3 Biotech (2023) 13:119
https://doi.org/10.1007/s13205-023-03539-6

REVIEW ARTICLE

Role of bio-electrochemical technology for enzyme activity stimulation in high-consumption pharmaceuticals biodegradation

Zohreh Moghiseh[1] · Yong Xiao[2] · Mojtaba Kalantar[3] · Barat Barati[4] · Mina Ghahrchi[5]

Received: 30 August 2022 / Accepted: 28 March 2023 / Published online: 3 April 2023

Abstract

Active pharmaceutical ingredients (APIs) and their intermediate residues have recently been considered a serious concern. Among technologies, bio-electrochemical technologies (BETs) have stimulated the production of bio-electrical energy. This review aims to examine the benefit and mechanism of BETs on the degradation of high-consumption pharmaceutical compounds, including antibiotic, anti-inflammatory, and analgesic drugs, and the stimulation of enzymes induced in a bioreactor. Moreover, intermediates and the proposed pathways of pharmaceutical compound biodegradation in BETs are to be explained in this review. According to studies performed exclusively, the benefit of BETs is using bio-electroactive microbes to mineralize recalcitrant pharmaceutical contaminants by promoting enzyme activity and energy. Since BETs use the electron transfer chain between bio-anode/-cathode and pharmaceuticals, the enzyme activity is essential in the oxidation and reduction of phenolic rings of drugs and the ineffective detoxification of effluent from the treatment plant. This study is suggested a vital and influential role of BETs in mineralizing and enzyme induction in bioreactors. Eventually, a content of future developments or outlooks of BETs are propounded to improve the pharmaceutical industries' wastewater problems.

Keywords Bio-electrochemical · Pharmaceutical · Enzyme activity · Toxicity · By-product · Antibiotic

Introduction

Pharmaceuticals have been developing in different formulations and forms in recent decades which has been consumed for treating various diseases such as cancer and increasing the health and life span of sick people. Today, the pharmaceutical residue is introduced into the wastewater treatment plant's (WWTP) influent and effluent, sludge, and receiving water bodies (surface water and groundwater) through different routes (Patel et al. 2019; Rivera-Utrilla et al. 2013) resulting in their presence in the environment as a severe threat on environmental and human health (Patel et al. 2019). As mentioned in the literature (Patel et al. 2019; Rivera-Utrilla et al. 2013; Martz 2012; Xiao et al. 2021; Ahmed et al. 2017; Tiwari et al. 2017), the pharmaceuticals in aquatic environments have been detected for decades. APIs sustain the environment significantly because of their persistence and low biodegradability (Martz 2012). The presence of antimicrobial resistance genes (ARGs), the stability of super pathogens, and thus deadly diseases can rise by APIs in WWTPs (Xiao et al. 2021). Most of the conventional treatment processes in WWTPs are unsuitable for removing pharmaceutical pollutants and their toxic intermediates or other xenobiotic compounds (Ahmed et al. 2017). The study reported the pharmaceuticals removal in sedimentation and flocculation processes as < 10% (Tiwari et al. 2017).

In addition, the adsorption process transfers the contaminants into another phase (Tiwari et al. 2017). The main disadvantage of this process is the production of secondary pollutants.

✉ Zohreh Moghiseh
zmoqise@yahoo.com

1 Department of Environmental Health Engineering, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran

2 CAS Key Laboratory of Urban Pollutant Conversion, Institute of Urban Environment, Chinese Academy of Sciences, Xiamen, Fujian 361021, People's Republic of China

3 Department of Occupational Health, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran

4 Department of Radiologic Technology, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran

5 Department of Environmental Health Engineering, Torbat Jam Faculty of Medical Sciences, Torbat Jam, Iran

Mainly, conventional biological processes are regarded as environmentally friendly treatment methods but they might not be resistant to contaminant toxicity at high concentrations (Huang et al. 2011). For example, an activated sludge process removes the low-concentration pharmaceutical residues for a long time but does not do at a specific contact time in the treatment plant. It has been noted that the activated sludge process raises the production of more dangerous metabolites than the original compound. In addition, the biological activated carbon process provides high sludge, so it augments the management costs of produced sludge (Ahmed et al. 2017). Activated carbon in the biological activated carbon process is an appropriate material for sludge development and improves its density characteristics, which include some degrading organic material of bacteria. Therefore, advancing cost-effective and confident techniques for the removal or degradation in the concentration of pharmaceuticals is necessary.

BETs, the combined electrochemical and microbial systems, can improve the degradability of pharmaceutical compounds owing to accelerated microbial degradation by collaborating electrochemical reactions with electrodes. BETs which are involved in microbial fuel cells (MFCs) and microbial electrolysis cells (MECs) manipulate the mineralization of compounds and thus are regarded as a favorable option for the cost-effective removal or bioremediation of recalcitrant or xenobiotic contaminants (Yan et al. 2019; Fernando et al. 2019; Ahmed et al. 2021). In addition, MFCs, as one of the typical BETs, can be used for producing electrical energy (Mook et al. 2013).

The electrical stimulation in BETs affects removal efficiency, energy production, microbial community and structure, antibiotic resistance genes, controlling of the fouling issue of membrane bioreactor, and new material development such as ammonium recovery as fertilizer using a low voltage at MECs through increasing oxygen reduction at cathode and cations transfer chain (Ahmed et al. 2021; Ramírez-Vargas et al. 2018) that several researchers have confirmed these results in their recent studies and literature reviews. For example, antibiotics are eliminated in MFC to enhance electrical energy generation by bio-sorption and biodegradation processes (Chakraborty et al. 2020). Cecconet et al. (2018) reported that they have found low energy consumption and high nitrate removal efficiency for treating groundwater nitrate in BETs. Other than electrical stimulation, the enzymes or enzyme activity (intracellular and extracellular) induced by BETs, especially electrical current, imply their effect on the degradation mechanism and metabolic pathway of pharmaceuticals. For example, dehydrogenase, laccase, and phosphatase enzymes are essential to degrading drugs or other contaminants in BETs (Bilal et al. 2020; Lloret et al. 2013). The principle aim of this study is to review the recent developments of BETs in the field of high-consumption pharmaceutical contaminants and to discuss the factors affecting them as enzyme activity, detoxification, and its pathway. Eventually, future developments or outlooks are suggested to improve the pharmaceutical wastewater problems.

