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Review

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ABSTRACT

Bacterial quinones are lipophilic redox compounds involved in important cellular roles such as electron transport in respiratory and photosynthetic chains. However, a growing body of research has now revealed that quinones have additional functions in bacterial physiology, with significant consequences for colonization and persistence in different ecological niches. The aim of this review is to provide an updated view of the functions of bacterial quinones, with particular emphasis on their importance for bacterial metabolism, gene regulation, and stress resistance. We provide evidence that quinones have also a deep impact on the composition and function of bacterial ecosystems.

1. Introduction

Quinones are redox-active organic compounds that are found in most living organisms. They are formed of unsaturated cyclic diketones that are usually prenylated by enzymes belonging to the UbiA superfamily of prenyltransferases; these enzymes add a lipid-soluble isoprenyl tail to the redox moiety that anchors it in membrane lipid bilayer (for a review see [1]). The number of isoprenoid units and modifications in the isoprenyl tail vary among species, and depending on whether the redox moiety undergoes reduction or oxidation, the molecule becomes either a quinol or quinone, respectively. The extensive degree of structural variation in bacterial isoprenoid quinones and elucidation of their complex biosynthetic pathways have been the focus of numerous studies and multiple recent reviews [2–7].

In this review, we will focus on the two main structural groups of isoprenoid quinones found in bacteria: benzoquinones and naphthoquinones. Rare groups, such as methionaquinones, benzothiophenquinones, calderiellaquinones, and sulfolobus-type quinones, will not be addressed here. Benzoquinones can be divided into three types: ubiquinones (UQ), plastoquinones (PQ), and rhodoquinones (RQ) (Fig. 1A). Ubiquinones are widely distributed in both prokayotes and eukaryotes, while plastoquinones are restricted to cyanobacteria and plants. Rhodoquinones are structural analogs of ubiquinones in which one methoxyl group (CH_3O) is replaced by an amino group (NH_2) (Fig. 1A); these are present in a limited number of bacterial species, such as some aerobic chemotrophic β-proteobacteria, as well as a few unicellular eukaryotic and animal species [7]. Naphthoquinones, the second group of bacterial quinones, include demethylmenaquinones (DMK) and menaquinones (MK) (Fig. 1A), and are present mainly in Gram-positive bacteria and archae; however, members of the former group, such as *Enterococcus faecalis* and *Streptococcus agalatiae,* produce only DMK because they lack a methyltransferase for converting DMK to MK. Certain bacteria, such as *Escherichia coli*, are able to produce both UQ and (D)MK [8]. DMKs and MKs are synthesized from the precursor 1,4-dihydroxy-2-naphthoic acid (DHNA) or 1,4-dihydroxy-6-naphthoic acid, which are produced via the classical Men pathway or the futalosine pathway, respectively [3]. Bacterial MKs belong to the vitamin K_2 group (Fig. 1A). In mammals, vitamin K_2 functions as an essential molecule required for the activation of several proteins involved in blood clotting and bone metabolism [9].

The reduction or oxidation of quinones usually involves two electron transfers associated with the addition or release of two individual H^+ protons (Fig. 1B). Transfer or removal of only a single electron generates a semiquinone radical (Fig. 1C), which can become toxic in the presence of oxygen by yielding the superoxide anion $^{\bullet}O_2^-$ (Fig. 1D). MK and RQ have low redox midpoint potentials (E_m around −70 mV), whereas values for UQ and PQ are higher (E_m of + 100 mV) and those for DMK are intermediate (E_m of + 35 mV). Evolutionarily speaking, menaquinones are considered to be the ancestral type of quinones, while UQ and PQ are thought to have appeared more recently with the rise in oxygen concentrations on Earth. High redox-potential quinones, like UQ, are less toxic than MK in oxygen-rich environments [10].

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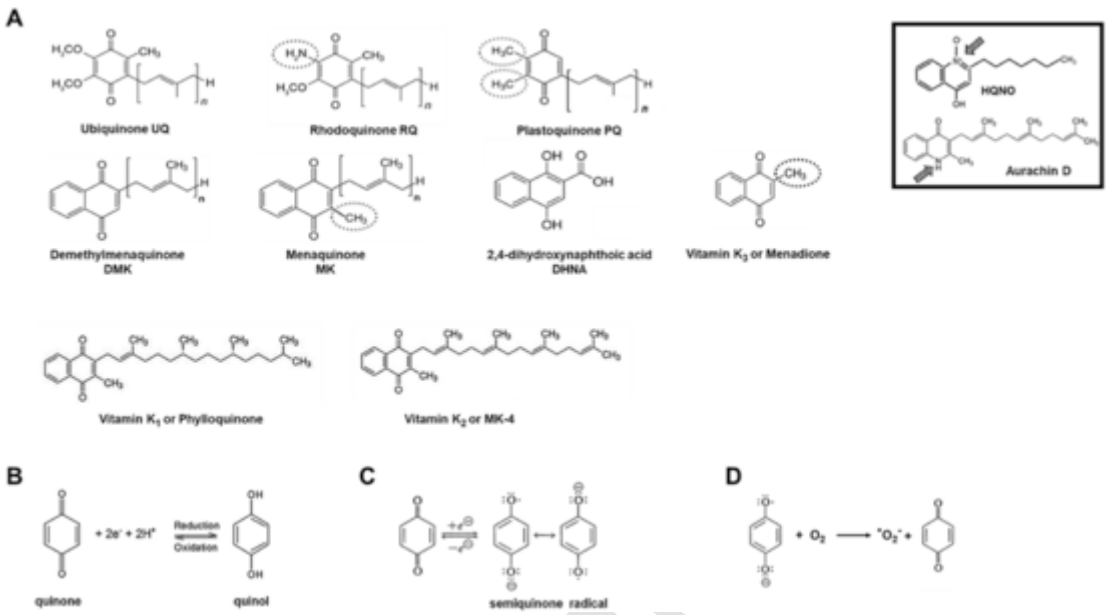

Fig. 1. Chemical structures and properties of quinones. **A:** Chemical structures of the major bacterial quinones and K vitamins. Some chemical changes between the different quinone structures are highlighted with circles. Vitamin K_1 (phylloquinone) is present in cyanobacteria and most photosynthetic eukaryotes. Vitamin K_2 (MK-4) is synthesized by mammals by conversion from vitamins K_1 or K_3. Potent inhibitors of respiratory electron transfer are presented in the solid box: HQNO (2-heptyl-4-hydroxyquinoline-N-oxide) is a quinoline-N-oxide (arrow), whereas aurachin D is a quinoline terpenoid (arrow) similar to (D)MK. Both molecules have no redox capacity. **B:** Reduction/oxidation of benzoquinone. **C:** Formation of a benzosemiquinone radical. **D:** Generation of superoxide anion from the semiquinone radical.

