

Review

Quinoid Redox Mediators and Their Involvement in Environmental Pollution Treatment

Haikun Zhang ^{1,2,*} , Manman Cheng ³, Yan Li ^{1,3,*} and Wenhao Chen ^{1,*}

¹ Solid-State Fermentation Resource Utilization Key Laboratory of Sichuan Province, Yibin University, Yibin 644000, China

² Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai 264000, China

³ College of Life Sciences, Yantai University, Yantai 264000, China; bcfybcc@gmail.com

* Correspondence: hkzhang@yic.ac.cn (H.Z.); liyan0709@hotmail.com (Y.L.); wenhao_chen1985@126.com (W.C.)

Abstract: In recent years, quinoid redox mediators (QRMs) have attracted increasing attention because of their key role in wastewater biotreatment. Previous studies have shown that the anaerobic respiration of many bacteria could be coupled to the reduction and reoxidation of quinone groups. Thus, QRMs are widely involved in the microbial transformation of various organic and inorganic substances. To date, few reviews have focused on the involvement of quinoid compounds in environmental pollution biotreatment processes. In this paper, we review the different types of QRMs that interact closely with microorganisms, the characteristics of those QRMs, the involvement of QRMs during the biotransformation of recalcitrant organic pollutants, heavy metal ions and metallic oxides, and their enhancement on microbial fuel cells. Finally, the future research focus and application prospects with regard to different types of QRMs are proposed. This study can improve our understanding of QRM-mediated environmental pollution biotreatment processes and provide fundamental guidance on what kinds of QRMs are practical for engineering applications.

Keywords: quinoid compounds; wastewater; organic pollutants; metals; microbial fuel cell



Citation: Zhang, H.; Cheng, M.; Li, Y.; Chen, W. Quinoid Redox Mediators and Their Involvement in Environmental Pollution Treatment. *Water* **2023**, *15*, 3981. <https://doi.org/10.3390/w15223981>

Academic Editor: Xinbai Jiang

Received: 17 October 2023

Revised: 7 November 2023

Accepted: 14 November 2023

Published: 16 November 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Quinone compounds are a class of substances that contain cyclic unsaturated diketones, especially carbocyclic compounds and their derivatives with quinone groups. These compounds contain either q-quinone or o-quinone groups and can be divided into benzoquinone, naphthoquinone, anthraquinone, and phenanthraquinone according to their structural characteristics (Figure 1). More broadly, quinoid compounds also include a variety of non-carbocyclic quinone-like substances, such as riboflavin, flavin mononucleotide, flavin adenine dinucleotide, and humic substances. They can be found in the pigments of plants (mainly Polygonaceae, Rubiaceae, Rheaceae, Liliaceae, and Leguminaceae), a few animals (Cochineal), and bacteria, as well as in the metabolites of some lower plant lichens and fungi. When these animals, plants, and bacteria die, the biological debris is subsequently decomposed and mineralized by microbes. During this process, numerous nonbiodegradable quinone compounds remain, leading to their wide distribution in natural environments (including almost all soils, waters and sediments). In fact, these quinoid compounds are not only widely found in nature but are also widely involved in environmental processes.

Since the 20th century (1970s), the environmental importance of these quinoid compounds has received increasing attention. In 1967, Roxon et al. [1] reported that riboflavin, a quinone-like compound, can accelerate the transformation of some organic contaminants. Subsequently, an increasing number of researchers began to focus on the application of quinone compounds (e.g., anthraquinone-2,6-disulfonate, anthraquinone-2-sulfonate, humus, carbon materials, etc.) for the transformation of environmental contaminants [2]. A

mechanistic study found that the quinone group can be reversibly oxidized and reduced between quinone and hydroquinone due to its electron affinity, which enables it to serve as an electron shuttle in multiple redox reactions. In addition, the presence of quinoid compounds can accelerate reactions by lowering the activation energy of the total reaction and may even be a prerequisite for the reaction to take place under some situations. To date, many kinds of quinoid compounds have been proven to be capable of facilitating electron transfer in redox reactions between diverse inorganic or organic compounds, including organic matter, metals, and minerals [1,2].

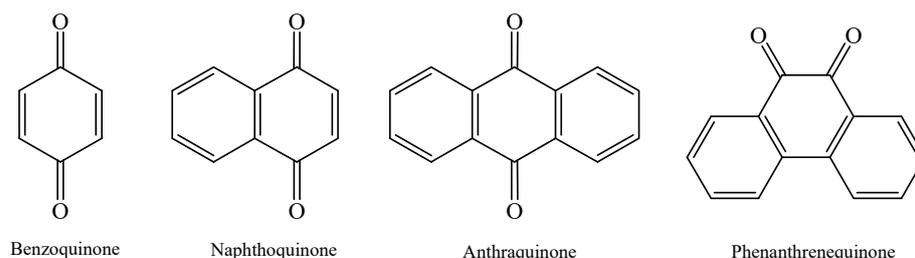


Figure 1. Structures of benzoquinone, naphthoquinone, anthraquinone, and phenanthrenequinone.

Over the past twenty years, quinoid compounds have attracted more attention than before because of their significant interactions with microbes, which may further increase their environmental importance. Since the 1990s, extensive studies have been conducted in this field [2–6]. Researchers have found that the reduction and reoxidation of quinone groups can be coupled to the anaerobic respiration of electrochemically active bacteria in the presence of various electron donors, such as saccharides, short-chain fatty acids, alcohol, H_2 , and even some organic pollutants. During this process, quinone is first reduced to hydroquinone; subsequently, hydroquinone can either directly reduce various electron acceptors, such as azo compounds [7,8], nitroaromatics [9], polyhalogenated pollutants [10,11], Fe(III) [12], Cr(VI) [13], Se(IV), and Te(IV) [14], or serve as electron donors to support the bioreduction of NO_3^-/NO_2^- [15], As(V) [16], and perchlorate [17] with their reoxidation. Overall, the presence of quinoid compounds considerably enhances the electron transfer in many anaerobic biotransformation processes.

To date, few reviews have focused on the involvement of quinoid compounds in biotransformation processes. For this purpose, we summarized the different types of QRMs and their characteristics. In addition, the involvement of different QRMs during organic pollutant reduction, metal reduction, and the electrical conductivity of electrodes were discussed. Finally, we identified future research focuses and application prospects with regard to different types of QRMs. In the present paper, those quinone compounds and quinone-like substances, along with composites based on them, are collectively referred to as quinoid redox mediators (QRMs).