Pharmaceutical and its intermediate residues in aquatic environments

Pharmaceuticals are considered micro-pollutants with their unique properties, including various structure forms and intermediates of drugs and their low concentration in aqueous solutions. Pharmaceutical compounds are composed of APIs, which are introduced into the environment in metabolized and non-metabolized forms through wastewater sewage systems. Several studies have detected the parent and by-products of pharmaceutical compounds in the effluent after traditional wastewater treatment and identified it as an environmental concern in many countries (Tiwari et al. 2017). Introducing these pollutants into the environment harms aquatic creatures and human health but will increase the growth of pharmaceutical-resistant microorganisms (Tiwari et al. 2017). The pharmaceutical compound's biological, physical and chemical activity will confirm the solubility or ionization of the mixture in water. A low ionization compound will tend to adsorb to solid surfaces such as soil, sludge, biomass, and sediments. The residues of pharmaceuticals and their intermediates may be polar or nonpolar components. Tiwari et al. (2017) reported that the presence of pharmaceutical residue in the environment depends on its removal mechanism in WWTPs, including adsorption, oxidation, photolysis, volatilization, and biodegradation. Similarly, Fatta-Kassinos et al. (2011) declared that the transformation of the main composition of pharmaceuticals occurs using biological and photolysis mechanisms during wastewater treatment so that high-polarity and low-activity intermediates are produced and then assessed their fate and effects in the environment. Although fluoroquinolone antibiotics concentration was determined from 0.32 μg L^{-1} to 5.7 mg L^{-1} in industrial effluent, the removal efficiency of biological degradation is high in the range of 94.5–99.9% is considered the primary removal mechanism rather than sorption by sludge (Guo et al. 2017). Hence, there is no problem with drug residue disposing of its effluent in the environment.

On the other hand, various studies often detected pharmaceuticals and their intermediate residues in the environment (especially effluent of WWTPs). Many researchers have investigated the pharmaceutical residues in wastewater, environmental waters, and sediment and their impacts in recent years (Matongo et al. 2015; Hernando et al. 2006; Sacher et al. 2008; Zhou et al. 2009; Dogan et al. 2020; K'oreje et al. 2016). The pharmaceutical residues in sewage

usually observe at the highest concentration compared to other environmental samples. For example, Alygizakis et al. (2016) determined 158 pharmaceutical components in the Eastern Mediterranean seawater with the highest concentration of ingredients related to antibiotics, e.g., amoxicillin, anti-inflammatory, and analgesics, e.g., caffeine and salicylic acid. It revealed wastewater discharge is the primary contamination in offshore seawater. Antibiotics and anti-inflammatory and analgesic drugs are the favorite drug groups that frequently detect at the inlet and outlet of wastewater treatment plants (Fatta-Kassinos et al. 2011). Penicillin, ciprofloxacin, sulfamethoxazole, cefixime, azithromycin, and tetracycline were identified in Oman and European countries. (Al-Riyami et al. 2018; Rodriguez-Mozaz et al. 2020, Tiwari et al. 2017). Widespread acetaminophen, aspirin, ibuprofen, and diclofenac residue, which are anti-inflammatory and analgesic drugs, have been observed in most of the studied wastewaters (PraveenKumarreddy et al. 2021; Kumar et al. 2020; Tyumina et al. 2020). Moreover, hormones, especially estrogen (both natural and anthropogenic) and its by-products introduce into wastewater because of their high consumption in treating disease (Syed et al. 2021; Griffith et al. 2013).

At WWTPs, the biological treatment of estrogen compounds has complicated due to their toxicity to microorganisms (Syed et al. 2021). Anthropogenic estrogens are an emerging concern in wastewater and aqueous ecosystems at nano-gram concentrations (Tiwari et al. 2017; Syed et al. 2021; Schröder et al. 2016). In addition, the residue of natural estrogens in municipal wastewater treatment plant effluent is less than other contaminants due to their low polarity or water solubility characteristics (Nakada et al. 2004). However, it can be present in various environments, e.g., water, soil, air, and wastewater. The disruptive effects and toxicity of the by-products can be more severe than the origin of estrogens.

On the other hand, the residue can be affected by factors such as seasonal variations. Jin et al. (2008) reported that the activities of estrogens in the influent and effluent of WWTPs varied during the winter and summer seasons in China. They confirmed that these compounds' concentration is high in influent and primary and secondary treatment effluent of wastewater plants in summer.

The benefits of BETs in the removal of pharmaceuticals

The benefit of BETs in pharmaceutical removal is using bioelectroactive to mineralize recalcitrant contaminants, e.g., pharmaceutical contaminants from wastewater, by promoting enzyme activity and producing energy (Pun et al. 2019) compared with other treatment processes. Direct and alternating current (DC and AC) use in BETs for pharmaceutical removal and low studies observed through AC (Moghiseh and Rezaee 2021; Hoseinzadeh et al. 2018). As mentioned before, although conventional biological plants produce less concentration of enzymes, both intracellular and extracellular, BETs can be a cost-effective technology for removing persistent pharmaceutical contaminants by producing more enzymes or energy. The induced enzymes from BETs not only promote pharmaceuticals removal efficiency but also show low toxicity of by-products as a biosensor. For example, the induced enzymes found at the highest level in 8 V_{pp} applied voltage of AC, which could affect the toxicity of aspirin (Moghiseh and Rezaee 2021).

BETs have catalyzed the electron transfer processes between enzyme or mediator and electron surface by biocatalysts or bio-electro activity from the microbial cells adhering to the electrodes (Mook et al. 2013). Bio-catalytic behaviors of microorganisms in BETs occur because of the electrical stimulation in microorganism metabolism. Another benefit of BETs that many studies have shown is provided higher treatment efficiency (> 80–85% removal percent) at low retention time (< 12-h contact time) for refractory contaminants (e.g., pharmaceutical) than traditional biological processes (Xu et al. 2022). Furthermore, the produced sludge can be low in BETs (Moghiseh et al. 2020). In addition, BETs can be easily combined with other systems to generate biogas, nitrogen gas, or bio-electricity, remove/recover heavy metals, and especially pharmaceutical degradation (Yuan and He 2015; Xu et al. 2019; Ghangrekar et al. 2020; Quarda et al. 2018; Yeruva et al. 2016; Hu et al. 2019; Nikhil et al. 2017). For instance, the combination of BETs and single plants enhanced the biological treatment of emerging contaminants in real-scale pharmaceutical wastewater treatment (Ghangrekar et al. 2020) is observed in Table 1. Recently, the application of mathematical models has increased to anticipate the treatment efficiency of bioelectroactive reactors for pharmaceutical compounds (Hu et al. 2019; Gadkari et al. 2018; Ismail and Habeeb 2017).

The effect of BETs on pharmaceuticals is shown in Fig. 1, and the summary of the literature review of BETs' performance in the removal of drugs is shown in Table 1.