This review focuses on the diverse roles of quinones in bacterial physiology. In light of recent data supporting the importance of bacterial relationships in the functioning of various ecosystems, we will present multiple lines of evidence that these molecules can serve as key ecological resources in microbial communities, even for bacteria that do not produce quinone. A full consideration of both aspects of bacterial quinones in cellular physiology and community ecology opens new fields of investigation for biotechnological applications and human health management.

2. Physiological functions of quinones

2.1. Electron shuttle in respiratory and photosynthetic chains

Early experiments on the physiological function of quinones (UQ, MK) in bacteria indicated that these molecules operate in electron transport chains [11]. Electron transfer generates a proton gradient across the cytosolic membrane, which is used by ATP synthase to produce ATP (for reviews see [12–14]). *In vivo* imaging experiments of *E. coli* established that ubiquinones can diffuse rapidly in membranes over long distance enabling electron transfer between multiple dehydrogenases and different electron transport complexes [15]. Thanks to their large repertoire of terminal electron transferases, bacteria can use a huge variety of compounds as direct electron acceptors, with the most common being oxygen, nitrite, nitrate, sulfate, sulfite, thiosulfate, trimethylamine, elemental sulfur, fumarate, and metals; this flexibility allows them to support growth and colonization in diverse environments [13,14]. In *E. coli,* high-redox-potential UQs are used under aerobiosis, whereas low-potential quinones like (D)MKs are rather involved in anaerobic respiratory chains. However, in Gram-positive bacteria, (D)MKs are used for both aerobic and anaerobic respiration. Likewise, some proteobacteria also employ UQs under anaerobic conditions [16]. In cyanobacteria, plastoquinones (PQ) are used as electron carriers in thylakoid membranes, where they transfer electrons from the photosystem II reaction center to the cytochrome b_6f complex. In addition, PQ replaces UQ in cyanobacterial respiratory electron transport chains [12]. Low-potential rhodoquinones RQ are thought to provide an advantage to some bacteria and protists for survival under anaerobic or anoxic conditions, but their exact role in anaerobic electron transfer chains remains to be fully understood [7].

2.2. Extracellular electron transfer

Beyond these respiratory processes, under anaerobic or microaerobic conditions many bacterial species utilize an extracellular electron transfer (EET) mechanism through which they can transfer electrons outside of the cell envelope to distant electron acceptors such as minerals, independently of classical respiratory chains. EET has been thoroughly investigated in two species of Fe(III)-reducing Gram-negative bacteria, *Shewanella oneidensis* and *Geobacter sulfurreducens* (γ and δ proteobacteria, respectively). In these species, electrons originating from the intracellular metabolism are shuttled from the cytoplasmic membrane to the extracellular acceptor by distinct pathways involving quinones and surface multiheme cytochromes (for a review see [17]). Depending on the electron gradient, EET can be a bidirectional process (cells to minerals and vice-versa), in which quinols and quinones behave as electron donors or acceptors, respectively (Fig. 2A) [18]. In the Gram-positive opportunistic pathogens *Listeria monocytogenes* and *E. faecalis*, EET is performed by a different set of proteins, using flavins instead of heme (Fig. 2B) [19,20]. In the latter species, DMK-9 production is necessary for EET activity, while the former uses a specific but as-yet-uncharacterized DMK. For *L. monocytogenes*, EET may be important under certain conditions, such as growth in the gastrointestinal tract [19]. Genome analysis has revealed that homologs of the *L. monocytogenes* EET system are conserved in many species from the Firmicutes phylum, suggesting that these species are also quinone producers [20,21].

EET can be accomplished by cell-to-cell transfer of electrons, electrical wire pili, or by redox proteins bound to extracellullar cell surfaces (Fig. 2C). EET can also occur at long distances from bacteria (millimeter to centimeter) thanks to diffusible aqueous redox carriers known as extracellular electron shuttles (EES) (Fig. 2D) [22]. EESs can be quinones, flavins, phenazines, and pyocyanin, among others (Fig. 2E).

