,77,240–242]. The presence of α-TQ has also been reported in non-green plant tissue [86,243], as has its accumulation during chromoplast development [244] and senescence of leaves [242,245]. Within chloroplasts, α-TQ was found as an integral component of thylakoids, where it has been recognized as a component of both photosystems [78], as well as in osmophilic plastoglobuli of the plastid stroma [80] and in chloroplast envelopes [84]. α-TQ has also been found to be an insect-feeding stimulant on the leaf surface of *Populus* [246].

The occurrence of oxidized and reduced forms of α-TQ in a variety of microorganisms, fungi and animals was also reported [247]. In order to verify the previous results, selected microorganisms, like *S. cerevisiae*, *Candida utilis*, *E. coli* and *Butyryvibrio fibrisolvens* were analyzed for α-TQ content. However, we were not able to detect any redox form of α-TQ in *E. coli* and yeast, whereas the total α-TQ content in *B. fibrisolvens* was 1.01 ± 0.23 nmol/g FW that is about one tenth the value reported previously. It should be also mentioned that the data on α-TQ content in rat liver [248] were questioned by others [249,250].

4.4.2. Biosynthesis

TQs are well known products of tocopherols oxidation and the presence of these isoprenoid quinones in both plants and animals is supposed to be the consequence of this reaction proceeding *in vivo* as a result of antioxidant action of tocopherols. However, it is still an open question whether, in some organisms, TQs can be synthesized *de novo* independently of tocopherol biosynthesis. The key enzyme in tocopherols biosynthesis is HGA phytyltransferase. We have searched for homologues of this enzyme from *Anabaena variabilis* in GenBank microbial protein sequence databases using BLAST algorithm. Close homologues were found in cyanobacteria, but not in all the species. Distant homologues were chlorophyll and bacteriochlorophyll synthetases, as well as 1,4-dihydroxy-naphthoate octaprenyltransferases. The homologues found in proteobacteria and green sulfur bacteria were chlorophyll/bacteriochlorophyll synthetases with less than 30% of identity and 45% of similarity. Surprisingly, the homologues were also found in green filamentous bacteria (*Chloroflexus*) which lack both PQ and tocopherols [62]. The other homologues found were UbiA prenyltransferases with about 40% of identity and 60% of similarity and bacteriochlorophyll synthetases and some prenyltransferases from archebacteria. The lack of close homologues of HGA phytyl transferases and tocopherol cyclases in all cyanobacterial species suggests that tocopherols are not synthesized in these species. This was confirmed for some species such as *Synechococcus elongatus* PCC 7942 [251]. Moreover, it raises the question on plastoquinone biosynthesis. In some cyanobacteria species there are only two genes of UbiA prenyltransferases family: 1,4-dihydroxy-2-naphthoate octaprenyltransferase homologues and the homologues of PHB octaprenyltransferase. This fact suggests either different specificity of PHB octaprenyltransferase homologues or a different plastoquinone biosynthetic pathway occurring in these cyanobacteria.

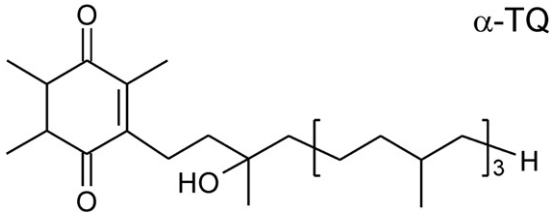

Fig. 10. α-Tocopherolquinone (α-TQ), the most widespread tocopherolquinone.

4.4.3. Function

While in many studies α-TQ was regarded just as a product of tocopherol oxidation without any specific function, several other studies have indicated that this prenylquinone interacts specifically with PSII components: cytochrome b-559 [252,253] and non-heme iron [253]. It has been shown that α-TQ shows a photoprotective effect on PSII by dissipation of excess absorbed light energy due to stimulation of cyclic electron transport around PSII [254] and due to excitation energy quenching [252]. Increased α-TQ accumulation, associated with decreased PSII efficiency, was observed in water-stressed plants [255,256]. α-TQ, together with γ-TQ, were formed during high light stress of *C. reinhardtii* cells [220], as well as seedlings of runner bean [257]. In addition to the oxidized α-TQ, the reduced form, α-tocopherol quinol (α-TQH_2), has also been found in young broad bean leaves [240]. In many studies, α-TQH_2 has been shown to scavenge reactive oxygen forms and to inhibit lipid peroxidation [174,221–223,258,259]. It showed even stronger antioxidant activity when compared to tocopherols and ubiquinol.

In mammalian cells, α-TQ interaction with NAD(P)H:quinone oxidoreductases was postulated [260]. There are experimental data indicating interaction of α-TQ with mitochondrial electron transport, where TQ/TQH_2 may act as a weak competitive inhibitor of cytochrome bc_1 complex and this way it participates in the regulation of mitochondrial electron transport [261]. Participation of α-TQH_2 and deoxy-α-TQH_2 in biohydrogenation of unsaturated fatty acids in rumen bacterium *Butyrivibrio fibrisolvens* was reported [262,263]. Moreover, it has been suggested that α-TQ functions as hydrogen acceptor in fatty acid desaturation in humans [264]. There are also data showing cytotoxic properties of α-TQ on cancer cells [265]. Recently, the structure of human supernatant protein factor (SPF) in complex with α-TQ has been resolved [266]. SPF is supposed to have a role in regulating cholesterol synthesis *in vivo* and its complex with α-TQ might have anti-atherosclerotic effects [266].

Acknowledgements

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