2. Quinone-Based Redox Mediators

Structurally, all compounds containing quinone groups have the potential to act as redox mediators to accelerate electron transfer. However, things do not work this way in real reactions. In addition to the functional groups, the redox potential (E'_0) of effective QRMs must also be between those of the terminal electron acceptor and electron donor to reduce the activation energy of reactions. In general, E'_0 is an indication of the catalytic capacity of QRMs and should be in the range of -440 mV to -50 mV [18,19]. Vitamin B12 (-530 mV) was reported to be a very poor redox mediator due to its low E'_0 [20]. In this study, taking the source and availability into consideration, we classified the common QRMs into four primary categories, including natural substances, artificially synthesized quinone compounds, microbiologically excreted small molecules, and immobilized QRMs.

2.1. Natural Substances

Humic substances, which widely exist in various environments, can be defined as some of the most important natural quinone mediators. Humic substances primarily originate from the degradation of plants and mainly include three types: humic acid, fulvic acid, and humin. In 1996, Lovley et al. [3] first reported that humic substances can participate in some microbial respiration processes. Subsequently, an increasing number of studies have confirmed that humic substances are important redox mediators in nature, especially for some microbe-driven redox reactions (for instance, dissimilatory metal reduction bacteria, sulfate reducing bacteria, and methanogens) [5,21,22]. Humic substances have complex structures; however, quinone groups are considered to be the most important functional groups that are directly involved in electron transport since they can flexibly interconvert between hydroquinone and semiquinone via a reversible electron transfer reaction [23]. It has been reported that some non-quinone groups in humic substances are also able to transfer electrons, but the capacity of some specific non-quinone groups is much lower than that of quinone groups [23,24]. Accordingly, considering their ubiquity in the environment and efficient conductive capacity, humic substances may play a significant role in the biogeochemical cycles of matter and elements on a global scale.

2.2. Artificially Synthesized Quinone Compounds

In addition to natural quinone mediators, there are also many artificially synthesized quinones, including 9,10-anthraquinone-2-carboxylic acid, anthraquinone-2,6-disulfonate (AQDS), anthraquinone-2-sulfonate (AQS), etc. Therein, AQDS and AQS are the most studied artificially synthesized quinone compounds. Both AQDS and AQS can be prepared via a chemical synthesis method: reacting anthraquinone (a natural raw material) first with sulfuric acid in the presence of mercury and then with sodium hydroxide (Reaction diagram 1). They were reported to play similar roles; however, their catalytic performance and mechanism during the electron transfer process vary greatly depending on their molecular structures and polarities, as well as the presence of different microorganisms and pollutants [7,18,25]. AQS is suggested to be a more powerful mediator than AQDS. This is because the redox potential of AQS is lower than that of AQDS. Moreover, the additional sulfonate group of AQDS diminishes the ease with which the compound approaches the functional enzyme. In addition, the roles of these artificially synthesized quinones change as reaction conditions change. For example, Zhou et al. [26] demonstrated that AQDS could first act as an electron acceptor during the anammox denitrification process in the presence of iron-reducing bacteria; then, the reduced AQDS can chemically react with Fe(III) (Figure 2a). In addition, for microbes, AQDS can simultaneously be used as an electron donor and an electron acceptor (Figure 2b). Wang et al. [27] reported that AQDS can enhance the coupled biotransformation of phenol and nitrate: AQDS is first reduced to AQH₂DS (electron acceptor) by *Shewanella* sp. XB in the presence of phenol, and then AQH₂DS (electron donor) provides electrons to strain XB for its further bioreduction of nitrate. On the whole, artificially synthesized quinone compounds are more targeted and efficient than humic substances.

2.3. Microbial Secretions That Function as QRMs

In addition to natural quinone mediators and artificially synthesized quinone compounds, the soluble small molecules, such as riboflavin (RF), flavin mononucleotide (FMN), flavin adenine dinucleotide, menadione, and phenazines, excreted by various bacteria (*Shewanella*, *Klebsiella*, *Pseudomonas*, *Enterococcus*, *Methylosinus*, *Bacillus*, etc.) can also function as QRMs [28–32]. These small molecules can be used not only extracellularly as electron shuttles in the biotransformation of solid metal oxides and electrodes but also intracellularly as coenzyme factors of some flavin proteins to participate in the anaerobic biotransformation of organic pollutants and heavy metals [21,29]. Taking the most studied bacteria, *Shewanella* sp., as examples, they were reported to have the ability to secrete RF and FMN, which can help bacterial cells transport electrons for reducing iron oxides,

such as hematite, goethite, ferrihydrite, and lepidocrocite [30,32]. Similarly, Tian et al. reported that the RF and FMN secreted by two Gram-positive bacteria, *Bacillus cereus* strain DIF1 and *Rhodococcus ruber* strain DIF2, can improve the electron transfer of microbial fuel cells [33]. In addition, researchers also found that FMN/FMNH₂ acts as a redox pair that may have multiple roles in the azo or chromium reductase-catalyzed reduction of azo dyes, Cr(VI), and nitroaromatic compounds. During this process, the FMN cofactor is first completely reduced to FMNH₂, and second, these electrons are transferred from FMNH₂ to the electron acceptor, resulting in the formation of the corresponding azo or chromium reductase FMNH₂ [34–40]. The results of these studies also demonstrated that FMN/FMNH₂ may play a similar role for the pairs of AQDS/AQH₂DS in the process of electron transfer (Figure 3).