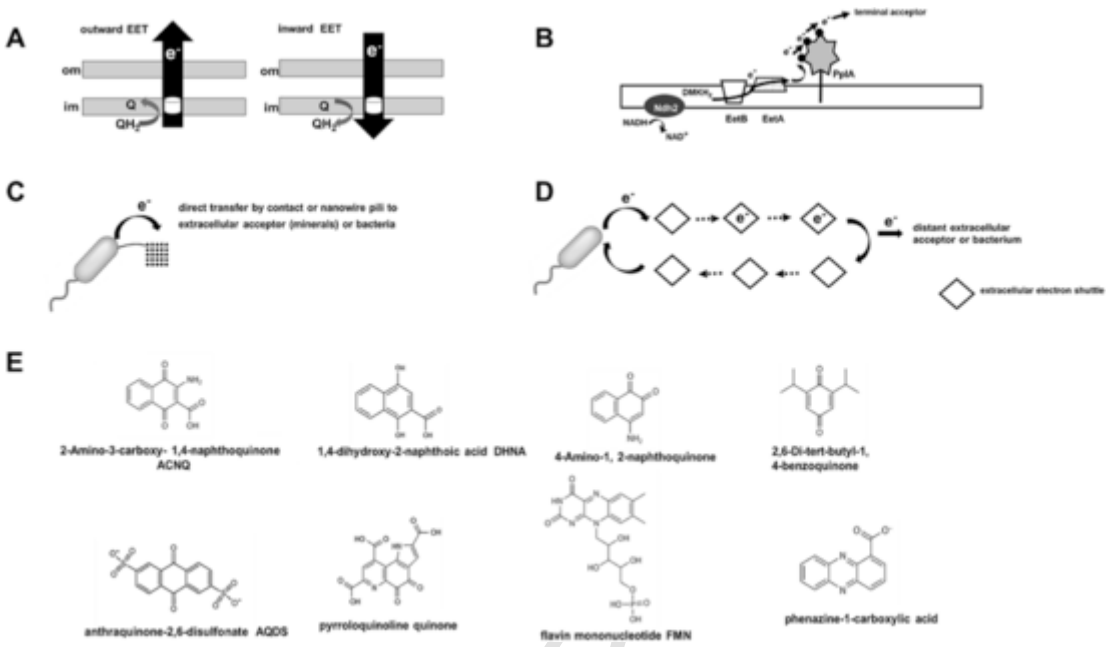

Fig. 2. Extracellular electron transfer in bacteria. **A:** Simplified drawing of the multiheme c-type cytochrome proteins (black arrow) involved in bidirectional extracellular electron transport (EET). White cylinders represent quinol oxidase (left) and reductase (right). Q: quinones (UQ or MK). QH_2: quinols (UQH_2 or MKH_2). im: inner membrane. om: outer membrane. **B:** Schematic representation of the EET system of the Gram-positive bacterium *Listeria monocytogenes*. The two membrane proteins EetA and EetB and the lipoprotein PplA transfer electrons from $DMKH_2$ to an unknown extracellular terminal acceptor. PplA is FMNylated (small black circles) and the flavins are in charge of the electron flow. **C** and **D:** Different means of extracellular electron transfer, by contact or nanowires to another bacterium or a mineral (C), or by extracellular electron shuttles (EES) (D). **E:** Chemical structures of some EESs, including quinones, flavins, and phenazines. EET can be performed by EES diffusion (concentration gradient) or by electron hopping between EESs (electron gradient).

EES can be essential in complex biofilm matrices where electron acceptors are at the periphery. These electron shuttles can be produced by bacteria (endogenous EES) or present in the environment (exogenous EES, like humic substances). The role of quinones in mediating EET was first discovered by Newman and Kolter [23] in the model bacterium *Shewanella putrefaciens* (now *S. oneidensis*) MR-1, which uses insoluble ferric oxides as extracellular electron acceptors. The quinone involved was just recently identified as 2-amino-3-carboxyl-1,4-napthoquinone (ACNQ; Fig. 2E) [24]. ACNQ is formed through the spontaneous modification of DHNA in the presence of an amine donor (amino acid, ammonium salt); all DHNA-producing bacteria are potentially able to produce ACNQ for EET. As an example, Freguia and collaborators established that ACNQ plays a role in anodic electron transfer in *Lactococcus lactis* [25]. Both ACNQ and DHNA have also been identified as growth stimulators in bifidobacteria. Besides ACNQ, the benzoquinone 2,6-di-tert-butyl-p-benzoquinone (Fig. 2E) was found to be involved in EET in *Klebsiella quasipneumoniae* sp. 203 [26]. It is plausible that other soluble quinones, such as short isoprenoid chain quinones, anthraquinone derivatives (anthraquinone-2,7-disulfonic acid, AQDS), and pyrroloquinoline (PQQ) synthesized by proteobacteria can connect the intracellular metabolism to extracellular redox reactions via EET (Fig. 2E). Interestingly, the pathogenic bacterium *Pseudomonas aeruginosa* and the myxobacterium *Stigmatella aurantiaca* excrete structural MK analogs, such as the 2-heptyl-4-hydroxyquinoline N-oxide (HQNO) and the quinoline aurachin D, respectively (Fig. 1A), that inhibit electron transfer and respiration [27,28]. HQNO can alter the physiology of other bacteria and has demonstrated antibacterial activity, presumably by binding to and inhibiting cytochrome oxidases [29].

2.3. Electron sink in metabolic pathways

In addition to electron transfer, quinones are also directly involved in certain biosynthetic and catabolic pathways.

2.3.1. Heme synthesis

In the *E. coli* heme biosynthesis pathway, the conversion of protoporphyrinogen IX into protoporphyrin IX is catalyzed by a protoporphyrinogen IX dehydrogenase/oxidase, HemG. This membrane flavoprotein catalyzes the oxidation of protoporphyrinogen IX, and in doing so, releases six electrons that are transferred to UQ or MK. The quinols then transfer their electrons to the appropriate terminal electron acceptor, determined by whether conditions are aerobic or anaerobic [30].

2.3.2. Pyrimidine synthesis

In *E. coli*, the class 2 dihydroorotate dehydrogenase PyrD enzyme is a flavoprotein catalyzing oxidation of (*S*)-dihydroorotate to orotate during *de novo* biosynthesis of the pyrimidine nucleotide precursor UMP. PyrD interacts with the inner side of the cytosolic membrane via its hydrophobic N-terminal domain and requires ubiquinone under aerobic conditions (or (D)MK during anaerobic growth) as an electron acceptor [31]. Class 2 PyrD is highly conserved in both Gram-negative and -positive bacteria, meaning that PyrD should be present only in quinone producers.

2.3.3. Steroid degradative oxidation

In many bacteria, certain steroid compounds can serve as a carbon source for use in growth. The corresponding catabolic pathways involve oxidation of the steroid ring. In *Pseudomonas* N.C.I.B. 10590, *Nocardia restrictus*, and *Corynebacterium simplex*, it was shown that MK-7 acts as an efficient electron carrier during steroid ring dehydrogenation [32]. However, the coupling of steroid oxidation with electron transfer via a respiratory chain has been demonstrated only in *Arthrobacter globiformis* [33].