Recent prospects of BETs in the removal of antibiotics

Antibiotics include a wide range of compounds. The structure of antibiotics is complicated, composed of carbon, hydrogen, nitrogen, and halogenated atoms. As a high-consumption drug for treating infectious diseases, the contamination of antibiotics in the environment is an emerging concern. The antibiotics usually detect in nano-gram or microgram in the aqueous media of different countries. For example, six antibiotics found in WWTPs in Wisconsin, USA, had ng L^{-1} or ppb concentrations ($\leq$1.3 µg L^{-1}) (Karthikeyan and Meyer 2006). In addition, the hospital

Table 1 BETs performance on the removal of pharmaceuticals

Pharmaceutical	Bio-electrode	Configuration	Culture medium	Chamber	Electrical current	Removal efficiency	Refs.
Oxytetracycline (OTC)	Bio-anode–bio-cathode	Photo-MFC	Anaerobic sludge with *Chlorella vulgaris*	Two-chamber	DC	75% at 50 mg L^{-1} and time = 160 h	Sun et al. (2019)
Sulfamethoxazole (SMX)	Bio-anode–bio-cathode	Moving-bed electrochemical membrane bioreactor (MEMBR)	Activated sludge	Two-chamber	DC	88.9% at 100 µg L^{-1} and time = 48 h	Chen et al. (2019)
Cefuroxime	Bio-anode–bio-cathode	Bio-electrochemical system (BES)	Activated sludge	Two-chamber	DC	> 90–100%, time = 20 days	Cheng et al. (2016)
Sulfonamide (SDZ)	Bio-anode–bio-cathode	Electrochemical membrane biofilm reactor (EMBFR)	Activated sludge	Single-chamber	DC	94.9%	Li et al. (2021)
Tetracycline hydrochloride (TCH)	Bio-anode–bio-cathode	Microbial electrochemical technology (MET)	Activated sludge	Single-chamber	–	85% at 50 mg L^{-1} and time = 100 h	Peng et al. (2020)
Carbamazepine, synthetic and real wastewater	Bio-anode	MFC-UV, MEC-UV	Primary sedimentation tank	Two-chamber	DC	Synthetic: 100% at 500 µg L^{-1} and time = 2 h real: 80% at time = 20 h	Zou et al. (2020)
β-Lactams antibiotics	Bio-anode–bio-cathode	Up-flow bio-electrochemical system (UBES)	Anaerobic sludge	Single-chamber	DC	86.2% at 15 mg L^{-1} and HRT = 48 h	Hu et al. (2019)
Real pharmaceutical wastewater	Bio-anode	Integrating sequencing batch (anoxic/aerobic) reactor (SBR) with bio-electrochemical treatment (BET)	Aerobic consortia	Single-chamber	DC	SBR (anoxic) with BET: 68.69%, SBR (aerobic) with BET: 60.27%	Yeruva et al. (2016)
Real pharmaceutical wastewater	Bio-anode	MFC with GAC	Anaerobic sludge	Two-chamber	–	83% at COD = 800 mg L^{-1} and time = 45 days	Ismail et al. (2017)
Ibuprofen	Bio-anode–bio-cathode	Microbial electrochemical system	Activated sludge	Single-chamber	AC	100% at 200 mg L^{-1} and time = 6.5 h	Hoseinzadeh et al. (2018)
Carbamazepine (CBZ) and sulfamethoxazole (SMX)	Bio-anode–bio-cathode	Microbial electrochemical fluidized bed reactor (ME-FBR)	Anaerobic consortium	Dual-chamber	DC	> 80% at 4 mg L^{-1} and time = 120 h	Asensio et al. (2021)
Real pharmaceutical wastewater	Bio-anode–bio-cathode	Nitrification (ANT) and bio-electrochemical denitrification (DNT)	Aerobic and anaerobic domestic effluent treatment plan	Dual-chamber	DC	78.5% COD at ANT and 61.1% COD at DNT after 12th cycle	Nikhil et al. (2017)

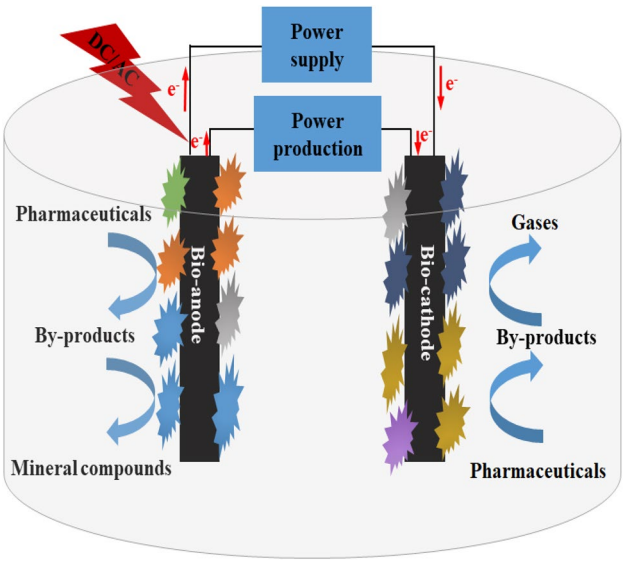

Fig. 1 The effect mechanism of BETs on the pharmaceuticals

effluent in Germany is contaminated with ampicillin and amoxicillin in the range of 20–80 µg L^{-1} and 28–82 µg L^{-1}, respectively, or the maximum concentrations limited to 48 ng L^{-1} in surface water (Githinji et al. 2011).

Biological treatment processes such as bio-sorption and biodegradation observe the main and cost-effective strategies compared to other treatment techniques (Huang et al. 2021). However, these processes' high contact time, low stability to organic load shock, low-concentration degradability, and high sludge production are their disadvantages (Ahmed et al. 2017). BETs such as MFCs have been introduced as favorable biotechnology for anthropogenic antibiotics that have resulted from cost-effective environmental applications (Chaturvedi et al. 2021). BETs can provide an electrochemical transfer chain between electrodes and microorganisms to accelerate antibiotic removal or mineralization, induced enzyme secretion, and microbial growth (Peng et al. 2020; Freguia et al. 2012). These stimulations can be affected by voltage or current, operation mode, salinity, temperature, pH, pollutant concentration, microorganism, frequency, electrode type and configuration, light (solar and UV), and co-substrate addition (Caubet et al. 2004; Hu et al. 2020; Li et al. 2020; Quejigo et al. 2019; Zhou et al. 2022).

Moderate addition of co-substrate assists in co-metabolic electroactive biodegradation performance of antibiotics with multi-ring phenolic structure. Zhou et al. (2022) acknowledged that tetracycline removal efficiency has increased to 44% by adding 0.1 g L^{-1} acetate as a co-substrate, which influenced the capability and stability in degrading tetracycline bacteria and intermediates and toxicity of effluent. Still, removal efficiency declined at 1 g L^{-1} acetate. By the study of Wang et al. (2015a; b) adding a low acetate dose, the same pollutant degraded > 90% by incrementing 0.5 g L^{-1} sodium acetate as an appropriate concentration in the MFCs bio-cathode, which may be due to microbial diversity and induced enzymes in the bioreactor.

Bio-stimulation provided by temperature and pH fluctuations in BETs is tiny. Kong et al. (2014) showed that the degradation of chloramphenicol was not affected significantly by temperature fluctuations on the adapted cathode biofilm-BETs, which produced more intermediates than those with only biological or electrochemical processes. However, the presence of light in BETs (e.g., photo-MFC) can stimulate oxygen production and its reduction, extracellular electron transformation, and enrichment of bacteria in a bioreactor. Thus, it raised the degradation rate of the antibiotics such as chloramphenicol or oxytetracycline. Similarly, florfenicol degradation was increased 5.82 times at the anode by integrating a solar photovoltaic capacitor discharge of 100 F into an algal–bacterial photo-bio-electrochemical system (Li et al. 2020; Sun et al. 2019).