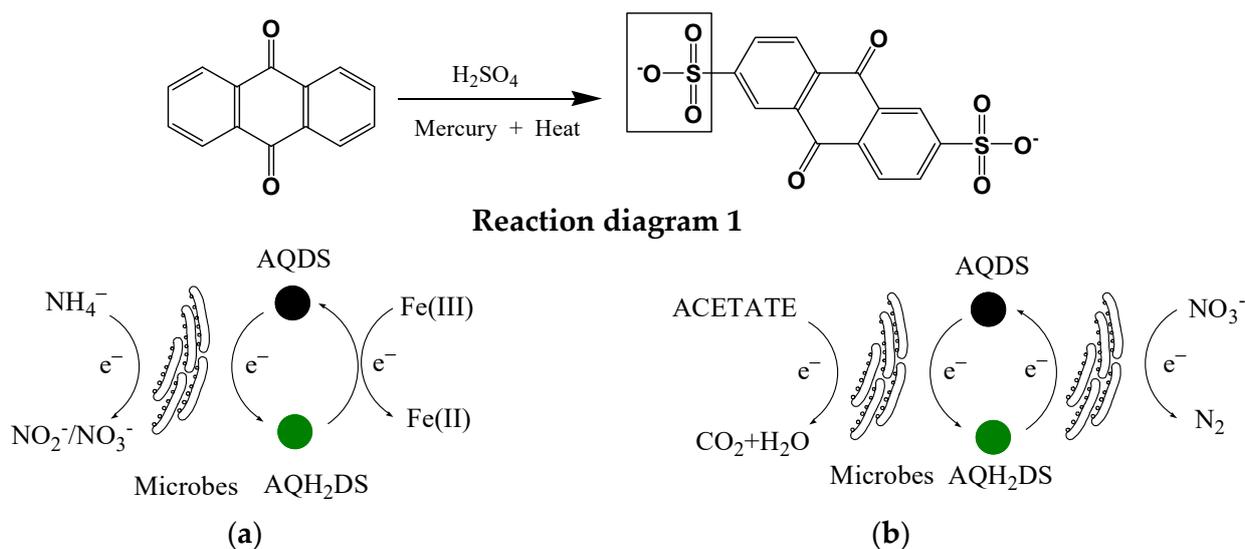


Figure 2. The role of AQDS in different reactions. (a) Anammox reaction; (b) denitrification reaction.

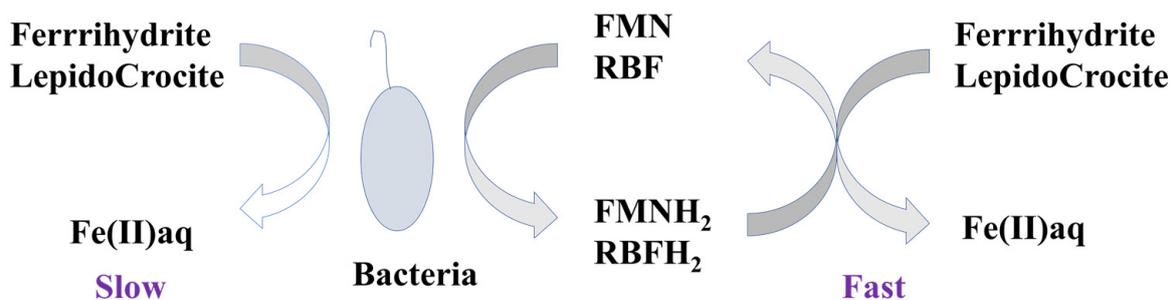


Figure 3. The role of FMN/RF during the bioreduction of iron(III) oxides [30].

2.4. Immobilized QRMs

Immobilized QRMs are designed for the practical application of known QRMs. Previous studies have demonstrated that quinone compounds can enhance the bioreduction of various contaminants [7,41–43]. In practical applications, however, these soluble quinone compounds, such as AQS and AQDS, need to be continuously added into reaction systems to increase the removal rates of contaminants, which results in an increase in running costs and secondary contamination. The immobilization of QRMs via physical or chemical methods not only maintains the catalytic performance of quinone groups but also realizes their effective recovery and reuse. This strategy is beneficial for their practical application. To date, many carriers, including activated carbon felt, anion exchange resins, and calcium alginate, have been developed for the immobilization of quinone compounds [44–46]. Our previous studies confirmed that soluble quinone compounds can be covalently immobi-

lized on the surface of polyurethane foam, graphene oxide and Fe_3O_4 , which can be used to enhance the bioreduction of azo dyes, nitrobenzene, and chloronitrobenzenes [47–50]. These immobilized QRMs can have better catalytic performance than soluble QRMs during some biocatalytic reactions, further indicating that immobilized QRMs have potential application prospects, especially in the field of water pollution treatment. When QRMs are immobilized, they act as solid redox mediators to facilitate electron transfer by extending the direct electron transfer distance or as equivalents of functional enzymes (e.g., MtrC) as substrates for enzymatic reactions [48,50].

3. Involvement of QRMs in Environmental Pollution Treatment

3.1. Biotransformation of Recalcitrant Organic Pollutants

The extensive use of petrochemical compounds results in their ubiquitous distribution in the environment, which may have the potential to elicit a variety of adverse cytotoxic, mutagenic, and carcinogenic responses [51–53]. Thus, the proper treatment of the related industrial effluents should be conducted before their release into the natural environment. Therein, various benzene-ring-containing organic pollutants are difficult to deal with using conventional treatment methods due to their electron-withdrawing effects and are thus defined as recalcitrant organic pollutants. Recently, it was proven that QRMs could enhance the biodegradation of diverse recalcitrant organic pollutants [7,41–43]. The standard potentials of QRMs are considerably lower than those of most recalcitrant organic pollutants, and thus, the electron transfer from the reduced QRMs to pollutants is thermodynamically feasible.

As reported, the transformation rate of diverse recalcitrant organic pollutants, mainly azo dyes, halogenated aromatics, and nitroaromatics, can be increased by several times to dozens of times in the presence of different QRMs. During this process, related pollutants undergo the first and most difficult transformation, and the secondary products are further degraded until completely mineralized. For example, Rau et al. [7] reported that the addition of QRMs to anaerobically incubated cultures of various taxonomically different bacterial species resulted in significantly increased reduction rates for azo dyes. Among the tested QRMs, AQS and lawsone caused the highest increase in reductase activities (~50-fold for *Sphingomonas xenophaga* BN6 and ~150-fold for *Escherichia coli* K12, respectively). The authors performed a mediated bioreduction of 2,5-dichloronitrobenzene to 2,5-dichloroaniline using immobilized QRMs, and the k (h^{-1}) value of the QRM-supplemented system was 7.7-fold greater than that of the control system. Cui et al. [54] reported that AQS, lawsone, and menadione can significantly enhance the performance of azo dye decolorization by anaerobic sludge: without quinones, a specific decolorization rate of methyl orange was $0.64 \pm 0.02 \text{ mg} \cdot \text{g sludge}^{-1} \cdot \text{h}^{-1}$; in the presence of 0.1 mmol L^{-1} AQS, lawsone, and menadione, the average decolorization rates of methyl orange were 1.09 ± 0.03 , 2.64 ± 0.03 , and $2.82 \pm 0.10 \text{ mg} \cdot \text{g sludge}^{-1} \cdot \text{h}^{-1}$, respectively. Unlike the findings of Rau et al. [7], menadione had the best catalytic effect in Cui et al.'s experiment [54], indicating that the catalytic effects of quinone mediators are different under different experimental conditions. In addition to E'_0 , pH and temperature are the most important factors affecting the catalytic efficiencies of QRMs [5]. In a certain range, reaction rates are enhanced with increasing pH and temperature. In terms of the mechanism, it was suggested that QRMs act in this system as mediators that are enzymatically reduced by the bacterial cells to the corresponding reduced state, which subsequently reduce the recalcitrant organic pollutants in a purely chemical redox reaction (Figure 4). In addition, our recent study further reported that multiple electron transfer pathways were involved in the bioreduction of QRMs, and outer membrane proteins should be related to the catalytic performance of QRMs [55].