2.4. Role in folding of extracytosolic proteins

In *E. coli*, oxidative formation of disulfide bonds that occurs during the folding of extracytosolic proteins is associated with an electron

transport system (Dsb) and quinones (for a review see [34]). The enzyme DsbA oxidizes protein by introducing disulfide bonds, and in the process, becomes reduced. To start a new catalytic cycle, the membrane enzyme DsbB reoxidizes DsbA and transfers the electrons to quinones. In aerobiosis, DsbB uses ubiquinones to shuttle electrons to the cytochrome *bo* or *bd* oxidases, while under anaerobiosis, it uses menaquinones to transport electrons to alternative substrates like fumarate. The electrons for this process are coming from the periplasmic side of the membrane via DsbB protein modification, and not from metabolic reactions. Dsb-like homologs have been found in other bacteria, such as Bdb in the Gram-positive bacterium *Bacillus subtilis*, but they seem to use as-yet-unknown substrates instead of quinones [34]. Instead, in actinobacteria, cyanobacteria, and some δ-proteobacteria, DsbB is replaced by a protein homologous to the human enzyme vitamin K epoxide reductase (VKOR). In humans, membrane-bound VKOR regenerates vitamin K hydroquinone by reducing the vitamin K epoxide formed during gamma-carboxylation of glutamic acids in vitamin K–dependent proteins [9]. Ke et al. [35] showed that in mycobacteria, VKOR contributes to DsbA oxidation by transferring electrons to menaquinones. Interestingly, *E. coli* DsbB can replace the VKOR protein in *Mycobacterium smegmatis* and, conversely, *Mycobacterium tuberculosis* VKOR can replace DsbB in *E. coli.* The close functional homology between these enzymes is further supported by the fact that warfarin, an inhibitor of human VKOR activity, also inhibits bacterial VKOR activity. These proteins appear to play an important role in the pathogenicity of certain plant- or animal-infecting bacteria, as many *dsbA*, *dsbB*, and *vkor* mutants have all demonstrated attenuated virulence in various infection models [34].

2.5. Quinones in stress resistance

2.5.1. Oxidative stress

The work of Søballe and Poole [36] highlighted the ability of ubiquinone-8 (UQ-8) to act as an important antioxidant compound in *E. coli*. *In vivo*, UQ-8 is capable of reducing the accumulation of superoxides and peroxides by limiting undesirable direct single-electron donation to oxygen. Ubiquinol can also behave as a radical scavenger. Subsequently, Agrawal et al. [37] provided further details on the antioxidant properties of UQ-8 in *E. coli*. Long-chain fatty acids (LCFAs) can be metabolized into acetyl-CoA via the β-oxidation pathway, an activity which requires the presence of terminal electron acceptors. During this process, electron leakage can occur via the enzyme FadE (acyl-CoA dehydrogenase), causing the formation of radical oxygen species (ROS) [37]. To prevent this, UQ-8 is necessary for transferring these electrons to terminal oxidases, thus avoiding ROS production. Interestingly, in animals, ubiquinol-10 is an important antioxidant involved in protecting membrane phospholipids and serum low-density lipoproteins from lipid peroxidation [38]. UQ-10 also protects mitochondrial components from free radicals. Furthermore, in *E. coli* UQ-8 is less toxic than MK-8 under high oxygen concentration [10]. In *Staphylococcus aureus*, Wakemann et al. [39] demonstrated that menaquinones potentiate heme toxicity by generating semiquinones and reducing heme. Similarly, in *L. lactis*, MKs seem to control heme homeostasis; under low oxygen conditions, extracellular heme can be sequestered relatively safely in the membrane following its reduction by MK [40].

2.5.2. Osmotic stress

A link between ubiquinone and osmotic stress tolerance was first proposed by Sévin and Sauer [41]. In their study of the BW25113 strain of *E. coli*, growth in high-salt solutions caused a 110-fold accumulation of UQ-8, and this effect was independent of the respiratory activity and antioxidant properties of this quinone. The authors hypothesized that UQ-8 accumulation might increase the hydrophobic thickness and/or stability of the inner membrane, contributing to the osmoprotection of cells. However, the results of Tempelhagen et al. [42] contradicted this model. These authors argued that osmotolerance is not dependent on any UQ-8–induced modification of the membrane's physical properties, but is instead caused by protection of the respiratory chain. Despite this, investigations based on the use of lipid vesicles that mimic the *E. coli* plasma membrane have demonstrated that UQ-8 and UQ-10 do have an osmoprotective effect [43]. Interestingly, phylloquinone (vitamin K_1) was shown to increase the fluidity of dipalmitoylphosphatidylcholine membranes [44]. This result was corroborated by work in the foodborne species *L. monocytogenes*, in which an increase in the concentration of the major menaquinone (MK-7) was shown to be important for membrane fluidity adaptation at low growth temperatures [45].

2.5.3. Cell differentiation

In *B. subtilis*, MK-7 production is required for the differentiation and formation of complex colony structures in which bacteria are held together by an extracellular matrix during growth on hard agar surfaces [46]. This complex colony development (CCD) is not found in mutants of *B. subtilis* that are deficient in MK-7 synthesis, but the phenotype can be alleviated by the addition of exogenous MK-4. In the same species, MK-7 is also required for sporulation, but the cause of this requirement is still unknown.

2.6. Quinones as signaling molecules involved in transcriptional regulation

Because of their redox and chemical properties, quinones can be key signaling molecules detected by sensor and/or regulatory proteins.