Besides, the operation mode under batch or continuous conditions can enhance the concentration and stability of produced enzymes and contaminant mineralization in a bioreactor. A constant feed of contaminants positively affects microbial growth and enzymes. Hu et al. (2020) treated SMX-contained wastewater using up-flow anaerobic BETs (UBES) and observed the operation mode is an important issue. In other words, the efficiency of the closed-circuit or continuous operation was higher than the open-circuit or batch operation of BETs and explained that closed-circuit could be operated on toxic compounds continually. However, antibiotics may be oxide at long times under batch operation and co-metabolically conditions (Harnisch et al. 2013).

Moreover, electrical current can positively influence the morphology, growth, diversity, viability, and permeability/cellular structure of microbial species in a bioreactor. A study has evaluated a combined CW-MFCs bioreactor performance in a high concentration of SMX ($C = 30$ mg L^{-1}) that can degrade because of the presence of the microbial consortium in this integrated system (Zhang et al. 2017). In another study, the electrical current affected the bacterial biofilm structure in the bioreactor, with an effect of 9.1% to 28.5% removal efficiency on cephalosporin antibiotics (Guo et al. 2022).

According to Table 1, the presence of membrane or conductive moving bed carries in BETs involves the benefits such as the treatment and mineralization of antibiotics, production of reactive oxygen species (e.g., $HO^{\cdot}$), controlling microbial fouling and the growth of specialized microorganisms and their structure (Li et al. 2021; Song et al. 2020; Chen et al. 2019; Zou et al. 2020). The interaction between electrochemical and biodegradation processes and specialized microbial growth in the membrane was confirmed by Ren et al. (2021) study. They have shown the SMX and

trimethoprim antibiotics efficiency was 60%, which depends on operation conditions such as oxygen dose and type of membrane applied in the system, and it brought in the study of Song et al. (Ren et al. 2021; Hassan et al. 2021; Song et al. 2020).

In addition, the reactor configuration can improve the operation, maintenance, and economic factors in BETs. Zhang et al. (2022) revealed that U-shape bioreactors with continuous flow had reduced by 95% of 20–80 mg L^{-1} tetracycline of influent at 8-h reaction time without needing a membrane. The quantity and quality of microbial genes are impacted by U-shape bioreactor operation.

Antibiotic contamination could provoke the presence of antibiotic-resistant bacteria (ARB) and ARGs. Although conventional microbial systems can remove antibiotics, they mainly produce ABR and ARGs (Singh and Saluja 2021).

Numerous studies showed that bio-electrochemical technologies could prohibit the increase of ARB and ARGs compared to conventional wastewater treatment technologies. Zhang et al. (2017) reviewed BETs impressively, eliminating antibiotics and decreasing ARGs and ARB production in a high current.

Recent prospects of BETs in the removal of anti-inflammatory and analgesic drugs

Other high-consumption drugs classified as anti-inflammatory and analgesic drugs have produced considerable amounts. These drugs include a wide range of compounds consumed to improve pain, fever, and inflammation without prescription. Anti-inflammatory drugs are diclofenac, ibuprofen, naproxen, ketoprofen, mefenamic acid, and analgesic drugs which are acetaminophen or paracetamol, aspirin or acetylsalicylic acid. Literature reviews have reported that anti-inflammatory and analgesic drugs and their intermediates contribute to the high-portion contamination in aqueous solutions (Ziylan and Ince 2011). Since the removal efficiency of pharmaceuticals is slight in the traditional wastewater treatment plant, the anti-inflammatory and analgesic drugs accumulate abundantly in the outlet of wastewater purification plants, soil, plant, and surface and ground waters. Several studies have measured anti-inflammatory and analgesic drug concentrations in different countries (Ziylan and Ince 2011). The concentration of aspirin, diclofenac, ibuprofen, ketoprofen, mefenamic acid, naproxen, and paracetamol is detected 100, 0.1–4.11, 0.17–83.50, > 0.32, 0.14–3.2, and 1.79–611 µg L^{-1} in the influent and 0.05–1.51, 0.04–1.95, < 95, 0.14–1.62, 0.09–2.4, 0.17–33, and 6.9 µg L^{-1} in the effluent of wastewater (Feng et al. 2013). Although the concentration of these compounds is low in the effluent because hydrolysis, sorption, and biodegradation processes occur during wastewater treatment plant stages, the solubility and stability of these compounds are especially intermediate. They are high to contaminate the water sources. There are anti-inflammatory and analgesic drug residues that percolate into groundwater (K'oreje et al. 2016; Ziylan and Ince 2011) that harms the environment and human health.

Various studies have shown that the conventional processes of treatment plants have not wholly mineralized the anti-inflammatory and analgesic drug residues and identified the intermediates with toxicity higher than the original composition. However, studies have shown that anti-inflammatory and analgesic drugs can be degraded and mineralized in bio-electrodes and bio-electro reactors (Wu et al. 2019; Qiu et al. 2022) brought in Table 1. Even the single-chamber BETs have been constructed and operated instead of two-chamber, which declines the ion-exchange membrane costs in the bioreactor-electrochemical (Xu et al. 2022). In addition to the study by Hoseinzadeh et al. (2018) (Table 1), Moghiseh and Rezaee (2021) studied the degradation of aspirin by electroactive bacteria in the single-chamber MEC induced by AC. Moghiseh et al. (2019a, b) demonstrated that the high aspirin concentration ($C_0 = 250$ mg L^{-1}) mineralization occurred at 2 V_{pp} voltage, 10 Hz frequency, and sine wave for six h. Erythromycin concentration and bacterial activity were investigated in a single-chamber MEC, which revealed complete degradation at an initial concentration of 20 mg L^{-1} (Ramirez-Vargas et al. 2018). In other studies, single-chamber BETs (MFC or MEC) have been conducted in lower cases (Qin et al. 2020).

The hydroxyl radicals ($HO^{\cdot}$) are obtained through different routes to degrade these drugs. Often studies have confirmed the production of oxidant species such as $HO^{\cdot}$, H, and reactive oxygen species can be produced by the culture medium and enzymatic and metabolic activities of microorganisms and used electrodes are adopted to enhance the electron transfer chain and thus the degradation and mineralization of pharmaceutical compounds in the bioreactor (Nadais et al. 2018). The coupled bio-electro-Fenton and MFC reactor can contribute to the decomposition of pharmaceuticals such as paracetamol (Zhang et al. 2015) using $^{\cdot}OH$ production in the bioreactor. The Fenton can be involved in oxidation and contamination reduction (Sathe et al. 2022). In contrast, diclofenac's mineralization and toxicity reduction are achieved by both reduction and oxidation reactions. At first, the chlorine of diclofenac is reduced through the reaction with hydrogen radical, and thus it oxidized through the reaction with hydroxyl radical as the prominent radical in the bioreactor (Qin et al. 2020). Moreover, the evolution of high conductivity anode (e.g., Pd, MnO_2, and Fe_3O_4) can be enhanced the electron transfer chain through the diversity in microbial culture medium and produced radicals, which provides the high removal of pharmaceutical residues in the bioreactor (Xu et al. 2018). For example, manganese

compounds are produced in MFC-permanganate to decompose the benzene ring of diclofenac (Wang et al. 2021).