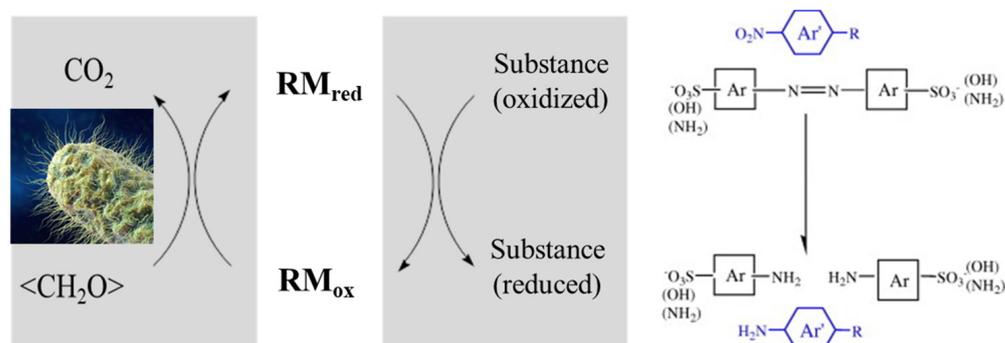


Figure 4. The proposed biotransformation process of QRM-mediated azo dyes and nitroaromatics. RMred, reduced redox mediator; RMox, oxidized redox mediator [49].

3.2. Biotransformation of Heavy Metal Ions and Metallic Oxides

Unlike organic pollutants, which can be completely mineralized by microbes, heavy metals can only be transformed between different valence states and forms. To date, QRMs have also been found to be able to catalyze the bioreduction of water-soluble heavy metal ions Cr(VI), Se(IV), Te(IV), U(VI), and Tc(VII) to water-insoluble Cr(III), Se(0), Te(0), U(IV), and Tc(IV), respectively [14,50,56–58]. For example, Wang et al. [14] studied the influence of quinoid redox mediators on the microbial reduction of Se(VI) and Te(IV), and their results showed that lawsone, menadione, AQS, and AQDS could all accelerate the reduction of Se(VI) and Te(IV) by *Escherichia coli*, and lawsone had the best acceleration effect. Similarly, the biological reduction rates of Se(VI) and Te(IV) were increased 10–15 times, and the extracellular formation and accumulation of Se(0)/Te(0) were also increased. We previously isolated a novel Cr(VI)-reducing bacterium, *Acinetobacter* sp. HK-1, which can reduce Cr(VI) to Cr(III) at a rate of $3.82 \text{ mg}\cdot\text{h}^{-1}\cdot\text{g cell}^{-1}$. After adding 2-amino-3-chloro-1,4-naphthoquinone/graphene oxide composites ($50 \text{ mg}\cdot\text{L}^{-1}$) into the reaction system, the Cr(VI) removal rate could reach $190 \text{ mg}\cdot\text{h}^{-1}\cdot\text{g cell}^{-1}$, which was ~50-fold higher than that of the control system [50]. Fredrickson et al. [56] reported that when 0.1 mM AQDS or $2 \text{ g}\cdot\text{L}^{-1}$ leonardite humic acid was added during the biological reduction of U(VI)/Tc(VII) to U(IV)/Tc(IV) by *Deinococcus radiodurans* R1, the bioreduction efficiencies of 0.2 mM U(VI) and Tc(VII) were 89% and 82%, respectively, while they were zero in the absence of these QRMs. These studies have proven that QRMs can greatly affect the bioreduction process of various heavy metal ions. In fact, this process is not only essential for the rapid purification of the water environment but also helps microorganisms reduce the toxic pressure of those heavy metal ions since excessive exposure to them is lethal for microorganisms.

In addition, QRMs can be involved in the biological corrosion of metal oxides, especially Fe(III)-containing oxides. Previous studies have reported that various QRMs can transfer electrons to solid-phase Fe(III). For example, Lovley et al. reported that the growth of *Geobacter metallireducens* with Fe(III) oxides was greatly stimulated by the addition of as little as 100 μM humic acid and AQDS [3,4]. O’Loughlin [43] found that quinones and humus promoted the reduction of γ -FeOOH by *Shewanella putrefaciens* CN32. Wolf et al. [12] reported that low concentrations (as low as $1 \text{ mg}\cdot\text{L}^{-1}$) of humus and quinones could still promote the biological reduction of iron (hydrogen) oxides. The presence of exogenous QRMs could facilitate electron transfer from bacterial cell surfaces to insoluble Fe(III)-containing oxides, resulting in significant enhancement in microbial Fe(III) reduction under anoxic conditions. First, QRMs function as electron shuttles and expand the distance over which the reaction between microbes and minerals can take place. On the other hand, QRMs can greatly improve the bioavailability of solid oxides. The electron shuttling between microbes and Fe(III) oxides via QRMs not only accelerates the bioreduction of poorly crystalline Fe(III) oxides but also facilitates the reduction of Fe(III) forms that are not typically reduced by microbes in the absence of QRMs. For instance, He and Sanford (2003) [59] reported that the addition of 0.13 mM AQDS into the reaction system can greatly increase the bioreduction rate of iron oxides by *Anaeromyxobacter dehalogenans*. In summary,

the involvement of QRM can greatly accelerate the biotransformation rate of heavy metal ions and Fe(III)-containing oxides.

3.3. Enhancement of Microbial Fuel Cells

As a previous study reported, many electrochemically active bacteria can oxidize organic matter and transfer the released electrons to anodes to generate current in a microbial fuel cell (MFC) [21]. To date, MFCs have been explored for promising environmental applications in the treatment of a variety of pollutants, including organic pollutants, heavy metals, and inorganic salts [21]. However, the large-scale practical application of MFCs as an alternative technology for environmental pollution disposal is currently subject to the challenge of improving the output and economic efficiencies [60]. There are many possible electron transfer pathways from the microbes to the electrode, the most important of which are those based on cytochrome and reductase (Figure 5). Accordingly, it has been reported that many QRMs can greatly increase the power output of MFCs due to their intimate relationships with cytochromes and reductases, which could lower the operation cost. For example, Marsili et al. [61] reported that RF (secreted by *Shewanella oneidensis* MR-1) acts as an electron shuttle and can enhance the electron transfer rate from cells to the electrode by ~3.3-fold. Additionally, many artificially synthesized QRMs also have the potential to be used in MFCs. Wu et al. (2014) [62] investigated the effects of a variety of exogenous QRMs, including AQS, AQDS, 2-hydroxy-1,4-naphthoquinone (HNQ), 10-anthraquinone-2-carboxylic acid (AQC), and resazurin sodium salt (RZ), on the electrical performance of *Shewanella putrefaciens* 200. The results suggested that the average constant current with and without QRMs followed the order AQS-supplemented system > AQC-supplemented system > AQDS-supplemented system > HNQ-supplemented system > RZ-supplemented system > control system, where the highest value in the AQS-supplemented system was 2.9-fold higher than that of the control system, and even the lowest value (with RZ) was 1.7-fold higher than that of the control system. Collectively, these promising modifications using QRMs increase the possibility of large potential applications of MFCs in environmental pollution control.