2.6.1. Gene control by redox activity

In both Gram-negative and -positive species, the composition and/or redox state of the quinone pool can serve as a regulatory signal that controls important physiological processes. The *E. coli* ArcB-ArcA pair, a two-component regulatory system (TCS), serves as a paradigm of this process. ArcA/B (aerobic respiration control) participates in a transcriptional regulatory network that is involved in the metabolic shift from anaerobic to aerobic growth, through which bacteria are able to respond to various environmental conditions [47]. ArcB is a sensor membrane protein with histidine kinase/phosphatase activities, while ArcA is its cognate transcriptional regulator. When phosphorylated by ArcB on its Asp-54 aspartic residue, ArcA binds to the promoters of target genes and accelerates their transcriptional activity. When dephosphorylated by ArcB, ArcA loses its DNA binding activity and becomes inactive. The kinase activity of ArcB is governed by the redox states of the ubiquinone and menaquinone pools, which depend directly on aerobic respiratory chain activity. Specifically, quinones can generate intermolecular disulfide bonds between two ArcB monomers at the Cys-180/Cys-180′ and Cys-241/Cys-241’ positions [48], located in the N-terminal extremity downstream of the transmembrane domains. Formation of this intermolecular disulfide bond inhibits the kinase activity of ArcB dimers. Van Beilen and Hellingwerf [8] demonstrated that, when the oxygen tension decreases, the three quinol species of *E. coli* (UQH_2, $DMKH_2$, and MKH_2) reduce these disulfide bonds and concomitantly activate ArcB, leading to ArcA phosphorylation *in vivo*. Numerous histidine kinases with a similar regulatory system have been characterized in various species (Table 1). Quinone control has also been documented in Gram-positive bacteria like *B. subtilis* (ResDE) and *S. aureus* (SrrAB). Indeed, the TCS system SrrA/SrrB (Staphylococcus respiration response) is an important regulator of genes involved in virulence, anaerobic metabolism, resistance to oxidative and nitrosative stress, biofilm formation, and programmed cell death [49,50]. By studying biofilm formation under hypoxia, Mashruwala et al. [49] showed that the redox states of MK control SrrB activity: membrane-bound SrrB is active when the menaquinol pool increases and inactive in the presence of menaquinone. This mechanism of SrrB activity was recently confirmed via structural analysis [50]. In contrast to ArcB, kinase activity stimulation of the SrrB homodimer requires the reduction of the in-

Table 1
Histidine kinases regulated by quinone sensing.

2 Component System: Kinase Sensor/ Regulator	Organism	Regulon function	Signal and *in vitro* mechanism	References
RegB/RegA	*Rhodobacter capsulatus*	control of metabolism	RegB kinase activity inhibition by UQ-0	Wu and Bauer 2010 [51]
BvgS/BvgA	*Bordetella pertussis*	colonization/ virulence	BvgS kinase activity inhibition by UQ-0	Bock and Gross 2002 [52]
EvgS/EvgA	*Escherichia coli*	acid stress/ drug resistance	EvgS kinase activity inhibition by UQ-0	Bock and Gross 2002 [52]
AccS/AccR	*Azoarcus sp.*	carbon catabolite repression	AccS kinase inhibition by UQ-0 thiol oxidation	Valderrama et al., 2019 [53]
TodS[a]/todT	*Pseudomonas putida*	toluene/ benzene degradation	menadione TodS inhibition by a cysteine-dependent uncharacterized mechanism	Silva-Jiménez et al., 2015 [54]
HskA[a]/ unknown	*Pseudomonas putida*	electron transport chain composition	autophosphorylation inhibited by UQ-0	Sevilla et al., 2013 [55]
CikA[a] KaiA[a]	*Synechococcus elongatus*	circadian clock control (circadian oscillator)	oxidized plastoquinone would reduce CikA and KaiA stability?	Ivleva et al., 2006 Wood et al., 2010 [56,57]
SrrB/SrrA	*Staphylococcus aureus*	virulence, biofilm anaerobic metabolism	activation of kinase, activity by intrasubunit disulfide bond reduction by MKH_2	Tiwari et al., 2020 [50]
ResE/ResD	*Bacillus subtilis*	anaerobic regulatory network, NO response	uncharacterized mechanism	Härtig and Jahn 2012 [58]

UQ-0: soluble oxidized ubiquinone-0 with no isoprenyl side chain (2,3-dimethoxy-5-methyl-1,4-benzoquinone). MKH_2: menaquinol (reduced form).
[a] TodS, HskA, CikA and KaiA kinases are not integral membrane proteins.

tramolecular Cys-464–Cys-501 disulfide bond in each SrrB monomer. These two residues are located in the C-terminal extremity close to the ATP-binding catalytic domain. Finally, a different model of quinone-dependent regulation was recently discovered in the α-proteobacterium *Sinorhizobium meliloti*. The *smc01818* gene of *S. meliloti* encodes a 557–amino acid protein that shares similarities with class III adenylate cyclase (CyaC). This membrane protein is predicted to be folded into six transmembrane domains and acts as a dimeric adenylate cyclase [59]. CyaC also contains a cytosolic [2Fe–2S] ferredoxin–type domain and two molecules of heme *b*, which are necessary for its activity. Specifically, Wissig and collaborators demonstrated that CyaC activity is modulated *in vitro* by the reversible oxidation and reduction of these hemes, caused by addition of the exogenous benzoquinone decylubiquinone (UQ-0 with a decyl residue in position 6) [59]. Thus, *in vivo*, quinones or quinols can lead to stimulation or inhibition, respectively, of adenylate cyclase activity. In this case, the membrane quinone signal is transduced into an intracellular signal: cyclic adenosine monophosphate (cAMP). However, the exact nature of the endogenous quinones of *S. meliloti* interacting with CyaC remains to be determined.

2.6.2. Quinone toxicity control via electrophilic activity

As electrophiles, no-tailed quinones (usually benzoquinone-type compounds) can form S-adducts with thiol groups via thiol-(S)-alkylation (Fig. 3A) [60]. Gram-positive bacteria, like *B. subtilis* and *S. aureus*, have developed an array of defenses for the detoxification of no-

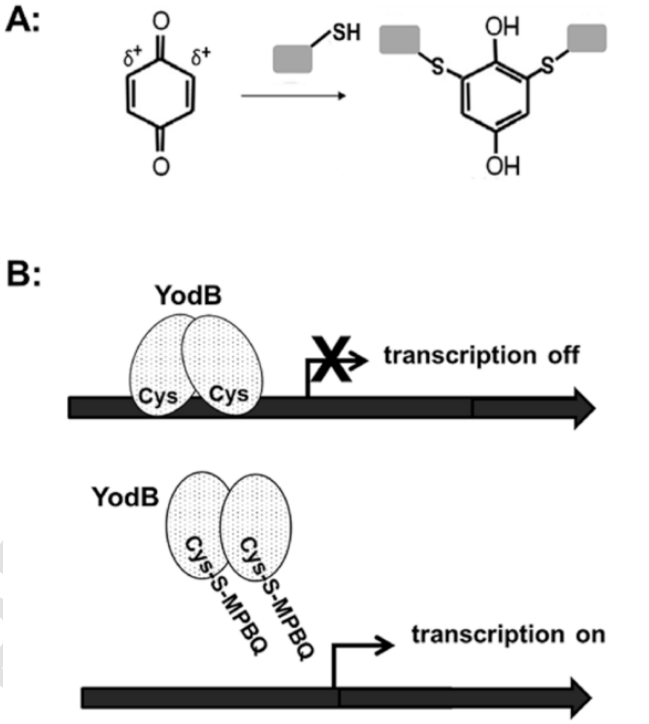

Fig. 3. S-quinonization. **A:** Electrophilic properties of benzoquinone lead to the formation of S-adducts with thiol-compounds or cysteines from protein (gray rectangles). **B:** Model of YodB regulation in *Bacillus subtilis*. YodB is a transcriptional repressor belonging to the MarR/DUF24 family of transcription factors. In the presence of methyl-p-benzoquinone (MPBQ), there is MPBQ-mediated S-alkylation of YodB, causing dissociation of the YodB dimer from its target DNA.