Nadais et al. (2018) have studied that the oxidation of ketoprofen, diclofenac, ibuprofen, and Naproxen was 59–61%, 87–97%, 80–86%, and 75–81% by the bio-electric-Fenton process at 5-h reaction time, 40 µg L^{-1} initial concentration, pH 2 and applied voltage 0.5 V. The oxidation efficiency was obtained lower in real wastewater. In addition, they reported that increasing the reaction time from 5 to 11 h, ibuprofen and diclofenac removal increased slightly, but naproxen and ketoprofen became 94% and 78%. Hence, naproxen and ketoprofen need more time for degradation because of their more intricate structure or slow degradation mechanism, in other words, their low rate constant (K_{app}) value.

Zhu et al. (2021) assessed nitrogen and phosphorus removal using ibuprofen in a bio-electrochemical-autotrophic denitrification system with sulfur/iron supplied by a direct current (DC) power which obtained a high reduction of ibuprofen 96.98%, total nitrogen 98.93%, and total phosphorus 82.67%. However, nitrate and ammonia ion concentrations accumulated in the operated system. This issue has mainly resulted from the electrochemical reduction of nitrate to ammonia in the presence of iron. Pharmaceutical compounds such as ibuprofen could inhibit denitrifying bacteria performance by the accumulation of nitrite ions and total nitrogen and phosphorous compounds removal efficiency in the first days of operation of the system; these concentrations declined gradually during operation time. The researchers reported that oxidizing factors break down ibuprofen into simpler compounds. In addition, ibuprofen affected the culture medium species, metabolism, and structure found in the study of Zhu et al. (2021).

The coupling of BETs and conventional processes has been conducted in recent years, which can raise the performance of bioreactors in achieving high removal of nonsteroidal anti-inflammatory pharmaceuticals. Among several constructed wetland (CW) types for the biodegradation of drugs, the coupling of MFCs or MECs and constructed wetland (CW-BET) systems has been introduced as novel systems. The removal efficiency of nonsteroidal-anti-inflammatory pharmaceuticals (e.g., diclofenac, ibuprofen, and naproxen) in CW-BET with a continuous and horizontal flow demonstrated slightly more than CW without current (control) in a studied synthetic wastewater at microgram concentrations. This removal resulted from the enhanced biological activity or electrodes. However, this coupled process did not favor the removal of studied components in real wastewater (Hartl et al. 2021). The removal efficiency of ibuprofen showed to be appropriate (63.2–78.7%) even at high concentrations (10 mg L^{-1}) in a performed study by Li et al. This study was done in CW-MFC bioreactors with up-flow. Li et al. (2019) reported that the highest contaminant removal occurred at the reactor's bottom and anode section because of the growing mixed culture of bacteria.

In addition, the Photo-MFC bioreactor catalyzes biodegradation using the stimulation of bio-anode by the visible photo-catalytic cathode (Xu et al. 2020). Xu et al. (2020) studied the degradation of ibuprofen (IBU) using the polymerization of carbon nanotubes and stainless steel as a bio-anode and $CuInS_2$ as a visible light-absorbing cathode in MFC. They demonstrated the presence of oxygen and hydroxyl radicals causes the efficiency of degradation and mineralization to reach 75.94% and 70.56% according to the 0.75 A/m^2 and 950 mV current density and voltage. In this study, both radicals could reduce IBU as a refractory contaminant to carbon dioxide and water.

Effect of electrical current, applied voltage, and frequency on induced enzyme activity in bioreactor

The enzyme activity of microorganisms rises using the electroactive bacteria as a biocatalyst on the bio-electrodes, stimulated by DC and AC under optimum conditions (Chatterjee et al. 2019). Enzyme activity improved the biodegradation of complex degradable compounds or xenobiotics (Moghiseh et al. 2019a, b; Yang et al. 2020). The enzyme is an effective catalyst that accelerates the electrochemical reactions of bioreactors, which involves the oxidation and reduction process and decomposing of compounds.

The induced extracellular and intracellular enzymes secreted in the electroactive bioreactor play a crucial role in the degradation and mineralization. The electron transfer chain can be enhanced using the extracellular enzyme of biofilm on the electrode in bio-electroactive reactors. The extracellular enzyme can provide the reaction between the electrode and biofilm, and accelerates the generation of simple-degradable compounds by microorganisms (Deutzmann et al. 2015). Studies have used DC more frequently than AC as an electrical current supply at bioreactors that decompose the xenobiotic or other compounds by incrementing enzyme activity by providing changes on the cell membrane surface (Zhou et al. 2019). The applied electrical current and voltage role in activating enzymes is essential to eliminate the environmental contaminants, so some studies have performed the biodegradation of contaminant (e.g., phenol) through enzyme activity of microorganisms rather than the electrochemical process in the bio-electrochemical reactor (Vasileva et al. 2021).

Figure 2 depicts the effect of electro-stimulation on removal efficiency and enzyme activity under the conditions induced by electrical current and without it.

Various enzymes facilitate the biodegradation of pharmaceuticals (Haroune et al. 2017). Cytochrome P450 enzyme, an intracellular enzyme secreted by fungi, has not

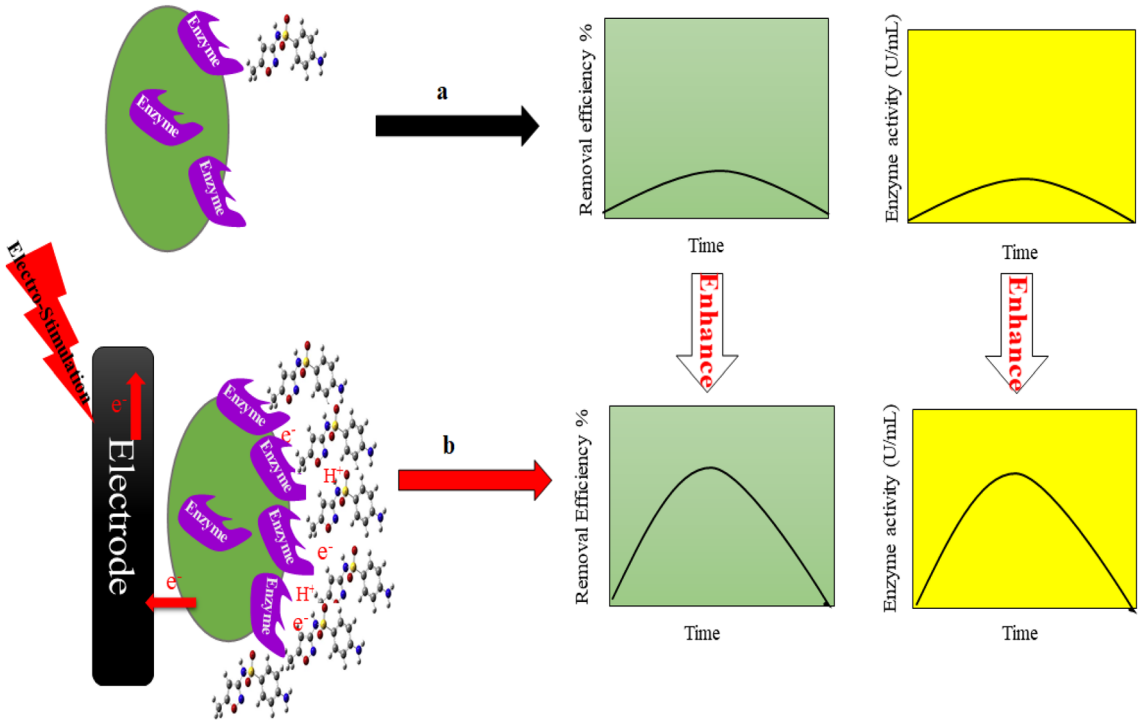

Fig. 2 Removal efficiency and enzyme activity under (**a**) without current (control) and (**b**) with electrical current