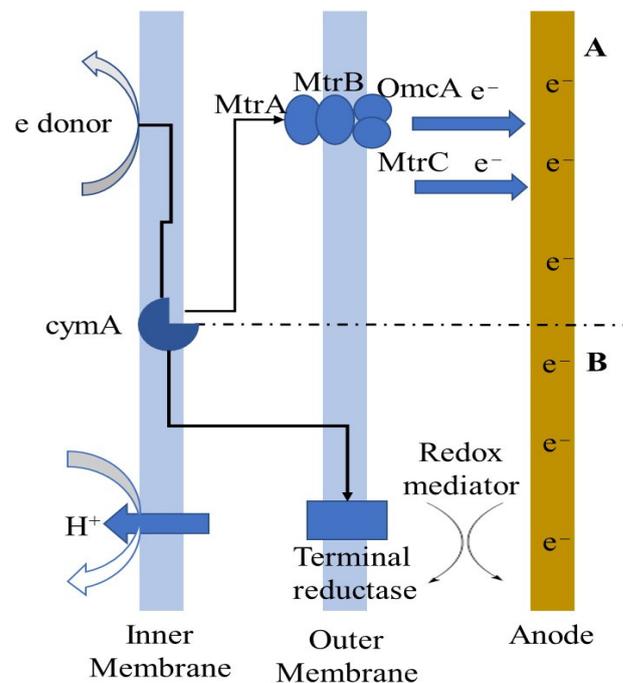


Figure 5. The proposed electron transfer pathways from microbes to the electrode [21]. (A) Mtr pathway; (B) terminal reductase.

3.4. Activity Description of QRMs and Their Disposal after Use

As mentioned above, the presence of QRMs can increase electron transfer efficiency, thus improving the biotransformation efficiency of organic pollutants, heavy metal ions, and metal oxides, and the electricity generation efficiency of MFC. So, what are the indicators that can characterize the changes brought by QRMs to the related systems? According to our own experimental experience and literature research, the following indexes are summarized: (1) redox potential (ORP), QRMs in the reduction state reduce the ORP value of the reaction system; (2) cyclic voltammetry (CV) curve, a pair of obvious redox peaks can be found on the CV curve regarding to the reaction system containing QRMs; (3) electron transport system activity (ETSA), the presence of QRMs improves the ETSA of the system containing QRM, and the ETSA determination can follow the method proposed by He et al. [63]. In addition, a pseudo first-order model (I) was recommended to describe the kinetic of QRM-involved redox reaction. The pseudo first-order rate constant k (h^{-1}) was determined using the following equation:

$$\ln C_i / C_t = kt \quad (\text{I})$$

where C_i (mg/L) and C_t (mg/L) are the initial and residual substrates at time zero and t , respectively, and t (h) is the reaction time. The catalytic effects of QRMs can be demonstrated by calculating the ratio of k value between the system containing QRMs and the control system.

At present, various QRMs have shown good catalytic effects and application prospects in laboratory-level research. However, it is worth noting that a large proportion of QRMs are water-soluble [54], which poses an obstacle to their application in wastewater treatment due to secondary pollution as they are released to the environment. Although very low concentrations of QRMs can improve the transformation efficiency of pollutants by an order of magnitude, we need to find a better way to apply QRMs without affecting the environment. Immobilized QRMs have the most practical application value in the future. For example, we could make these immobilized QRMs into replaceable filter elements to facilitate inspection and replacement. In addition, some filters can also be considered for practical use, and the worn immobilized QRMs can be captured and collected to avoid their release into the environment. Above all, there is still much work to be conducted on the disposal of used QRMs, including but not limited to the development of new immobilized QRMs, post-processing devices, and instruments.

4. Conclusions and Perspectives

In conclusion, the presence of QRMs, including natural substances, artificially synthesized quinone compounds, microbial secretions, and immobilized QRMs, can greatly facilitate the biotransformation of organic pollutants, heavy metals, and metallic oxides, as well as enhance the performance of MFCs. From the perspective of engineering applications, however, the existing research is not comprehensive, and there are still many studies worth carrying out in the future.

- (i) More practical immobilized QRMs should be developed. Over the past few decades, diverse QRMs have been found to be capable of accelerating environmental remediation efficiency. For engineering applications, QRMs can be immobilized with many carriers. However, some immobilized mediators are not practical. Thus, we need to pay more attention to their practicality (including cost and ease of recycling and reuse).
- (ii) How to select the suitable QRM? In the actual reaction system, the catalytic effects of QRMs are highly affected by many reaction parameters, including redox potential, electron transfer capacity, diffusive rate, and even environmental factors (e.g., pH, temperature, and salinity). Therefore, we should carry out more studies to determine what kind of QRMs should be chosen for different reaction systems.

- (iii) What are the molecular mechanism of the QRMs-catalyzed biotransformation process? Although the electron transfer mechanism of electrochemically active bacteria, especially for the genera *Geobacter* and *Shewanella*, has been studied widely, the interaction between cells and QRMs, and the related molecular mechanism, remain to be further understood. Moreover, QRM-catalyzed long-distance electron transfer is still unclear at the molecular level. Thus, the molecular mechanisms of QRM-catalyzed biotransformation processes should be studied further.

In summary, further studies in this emerging field should focus on the development of efficient immobilized QRMs, the optimization of the application conditions, and the investigation of QRM-catalyzed reaction mechanisms.

Author Contributions: Conceptualization, H.Z.; writing—original draft preparation, H.Z.; writing—review and editing, Y.L., W.C. and H.Z.; visualization, M.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Natural Science Foundation of China (42077305), Youth Innovation Promotion Association CAS (2022212), CSC Scholarship (202104910148) and Solid-state Fermentation Resource Utilization Key Laboratory of Sichuan Province (No.2018GTY001).