tail quinones (degradation or reduction by reductases, generating less-toxic hydroquinol) and for damage repair (replacement or depletion of thiol-containing proteins) [60,61]. This response depends on the activation of specific transcriptional regulators, for which the archetypes are YodB (*B. subtilis*) and QsrR (*S. aureus*) [62,63]. Both proteins belong to the MarR/DUF24 family of transcription factors and act as repressors. YodB and QsrR share 38% identity (60% similarity) and each forms a homodimer that senses quinones by thiol-S-alkylation *in vitro* (Fig. 3B) [62,63]. In their 2016 study, Lee and colleagues described how YodB is able to respond quickly to methyl-p-benzoquinone (MPBQ). The MPBQ-mediated S-alkylation of YodB results in the formation of a quinone adduct on the Cys-6 residue of YodB, which causes the dimer to dissociate from its target DNA site (Fig. 3B) [63]. In *S. aureus*, QsrR (quinone-sensing response repressor) controls the transcription of genes encoding quinone reductases, dioxygenases, and a nitroreductase [62,63]. *In vitro*, the binding of QsrR to its operator sequences is inhibited by menadione (abusively named vitamin K_3) and 2,3-dimethoxy-5-methyl-p-benzoquinone (a UQ precursor) [62]. A crystal structure of QsrR with menadione revealed that the latter covalently binds to the thiol group of the Cys-5 residue in each QsrR monomer; in this way, menadione-S-alkylation causes conformational changes that perturb QsrR dimerization and inhibit its binding to the DNA operator. Based on this, S-quinonization of regulators has been proposed as a common mechanism of quinone sensing in bacteria. However, in a 2019 study of *S. aureus*, Fritsch and collaborators [64] suggested a new mechanism of quinone sensing based on the MhqR protein. MhqR also belongs to the MarR/DUF24 protein family, but is not related to YodB and QsrR. It is a repressor of the *mhqRED* operon, which is involved in benzoquinone and antimicrobial drug resistance. Methylhydroquinone (MHQ), a benzoquinol, inhibits the binding of MhqR to its operator sequence *in vitro*. Unexpectedly, activation of MhqR does not require its sole cysteine

residue (Cys-95). The authors thus proposed the existence of a putative pocket for quinone binding; the presence of MHQ in this binding site would inhibit MhqR DNA-binding activity [64]. Overall, the MarR/DUF24 family of transcription factors is overrepresented in Gram-positive bacteria, but their specific roles in the quinone response remain poorly investigated [61]. Finally, a study of *L. lactis* strain IL1403 revealed that it possesses two enzymes, YaiA and YaiB, that are involved in quinone degradation [65]. However, the corresponding genes for these enzymes are not regulated by a quinone sensor or a MarR-like regulator, but by the repressor CopR, which responds to levels of copper ions.

3. Quinone roles in bacterial ecosystems

Although quinones fulfill important physiological functions, early investigations clearly demonstrated that several bacterial species do not produce quinone [66]. Nevertheless, several studies revealed that a majority of these auxotrophic species were able to use exogenous quinones or their biosynthetic precursors for growth, suggesting that some species possess a partial quinone biosynthetic pathway. Indeed, quinone production was found to be restored by intraspecies crossfeeding between different auxotrophic mutants of *E. coli*, *B. subtilis*, and the γ-proteobacterium *S. oneidensis* [67]. In particular, Hammer et al. [68] reported an important role for intraspecies quinone complementation in pathogenic bacteria. By coculturing a heme auxotroph of *S. aureus* together with quinone auxotrophs, they were able to enhance the growth and fitness of both types of mutants. In this way, quinone exchange may increase the fitness and virulence of small colony variant cells (SCV) of *S. aureus*, which have mutations in the biosynthetic pathways for menaquinone or heme, and are frequently isolated from hosts [69]. Quinone nutritional exchange can also occur between species of different genera. For example, our group characterized interpecific metabolic crossfeeding in *Streptococcus agalactiae* (Group B *streptococcus*, GBS), a Gram-positive bacterium colonizing the gastrointestinal and urogenital tracts in humans. Under certain conditions, GBS causes severe infections in neonates, pregnant women, immunocompromised patients, and the elderly. In the presence of exogenous heme and MK-4, GBS can shift from a fermentative metabolism toward a respiratory metabolism [27,70]. Specifically, heme and menaquinones activate a CydACydB cytochrome *bd* oxidase, which reduces oxygen from NADH dehydrogenase. Cells of *E. faecalis*, *L. lactis*, and *E. coli*, but not *S. aureus*, are all able to crossfeed GBS and thus induce a shift to respiration (Fig. 4A) [70,71]; this enhances growth, increases the final pH of the culture, and promotes the survival of GBS cells *in vitro*. Furthermore, respiration plays an important role in host colonization, as demonstrated by the finding that a *cydA* mutant of GBS displayed reduced virulence in a neonate rat model [27]. We determined that GBS uses the menaquinone precursor 1,4-dihydroxy-2-naphthoic acid (DHNA) to synthesize its own DMK-10, specifically using the *menA* gene which encodes a 1,4-dihydroxy-2-naphthoate prenyltransferase enzyme (Fig. 4B) [70]. This gene is clustered in an operon that also contains *gbs1788*, coding for a type-2 NADH dehydrogenase, and the *cydAB* genes, which encode the cytochrome *bd* oxidase. The adjacent gene *gbs1783* encodes an IspB polyprenyldiphosphate synthase, which is responsible for synthesizing the isoprenoid side tail. Many species of the human gut microbiota produce the intermediate metabolite DHNA [72], which has the advantage of being more diffusible than MK. In this ecological niche, certain pathogenic bacteria may thus acquire DHNA in order to perform respiration and enhance their ability to colonize, persist, and thrive *in vivo*.