contributed to the exclusive biodegradation of ketoprofen, as a nonsteroidal and anti-inflammatory. Reports indicate that peroxidase, dehydrogenase, laccase, phosphatase, etc. could have decomposed the pharmaceutically active components (Bilal et al. 2020). The degradation of antibiotics and analgesic drugs is performed by laccase and peroxidase (especially lignin, manganese, and versatile peroxidases) enzymes (Chaturvedi et al. 2021; Eibes et al. 2011; Zhang and GeiBen 2010; Pylypchuk et al. 2020; Wen et al. 2010). Peroxidase oxidase–reductase drug uses hydrogen peroxide (H_2O_2) and produces hydrogen peroxide/superoxide at low concentrations (Hey-Mogensen et al. 2014). Bio-electro-reactors synthesize hydrogen peroxide through the reducing condition of oxygen on the cathode that applied voltage, or current density is considered the most impressive operating factor in accelerating the reactor performance by electron transformation on the cathode (Chung et al. 2020; Khan et al. 2019). Literature reviews express that the applied voltage from 0.2 to 2 V is used for hydrogen peroxide production in BETs (Chung et al. 2020), where studies have often concluded that 0.4 V is the optimum applied voltage at the H_2O_2 generation rate due to high cathodic Faradic efficiency (Chung et al. 2020). Miran et al. reported that hydrogen peroxide (H_2O_2) production obtained 13.3 g/L m^2 in MEC supplied with DC power; this was the highest concentration at 0.4 V voltage during 6-h time in the cathode electrode for the degradation of xenobiotic compounds such as chlorinated phenol (Miran et al. 2017). Another study used a 20 L scale-up BET to achieve the maximum hydrogen peroxide production rate (10.82 mg L^{-1} h^{-1}) at a 0.6 V voltage for 42 h. Moreover, the presence of the peroxidase enzyme fixed (Tang et al. 2010; Cho et al. 2009) on the electrode at an enzymatic electrical reactor caused the treatment and effective detoxification of textile wastewater which was accompanied by the high production of hydrogen peroxide at 10 Am^{-2} current density (Cho et al. 2009).

Whether combined with other processes, for instance, Fenton and UV/visible light, bio-electrochemical technologies participate in the simultaneous production of H_2O_2 through air–cathode at bioreactor with energy production and mineralization of environmental contaminants such as emerging contaminants (Zhao et al. 2021).

Laccase contributes to the degradation of antibiotics (e.g., ciprofloxacin, amoxicillin, sulfamethoxazole, and tetracycline) (Bilal et al. 2020) and anti-inflammatory and analgesic drugs (e.g., acetaminophen, diclofenac, and naproxen) (Lloret et al. 2013, 2010; Zhang et al. 2015). Their degradation rate depends on different factors such as applied voltage, current density, frequency, initial concentration of the drug, temperature, pH, and enzyme concentration are explained in the following sections (Chaturvedi et al. 2021; Zhang and GeiBen 2010). Hence, the stability and activity of enzymes are necessary for a bio-electrochemical reactor.

Ratanapongleka and Punbut (2018) revealed that the efficiency of fixed laccase (0.57 U/g) was excellent at a neutral pH and 35 ºC temperature for acetaminophen removal during 240 min contact time without electrical current at the enzymatic reactor. In contrast to Ratanapongleka and Punbut's (2018) study, bio-electroactive-enhanced laccase enzyme activity was observed in Moghiseh and Rezaee's (2021) study. They found the bacterial laccase and dehydrogenase activity have increased by 30.6 U/mL and 75.5 micro grTF/cm^2.gr biomass using AC with a low voltage–low frequency at optimum conditions of mineralization of aspirin with an applied voltage of 8 V_{pp} and 12 h. While activation of laccase with 6 V voltage of DC performed by Wang et al. (2015a, b) has shown that the maximum laccase (5 U/mL) occurred in the anodic section instead of the cathode at 5-h time. The laccase concentration obtained from DC was lower than AC, possibly due to the difference in the culture medium used in the bioreactor.

Laccase could thus reduce the drug's toxicity and it intermediates using oxidation–reduction reactions in the phenolic compounds. Extracellular laccase oxidized aspirin to more biodegradable ingredients as a carbon source in Moghiseh and Rezaee's (2021) study. The enzyme secreted by fungus mainly, however, can be produced by bacteria such as pseudomonas. Figure 3 shows the performance of the laccase enzyme at the bioreactor.

According to Fig. 3, laccase involves the breaking and hydroxyl groups oxidation of phenolic rings, e.g., pharmaceuticals simultaneously reduce O_2 to H_2O (Moghiseh and Rezaee 2021; Agrawal et al. 2018).

The current density of 200 mA/m^2 and iron, copper, and molybdenum elements have stimulated the reductase enzyme activity of denitrifying bacteria, which rise to 11% and 15% with only DC power. In contrast, the enzyme activity reaches 14% and 16% in the presence of elements (Liu et al. 2021). Zhang et al. (2014) concluded that DC power with low current density (10–15 mA) stimulates the degrading enzyme of fluoroaromatic compounds, where the enzyme shows a significant role in their mineralization.

In addition, the dehydrogenase (DH) enzyme is an intracellular enzyme that implies the reaction of H^+ with substrate and its intermediates, increasing the potential difference and electron transfer. DH activity trend can be affected by applied voltage or current parameters in the BETs. As cited above, the DH enzyme was secreted appropriately in a bioreactor induced with an external low-voltage AC. However, DH activity has represented a slightly increasing trend at 24 h through 2000 mV external potential (6.4 µg/mL) in comparison to control (5.9 µg/mL) in the estrogens removal (Kumar et al. 2012). There may likely be a further increase in enzyme activity at a potential of less than 2000 mV. DH activity in an MFC reactor reached the highest value of 18 µg/mL at 12 h. The trend of each enzyme activity is different; the DH activity trend was depicted as high at first and then low; however, the phosphatase activity trend shows as contrary to DH activity (Reddy et al. 2010).