Acknowledgments: The authors thank Hong Lv from Dalian university of Technology for her kind supervision.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Roxon, J.J.; Ryan, A.J.; Wright, S.E. Enzymatic reduction of tartrazine by *Proteus vulgaris* from rats. *Food Cosmet. Toxicol.* **1967**, *5*, 645–656. [[CrossRef](#)] [[PubMed](#)]
2. Husain, M.; Husain, Q. Applications of Redox Mediators in the Treatment of Organic Pollutants by Using Oxidoreductive Enzymes: A Review. *Crit. Rev. Environ. Sci. Technol.* **2008**, *38*, 1–42. [[CrossRef](#)]
3. Lovley, D.R.; Bluntharris, E.L.; Ejj, P.; Woodward, J.C.; Coates, J.D. Humic substances as electron acceptors for microbial respiration. *Nature* **1996**, *382*, 445–448. [[CrossRef](#)]
4. Lovley, D.R.; Fraga, J.L.; Coates, J.D.; Blunt-Harris, E.L. Humics as an electron donor for anaerobic respiration. *Environ. Microbiol.* **1999**, *1*, 89–98. [[CrossRef](#)]
5. Van der Zee, F.P.; Cervantes, F.J. Impact and application of electron shuttles on the redox (bio)transformation of contaminants: A review. *Biotechnol. Adv.* **2009**, *27*, 256–277. [[CrossRef](#)]
6. Zhang, Y.; Zhang, Z.; Liu, W.; Chen, Y. New applications of quinone redox mediators: Modifying nature-derived materials for anaerobic biotransformation process. *Sci. Total Environ.* **2020**, *744*, 140652. [[CrossRef](#)]
7. Rau, J.; Knackmuss, H.J.; Stolz, A. Effects of different quinoid redox mediators on the anaerobic reduction of azo dyes by bacteria. *Environ. Sci. Technol.* **2002**, *36*, 1497–1504. [[CrossRef](#)]
8. van der Zee, F.P.; Bouwman, R.H.; Strik, D.P.; Lettinga, G.; Field, J.A. Application of redox mediators to accelerate the transformation of reactive azo dyes in anaerobic bioreactors. *Biotechnol. Bioeng.* **2001**, *75*, 691–701. [[CrossRef](#)] [[PubMed](#)]
9. Li, L.; Wang, J.; Zhou, J.; Yang, F.; Jin, C.; Qu, Y.; Li, A.; Zhang, L. Enhancement of nitroaromatic compounds anaerobic biotransformation using a novel immobilized redox mediator prepared by electropolymerization. *Bioresour. Technol.* **2008**, *99*, 6908–6916. [[CrossRef](#)] [[PubMed](#)]
10. Fu, Q.S.; Barkovskii, A.L.; Adriaens, P. Reductive transformation of dioxins: An assessment of the contribution of dissolved organic matter to dechlorination reactions. *Environ. Sci. Technol.* **1999**, *33*, 3837–3842. [[CrossRef](#)]
11. Perlinger, J.A.; Angst, W.; Schwarzenbach, R.P. Kinetics of the reduction of hexachloroethane by juglone in solutions containing hydrogen sulfide. *Environ. Sci. Technol.* **1996**, *30*, 3408–3417. [[CrossRef](#)]
12. Wolf, M.; Kappler, A.; Jiang, J.; Meckenstock, R.U. Effects of humic substances and quinones at low concentrations on ferrihydrite reduction by *Geobacter metallireducens*. *Environ. Sci. Technol.* **2009**, *43*, 5679–5685. [[CrossRef](#)]
13. Liu, G.; Yang, H.; Wang, J.; Jin, R.; Zhou, J.; Lv, H. Enhanced chromate reduction by resting *Escherichia coli* cells in the presence of quinone redox mediators. *Bioresour. Technol.* **2010**, *101*, 8127–8131. [[CrossRef](#)]
14. Wang, X.; Liu, G.; Zhou, J.; Wang, J.; Jin, R.; Lv, H. Quinone-mediated reduction of selenite and tellurite by *Escherichia coli*. *Bioresour. Technol.* **2011**, *102*, 3268–3271. [[CrossRef](#)]
15. Aranda-Tamara, C.; Estrada-Alvarado, M.I.; Texier, A.C.; Cuervo, F.; Gómez, J.; Cervantes, F.J. Effects of different quinoid redox mediators on the removal of sulphide and nitrate via denitrification. *Chemosphere* **2007**, *69*, 1722–1727. [[CrossRef](#)]
16. Field, J.A.; Sierra-Alvarez, R.; Cortinas, I.; Feijoo, G.; Moreira, M.T.; Kopplin, M.; Gandolfi, A.J. Facile reduction of arsenate in methanogenic sludge. *Biodegradation* **2004**, *15*, 185–196. [[CrossRef](#)]