Since the pioneering work of Gustafsson and collaborators [73] on gnotobiotic rats in 1962, it has been well known that the gut microbiota participates in the production of certain vitamins, notably vitamin K (menaquinones MK-6 to MK-12). More recently, Fenn et al. [74] investigated growth factors that enabled the cultivation and identification of as-yet-uncultured gut bacterial species. They determined that quinones produced by cultivable bacteria act as required growth factors for several microorganisms of the gut microbiota. Indeed, their work showed that diverse bacterial species of the human microbiome can only grow in the presence of quinone-producing gut bacteria. These quinone-requiring species belong to the genera *Bacteroides*, *Faecalibacterium*, *Bilophila*, *Gordonibacter*, and *Sutterella*, and can be crossfed by "quinone helpers" such as *E. coli*, *Eggerthella lenta*, *Eubacterium rectale*, and several

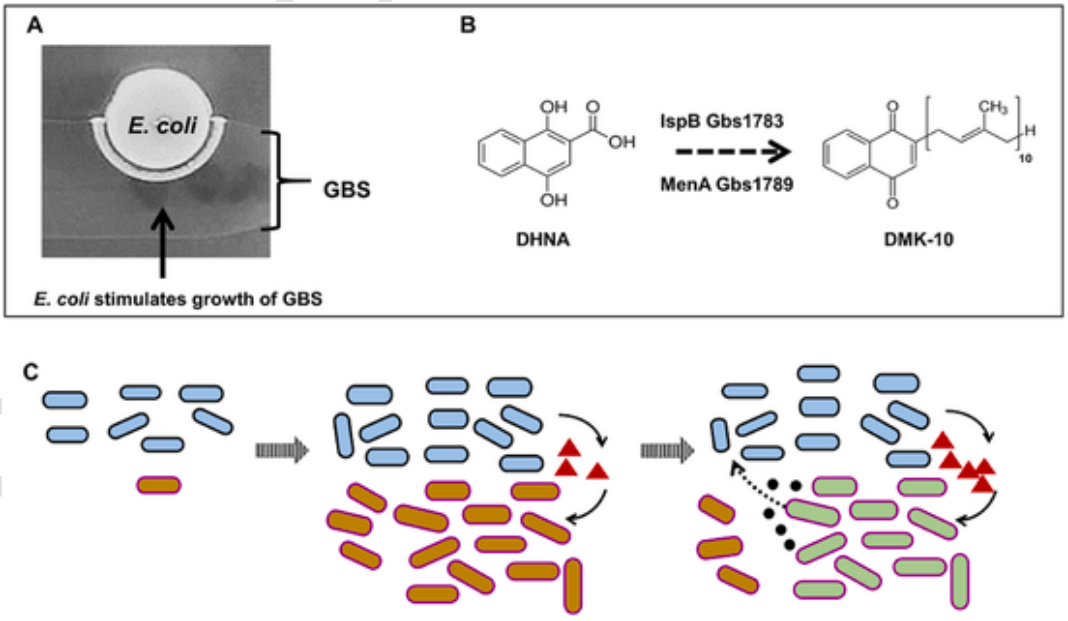

Fig. 4. Quinones and crossfeeding in bacteria. **A:** DHNA crossfeeding and DMK-10 biosynthesis in *Streptococcus agalactiae* (GBS). The *ubiA menA* mutant of *Escherichia coli* releases DHNA, which stimulates GBS growth via activation of its respiration metabolism. **B:** GBS converts DHNA into DMK-10 via the activities of the IspB (prenyl synthase) and MenA (prenyl transferase) enzymes. **C:** Hypothetical model for quinone crossfeeding in the gut microbiota. As populations of "quinone helper" bacteria (blue cells producing red triangles) increase, quinone-auxotroph bacteria (brown cells) can grow and shift their metabolism(s) (green cells). These bacteria may in turn provide new nutrients (black circles, dotted arrow) to helper cells. In a polymicrobial population, metabolic differentiation and cooperation can happen via exchange of quinones or their biosynthetic precursors.

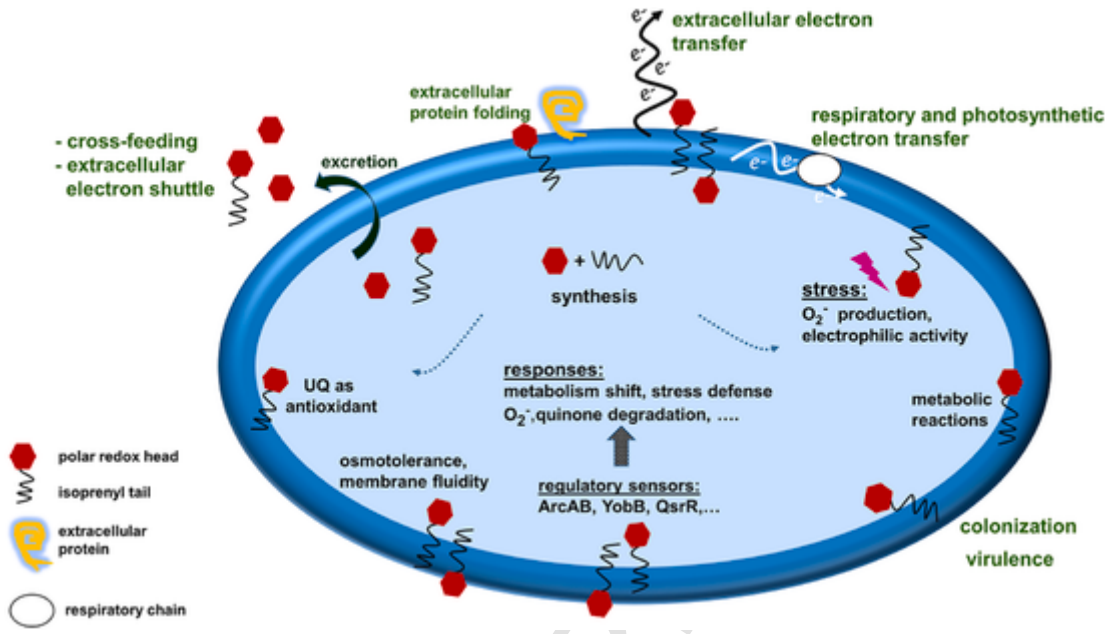

Fig. 5. Schematic summary of the different roles attributed to bacterial quinones.