Moreover, the low-frequency factor in AC can play a crucial role in stimulating enzymes in the bio-electroactive reactor. Since laccase and DH enzyme activity in a mixed microbial culture has enhanced by a 10 Hz frequency on the reactor biofilm (Moghiseh and Rezaee 2021), but a radio-frequency AC (10 MHz) had a harmful electromagnetic field bio-electric effect on polar molecules of biofilm matrix that exacerbated the antibiotic effect on the bacterial biofilm (Caubet et al. 2004).

As a result, electrical current can stimulate the enzymatic activity of microorganisms on the bio-electrodes and its higher efficiency in biotransformation than only enzymatic or biological reactors. Nevertheless, there is no optimum applied voltage, especially for stimulating enzyme activity.

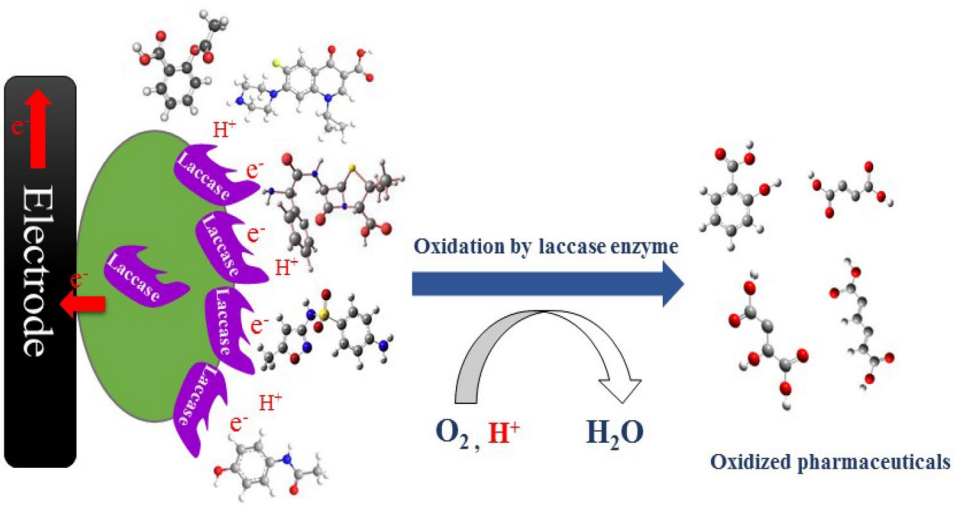

Fig. 3 The performance of the laccase enzyme at the bioreactor

It can depend on operating and design parameters, namely feed, membrane, electrode materials' properties, and electrode distance, which affect electron reactions and material transport (Chung et al. 2020).

Intermediates or by-products and the effect of BETs on the degradation pathways

Another issue is that the presence of pharmaceutical intermediate or by-product residues in the environment leads to health and environmental concerns (Caban et al. 2016). Their negative long-time and accumulative effects on living things are confirmed in several works of the literature (Patel et al. 2019; Rivera-Utrilla et al. 2013; Martz 2012; Xiao et al. 2021; Ahmed et al. 2017; Tiwari et al. 2017; Murdoch 2015). Pharmaceuticals undergo hydrolytic, biological, and chemical reactions in WWTPs where intermediates of these compounds are thus abundant. Their fate is an important issue because of the resistance of these components to biodegradation and/or providing a synergist effect on microbial resistance. Therefore, it is necessary to detect and identify the possible degradation pathways of pharmaceuticals by analyzing their intermediates using appropriate techniques.

Although the measurement devices of pharmaceuticals are available and inexpensive (Siddiqui et al. 2017), the detection of by-products or intermediates must be performed by advanced devices. Graffius et al. (2017) identified the volatile amines in pharmaceutical compounds by GC-FID instrument. In addition, they used this instrument for analyzing other components. However, LC–MS/MS may be more suitable for analyzing pharmaceutical residues in influent and effluent from WWTPs than other devices (Shraim et al. 2017).

Moreover, the used processes for pharmaceutical degradation have influenced the production of intermediates and their degradation pathway. Advanced oxidation processes produce hydrogen peroxide (H_2O_2) or hydroxyl radical ($^{\cdot}OH$) abundantly, but they may decompose recalcitrant (e.g., pharmaceutical) intermediates entirely for a longer time. For example, plasma processes need to combine other strategies for enhancement $^{\cdot}OH$ in comparison with other advanced oxidation processes (Banaschik et al. 2018).

The effect of BETs supplied by AC on the biodegradation pathway of aspirin is shown in Fig. 4. Aspirin was analyzed using LC–MS and GC–MS by Moghiseh and Rezaee (2021). They found salicylic acid, phenol, and organic and inorganic acids in the proposed pathway by degradation of aspirin. Phenol rings have degraded using enzyme metabolic (e.g., laccase enzyme) based on Fig. 4. In addition, in this pathway, inorganic acids such as acetic and oxalic acids are converted into water and carbon dioxide. The proposed pathway from the biodegradation of phenol ring using BETs supplied by DC power exhibited the same organic and inorganic acids, e.g., propanoic acid and then oxalic acid and acetic acid, that were detected using the GC–MS instrument (Moghiseh et al. 2019a, b). It is reported that the toxicity of produced final intermediates from the phenol electrobiodegradation is less than the main compound (Moghiseh et al. 2019a, b).

Moreover, hydroxy-ibuprofen is identified as an essential by-product in the mineralization pathway of ibuprofen. Afterward, this by-product can be decomposed into inorganic intermediates using the coupled MFC with a constructed wetland bioreactor (CW-MFC) because of the adaptation and growth of various bacteria species and production-induced enzymes in the bioreactor (Li et al. 2019).

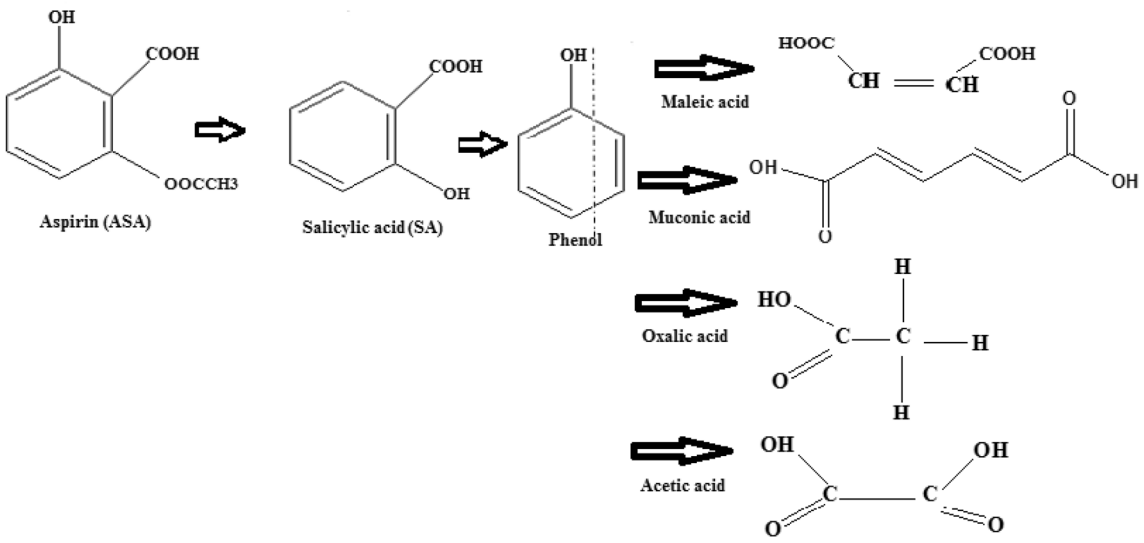

Fig. 4 The effect of alternating current (AC) on the biodegradation pathway of aspirin (Moghiseh and Rezaee 2021)