17. Thrash, J.C.; Van Trump, J.I.; Weber, K.A.; Miller, E.; Achenbach, L.A.; Coates, J.D. Electrochemical stimulation of microbial perchlorate reduction. *Environ. Sci. Technol.* **2007**, *41*, 1740–1746. [[CrossRef](#)] [[PubMed](#)]
18. Brown, J.P. Reduction of polymeric azo and nitro dyes by intestinal bacteria. *Appl. Environ. Microbiol.* **1981**, *41*, 1283–1286. [[CrossRef](#)] [[PubMed](#)]
19. Rau, J.; Stolz, A. Oxygen-insensitive nitroreductases NfsA and NfsB of *Escherichia coli* function under anaerobic conditions as lawsone-dependent azo reductases. *Appl. Environ. Microbiol.* **2003**, *69*, 3448–3455. [[CrossRef](#)] [[PubMed](#)]
20. Santos, A.B.D.; Bisschops, I.A.; Cervantes, F.J.; van Lier, J.B. Effect of different redox mediators during thermophilic azo dye reduction by anaerobic granular sludge and comparative study between mesophilic (30 °C) and thermophilic (55 °C) treatments for decolourisation of textile wastewaters. *Chemosphere* **2004**, *55*, 1149–1157. [[CrossRef](#)] [[PubMed](#)]
21. Liu, X.; Shi, L.; Gu, J.-D. Microbial electrocatalysis: Redox mediators responsible for extracellular electron transfer. *Biotechnol. Adv.* **2018**, *36*, 1815–1827. [[CrossRef](#)]
22. Smith, J.A.; Nevin, K.P.; Lovley, D.R. Syntrophic growth via quinone-mediated interspecies electron transfer. *Front. Microbiol.* **2015**, *6*, 121. [[CrossRef](#)]
23. Ratasuk, N.; Nanny, M.A. Characterization and quantification of reversible redox sites in humic substances. *Environ. Sci. Technol.* **2007**, *41*, 7844–7850. [[CrossRef](#)] [[PubMed](#)]
24. Kaden, J.; Galushko, A.S.; Schink, B. Cysteine-mediated electron transfer in syntrophic acetate oxidation by cocultures of *Geobacter sulfurreducens* and *Wolinella succinogenes*. *Arch. Microbiol.* **2002**, *178*, 53–58. [[CrossRef](#)] [[PubMed](#)]
25. Hong, Y.G.; Guo, J.; Xu, Z.-C.; Xu, M.-Y.; Sun, G.-P. Humic substances act as electron acceptor and redox mediator for microbial dissimilatory azoreduction by *Shewanella decolorationis* S12. *J. Microbiol. Biotechnol.* **2007**, *17*, 428–437. [[PubMed](#)]
26. Zhou, G.W.; Yang, X.-R.; Li, H.; Marshall, C.W.; Zheng, B.-X.; Yan, Y.; Su, J.-Q.; Zhu, Y.G. Electron shuttles enhance anaerobic ammonium oxidation coupled to iron(III) reduction. *Environ. Sci. Technol.* **2016**, *50*, 9298–9307. [[CrossRef](#)]
27. Wang, J.; Zhou, Y.; Li, P.; Lu, H.; Jin, R.; Liu, G. Effects of redox mediators on anaerobic degradation of phenol by *Shewanella* sp. XB. *Appl. Biochem. Biotechnol.* **2015**, *175*, 3162–3172. [[CrossRef](#)] [[PubMed](#)]
28. Bosire, E.M.; Rosenbaum, M.A. Electrochemical potential influences phenazine production, electron transfer and consequently electric current generation by *Pseudomonas aeruginosa*. *Front. Microbiol.* **2017**, *8*, 892. [[CrossRef](#)] [[PubMed](#)]
29. Light, S.H.; Su, L.; Rivera-Lugo, R.; Cornejo, J.A.; Louie, A.; Iavarone, A.T.; Ajo-Franklin, C.M.; Portnoy, D.A. A flavin-based extracellular electron transfer mechanism in diverse Gram-positive bacteria. *Nature* **2018**, *562*, 140–144. [[CrossRef](#)]
30. Shi, Z.; Zachara, J.M.; Shi, L.; Wang, Z.; Moore, D.A.; Kennedy, D.W.; Fredrickson, J.K. Redox reactions of reduced flavin mononucleotide (FMN), riboflavin (RBF), and anthraquinone-2, 6-disulfonate (AQDS) with ferrihydrite and lepidocrocite. *Environ. Sci. Technol.* **2012**, *46*, 11644–11652. [[CrossRef](#)]
31. Wang, Y.; Newman, D.K. Redox reactions of phenazine antibiotics with ferric (hydr)oxides and molecular oxygen. *Environ. Sci. Technol.* **2008**, *42*, 2380–2386. [[CrossRef](#)]
32. Wang, Z.; Shi, Z.; Shi, L.; White, G.F.; Richardson, D.J.; Clarke, T.A.; Fredrickson, J.K.; Zachara, J.M. Effects of soluble flavin on heterogeneous electron transfer between surface-exposed bacterial cytochromes and iron oxides. *Geochim. Cosmochim. Acta* **2015**, *163*, 299–310. [[CrossRef](#)]
33. Tian, T.; Fan, X.; Feng, M.; Su, L.; Zhang, W.; Chi, H.; Fu, D. Flavine-mediated extracellular electron transfer in Gram-positive bacteria *Bacillus cereus* DIF1 and *Rhodococcus ruber* DIF2. *RSC Adv.* **2019**, *9*, 40903–40909. [[CrossRef](#)]
34. Ackerley, D.; Gonzalez, C.; Keyhan, M.; Blake, R.; Matin, A. Mechanism of chromate reduction by the *Escherichia coli* protein, NfsA, and the role of different chromate reductases in minimizing oxidative stress during chromate reduction. *Environ. Microbiol.* **2004**, *6*, 851–860. [[CrossRef](#)] [[PubMed](#)]
35. Liu, G.; Zhou, J.; Jin, R.; Zhou, M.; Wang, J.; Lu, H.; Qu, Y. Enhancing survival of *Escherichia coli* by expression of azoreductase AZR possessing quinone reductase activity. *Appl. Microbiol. Biotechnol.* **2008**, *80*, 409–416. [[CrossRef](#)] [[PubMed](#)]
36. Liu, G.; Zhou, J.; Lv, H.; Xiang, X.; Wang, J.; Zhou, M.; Qv, Y. Azoreductase from *Rhodobacter sphaeroides* AS1. 1737 is a flavodoxin that also functions as nitroreductase and flavin mononucleotide reductase. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 1271–1279. [[CrossRef](#)]
37. Morokutti, A.; Lyskowski, A.; Sollner, S.; Pointner, E.; Fitzpatrick, T.B.; Kratky, C.; Gruber, K.; Macheroux, P. Structure and function of YcnD from *Bacillus subtilis*, a flavin-containing oxidoreductase. *Biochemistry* **2005**, *44*, 13724–13733. [[CrossRef](#)]
38. Park, C.; Keyhan, M.; Wielinga, B.; Fendorf, S.; Matin, A. Purification to homogeneity and characterization of a novel *Pseudomonas putida* chromate reductase. *Appl. Environ. Microbiol.* **2000**, *66*, 1788–1795. [[CrossRef](#)]
39. Thatoi, H.; Das, S.; Mishra, J.; Rath, B.P.; Das, N. Bacterial chromate reductase, a potential enzyme for bioremediation of hexavalent chromium: A review. *J. Environ. Manag.* **2014**, *146*, 383–399. [[CrossRef](#)]
40. Vorontsov, I.I.; Minasov, G.; Brunzelle, J.S.; Shuvalova, L.; Kiryukhina, O.; Collart, F.R.; Anderson, W.F. Crystal structure of an apo form of *Shigella flexneri* ArsH protein with an NADPH-dependent FMN reductase activity. *Protein Sci.* **2007**, *16*, 2483–2490. [[CrossRef](#)]
41. Gu, B.; Yan, H.; Zhou, P.; Watson, D.B.; Park, M.; Istok, J. Natural humics impact uranium bioreduction and oxidation. *Environ. Sci. Technol.* **2005**, *39*, 5268–5275. [[CrossRef](#)]
42. Luan, F.; Burgos, W.D.; Xie, L.; Zhou, Q. Bioreduction of nitrobenzene; natural organic matter, and hematite by *Shewanella putrefaciens* CN32. *Environ. Sci. Technol.* **2010**, *44*, 184–190. [[CrossRef](#)]