Bacteroides species. Genome analysis revealed that some of the "uncultured" bacteria possess at least one *menA*-like gene, indicating that they can use DHNA to produce their own (demethyl)menaquinones. A particularly interesting example is *Faecalibacterium*, a genus of Gram-positive anaerobic bacteria of the human gut microbiota that has been proposed to be beneficial for health because of its anti-inflammatory properties [75]. Members of this genus are devoid of genes involved in quinone biosynthesis and may instead use quinones directly from other species. Indeed, Fenn and collaborators suggested that this may be true for the majority of these species, i.e., that exogenous menaquinones may be important for performing anaerobic respiration in the gut (Fig. 4C) [74]. This hypothesis was supported by a genome survey that uncovered the presence of numerous genes involved in anaerobic respiration. Thus, it seems likely that the production and presence of substantial levels of quinones (or their biosynthetic precursors) in the gut enable the persistence of quinone-auxotrophic bacteria. Furthermore, variations in quinone level and diversity can disturb the composition of the gut flora. Depending on the conditions at hand, quinone nutritional complementation may favor pathogenic bacteria as well as, or instead of, beneficial bacteria, creating a "Dr. Jekyll and Mr. Hyde" effect. Vitamin K supplementation in the human diet must thus be undertaken with caution [76].

The idea of quinones as exported growth factors is quite paradoxical, since isoprenoid quinones are poorly hydrosoluble. Quinone excretion or secretion is thus a topic of much debate [74,77]. For quinone diffusion in the environment, it has been proposed that these compounds can be modified into a water-soluble form, or excreted in vesicles or by nanotubes. Interestingly, bacterial proteins from the YceI family are able to bind polyprenyl molecules, including UQ-8 [78–80]. These proteins belong to the large, diverse group of lipocalins, which have an affinity for small hydrophobic molecules. YceI homologs are found in a large number of Gram-negative and -positive bacteria, where they can be periplasmic or extracellular proteins. The work of Ikeda and Doi [77] in *B. subtilis* provided evidence for exportation, as they reported that 40% of all menaquinone (MK-7) produced was present outside the bacterial cells during the stationary phase. The cell supernatant also contained a 100-kDa glycoprotein that demonstrated binding affinity for MK-4 and MK-7 but not for menadione [77]. Thus, it seems likely that quinones with a polyprenyl side chain may be effectively excreted/secreted in the environment. Quinone nutritional exchanges can occur within a microbial community and impact its stability and function.

4. Conclusion and perspectives

The aim of this review is to discuss recent advances in our understanding of the crucial roles of quinones in bacterial metabolism, physiology, regulation, and syntrophy (summarized in Fig. 5). Notably, the experimental works presented here suggest that quinones may contribute to host colonization and virulence, with evidence obtained from pathogenic bacteria such as *Salmonella enterica*, *M. tuberculosis*, *L. monocytogenes*, and *Francisella tularensis* [38,81–84]. Because menaquinone biosynthesis pathways are absent in humans, they represent an appealing target for efforts to design new antibacterial drugs [6]. Such works have already resulted in the discovery of new enzymes that catalyze the synthesis of MK derivatives, including two class C radical *S*-adenosylmethionine methyltransferases in Coriobacteriia that performs specific methylations of 8-methylmenaquinone and dimethylmenaquinone [85]. Members of this class are present in the gastrointestinal tract and can be pathogenic, but the precise functions of these novel quinones are not known and require further investigation. Interestingly, in the anaerobic γ-proteobacterium *Syntrophus aciditrophicus*, 8-methylmenaquinone (8-MMK-7) has been proposed to participate in fatty acid β-oxidation coupled to CO_2 reduction during syntrophic methane formation from fatty acids [86]. In addition, the MenJ oxidoreductase, a novel enzyme belonging to the geranylgeranyl reductase enzyme family, was found to reduce a single C = C double bond of the second prenyl group in the isoprenyl side-chain of the mycobacterial menaquinone MK-9 [87]. However, the physiological function of this partial saturation of the MK-9 isoprenoid side chain is not understood. Recent structural analyses of *E. coli* cytochrome *bd* oxidases have revealed a new structural stabilizing role for ubiquinone-8, and, in *B. subtilis*, the characterization of a new type of formate dehydrogenase utilizing MK-7 has expanded our knowledge of quinone roles [88,89]. Generally speaking, recent advances have highlighted the importance of quinones in bacterial life and ecology, which raises the question of their evolutionary history. The presence of quinone-like molecules in stellar dust supports the hypothesis that these compounds were essential in the earliest chemical reactions on Earth [90]. Their redox and chemical properties could have enabled simple life forms to carry out energy me-

tabolisms, facilitating the colonization of diverse environments. For instance, quinone profiling (abundance and distribution patterns) in marine water and sediments is a useful way to investigate and understand biogeochemical element cycling and energy flow processes such as respiration, photosynthesis, nitrification, and methanotrophy in these ecosystems [91]. Similarly, quinones may have assisted bacteria in adapting to the anaerobic reductive environment of the human gut. The ecophysiological functions of the numerous quinones present in the gut microbiota require much additional investigation. For example, there is now evidence that several bacteria in the human microbiota, such as enterococci, *Faecalibacterium prausnitzii*, and *K. pneumoniae*, are also capable of performing EET [92]. Future inquiries into quinone biosynthesis and functions thus constitute a promising and exciting field of microbial research.

Declaration of competing interest

The authors declare no conflict of interest for this work.

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