43. O'Loughlin, E.J. Effects of electron transfer mediators on the bioreduction of lepidocrocite (γ -FeOOH) by *Shewanella putrefaciens* CN32. *Environ. Sci. Technol.* **2008**, *42*, 6876–6882. [[CrossRef](#)]
44. Alvarez, L.; Perez-Cruz, M.; Rangel-Mendez, J.; Cervantes, F. Immobilized redox mediator on metal-oxides nanoparticles and its catalytic effect in a reductive decolorization process. *J. Hazard. Mater.* **2010**, *184*, 268–272. [[CrossRef](#)] [[PubMed](#)]
45. Cervantes, F.J.; Garcia-Espinosa, A.; Moreno-Reynosa, M.A.; Rangel-Mendez, J.R. Immobilized redox mediators on anion exchange resins and their role on the reductive decolorization of azo dyes. *Environ. Sci. Technol.* **2010**, *44*, 1747–1753. [[CrossRef](#)] [[PubMed](#)]
46. Li, L.; Zhou, J.; Wang, J.; Yang, F.; Jin, C.; Zhang, G. Anaerobic biotransformation of azo dye using polypyrrole/anthraquinonedisulphonate modified active carbon felt as a novel immobilized redox mediator. *Sep. Purif. Technol.* **2009**, *66*, 375–382. [[CrossRef](#)]
47. Lu, H.; Zhang, H.; Wang, J.; Zhou, J.; Zhou, Y. A novel quinone/reduced graphene oxide composite as a solid-phase redox mediator for chemical and biological Acid Yellow 36 reduction. *RSC Adv.* **2014**, *4*, 47297–47303. [[CrossRef](#)]
48. Zhang, H.K.; Hu, X. Catalytic reduction of NACs by nano Fe₃O₄/quinone composites in the presence of a novel marine exoelectrogenic bacterium under hypersaline conditions. *RSC Adv.* **2017**, *7*, 11852–11861. [[CrossRef](#)]
49. Zhang, H.K.; Lu, H.; Zhang, S.; Liu, G.; Li, G.; Zhou, J.; Wang, J. A novel modification of poly (ethylene terephthalate) fiber using anthraquinone-2-sulfonate for accelerating azo dyes and nitroaromatics removal. *Sep. Purif. Technol.* **2014**, *132*, 323–329. [[CrossRef](#)]
50. Zhang, H.K.; Lu, H.; Wang, J.; Zhou, J.T.; Sui, M. Cr(VI) reduction and Cr(III) immobilization by *Acinetobacter* sp. HK-1 with the assistance of a novel quinone/graphene oxide composite. *Environ. Sci. Technol.* **2014**, *48*, 12876–12885. [[CrossRef](#)] [[PubMed](#)]
51. Ju, K.-S.; Parales, R.E. Nitroaromatic compounds, from synthesis to biodegradation. *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 250–272. [[CrossRef](#)]
52. Kovacic, P.; Somanathan, R. Nitroaromatic compounds: Environmental toxicity, carcinogenicity, mutagenicity, therapy and mechanism. *J. Appl. Toxicol.* **2014**, *34*, 810–824. [[CrossRef](#)] [[PubMed](#)]
53. Pandey, A.; Singh, P.; Iyengar, L. Bacterial decolorization and degradation of azo dyes. *Int. Biodeterior. Biodegrad.* **2007**, *59*, 73–84. [[CrossRef](#)]
54. Cui, D.; Zhang, M.; Wang, J.; Wang, H.; Zhao, M. Effect of quinoid redox mediators during azo dye decolorization by anaerobic sludge: Considering the catalyzing mechanism and the methane production. *Ecotoxicol. Environ. Saf.* **2020**, *202*, 110859. [[CrossRef](#)] [[PubMed](#)]
55. Zhang, H.; Han, K.; Hu, X. Enhanced bioreduction of 2, 5-dichlorobenzene by an AHQ/RGO binary nanocomposite through a synergistic effect with outer membrane proteins of *Shewanella oneidensis* MR-1. *Chem. Eng. J.* **2020**, *389*, 124464. [[CrossRef](#)]
56. Fredrickson, J.K.; Kostandarthes, H.M.; Li, S.; Plymale, A.E.; Daly, M. Reduction of Fe(III), Cr(VI), U(VI), and Tc(VII) by *Deinococcus radiodurans* R1, Applied and environmental microbiology. *Appl. Environ. Microbiol.* **2000**, *66*, 2006–2011. [[CrossRef](#)]
57. Hashim, M.A.; Mukhopadhyay, S.; Sahu, J.N.; Sengupta, B. Remediation technologies for heavy metal contaminated groundwater. *J. Environ. Manag.* **2011**, *92*, 2355–2388. [[CrossRef](#)] [[PubMed](#)]
58. Shi, L.; Dong, H.; Reguera, G.; Beyenal, H.; Lu, A.; Liu, J.; Yu, H.-Q.; Fredrickson, J.K. Extracellular electron transfer mechanisms between microorganisms and minerals. *Nat. Rev. Microbiol.* **2016**, *14*, 651–662. [[CrossRef](#)]
59. He, Q.; Sanford, R.A. Characterization of Fe (III) reduction by chlororespiring *Anaeromyxobacter dehalogenans*. *Appl. Environ. Microbiol.* **2003**, *69*, 2712–2718. [[CrossRef](#)]
60. Kim, B.H.; Chang, I.S.; Gadd, G.M. Challenges in microbial fuel cell development and operation. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 485–494. [[CrossRef](#)]
61. Marsili, E.; Baron, D.B.; Shikhare, I.D.; Coursolle, D.; Gralnick, J.A.; Bond, D.R. *Shewanella* secretes flavins that mediate extracellular electron transfer. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3968–3973. [[CrossRef](#)] [[PubMed](#)]
62. Wu, Y.; Liu, T.; Li, X.; Li, F. Exogenous electron shuttle-mediated extracellular electron transfer of *Shewanella putrefaciens* 200: Electrochemical parameters and thermodynamics. *Environ. Sci. Technol.* **2014**, *48*, 9306–9314. [[CrossRef](#)] [[PubMed](#)]
63. He, Y.; Guo, J.; Song, Y.; Chen, Z.; Zhao, R. Acceleration mechanism of bioavailable Fe(III) on Te(IV) bioreduction of *Shewanella oneidensis* MR-1: Promotion of electron generation, electron transfer and energy level. *J. Hazard. Mater.* **2020**, *403*, 123728. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.