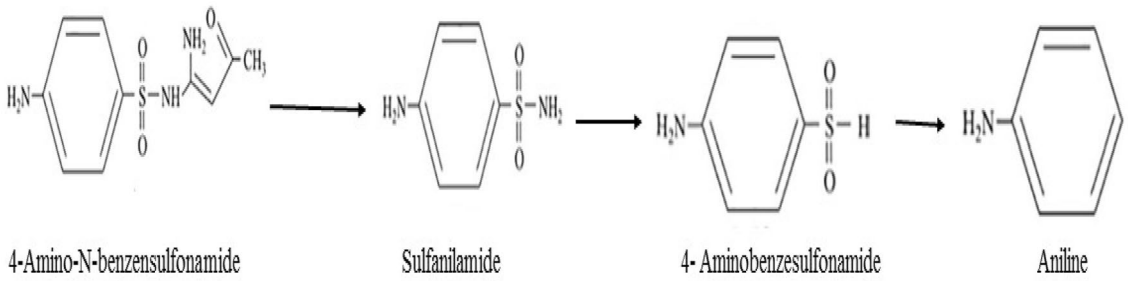

Fig. 5 Main pathway of biodegradation of SMX (Wu et al. 2020)

In addition, the degradation pathways of antibiotic drugs are observed to be more complicated than anti-inflammatory and analgesic drugs because of their multi-ring structure and degradation mechanism. Several researchers have shown that low-weight acids are the final by-product in an electro-biodegradation reactor. Wu et al. (2020) analyzed SMX by-products using LC–MS/MS and depicted three potential pathways of biodegradation of SMX in MFC. The main pathway of SMX is started from the breakage of nitrogen and oxygen in SMX to aniline as the final product by sulfate-reducing bacteria (SRB) activity (Fig. 5).

The removal of SMX attributed to the growth of main microorganism species in mixed cultures by Wu et al. (2020). However, the probable components of the pathway of SMX biodegradation in the integrated reactor of up-flow anaerobic and bio-electrochemical are detected in the low-molecular-weight compounds by UPLC analysis. Hu et al. (2020) only presented one pathway for the biodegradation of SMX. Finally, components convert into CH_4 gas. Another high-consumption drug is carbamazepine. Zou et al. (2020) performed carbamazepine degradation under a MEUC, in which they detected five essential intermediates. A low-weight compound such as succinic acid as end-intermediate was obtained by the reaction of hydroxyl radical with benzene ring in the studied reactor.

Conclusions and outlooks

BETs are novel approaches for treating high-consumption active pharmaceutical components, one class of refractory or recalcitrant contaminants. This study reviewed the efficiency and mechanism of BETs for degrading anti-inflammatory and analgesic drugs other than antibiotics, and recent prospects of BETs in stimulating induced enzymes and oxidative species (e.g., hydroxyl radical), which influence the degradation of high-consumption pharmaceutical compounds. The mineralization of pharmaceutical contaminants is performed by the oxidation and reduction reactions between microorganisms and electrodes using a low current, voltage, and frequency during a low reaction time. In addition, the proposed pathways and intermediate components are short and non-toxic for most pharmaceuticals.

While the operated bioreactors often are supplied with DC power, it is needed to provide the bioreactor with AC power and other currents.

Moreover, applying mathematical modeling and theories is another issue for future studies that can confirm the BETs' mechanism and performance for treating contaminants and their intermediates at different operation modes. Finally, the kinetics used in BETs or combined or coupled BETs with other processes can introduce to compare with other systems, which shows the degradation rate of contaminants per time. Therefore, BETs provide advanced treatment for micro-pollutants such as pharmaceuticals. It also suggests that different stimulations of the electrical bioreactor can be investigated in future research.

Author contributions All the authors contributed to the study conceptualization and methodology. In addition, ZM performed the investigation and formal analysis of the research and wrote the manuscript. All the authors read and approved the final manuscript.

Funding This study was supported by the Shoushtar Faculty of Medical Sciences, Shoushtar, Iran, from grant I.R.SHOUSHTAR.REC.1400.015.

Data availability statement The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Conflict of interests The authors declare that they have no conflict of interests.

Ethics approval and consent to participate This research did not involve any human participants and/or animals.

Consent for publication The authors accepted the publication.

References

Agrawal K, Chaturvedi V, Verma P (2018) Fungal laccase discovered but yet undiscovered. Bioresour Bioprocess 5(4):1–12

Ahmad A, Priyadarshani M, Das S, Ghangrekar MM (2021) Role of bioelectrochemical systems for the remediation of emerging contaminants from wastewater: a review. J Basic Microbiol 62(3–4):201–222

Ahmed MB, Zhou JL, Ngo HH, Guo W, Thomaidis NS, Xu J (2017) Progress in the biological and chemical treatment technologies for emerging contaminant removal from wastewater: a critical review. J Hazard Mater 323:274–298

Al-Riyami IM, Ahmed M, Al-Busaidi A, Choudri BS (2018) Antibiotics in wastewaters: a review with focus on Oman. Appl Water Sci 8:199

Alygizakis NA, Gago-Ferrero P, Borova VL, Pavlidou A, Hatzianestis I, Thomaidis NS (2016) Occurrence and spatial distribution of 158 pharmaceuticals, drugs of abuse and related metabolites in offshore seawater. Sci Total Environ 541:1097–1105

Asensio Y, Llorente M, Tejedor-Sanz S, Fernandez-Labrador P et al (2021) Microbial electrochemical fluidized bed reactor (ME-FBR): an energy-efficient advanced solution for treating real brewery wastewater with different initial organic loading rates. J Environ Chem Eng 9:106619

Banaschik R, Jablonowski H, Bednarski PJ, Kolb JF (2018) Degradation and intermediates of diclofenac as instructive example for decomposition of recalcitrant pharmaceuticals by hydroxyl radicals generated with pulsed corona plasma in water. J Hazard Mater 342:651–660

Bilal M, Iqbal H, Barceló D (2020) Perspectives on the feasibility of using enzymes for pharmaceutical removal in wastewater. Removal and degradation of pharmaceutically active compounds in wastewater treatment. Springer, Cham, pp 119–143

Caban M, Białk-Bielińska A, Stepnowski P, Kumirska J (2016) Current issues in pharmaceutical residues in drinking water. Curr Anal Chem 12(3):249–257

Caubet R, Pedarros-Caubet F, Chu M, Freye E, de Bele'm RM et al (2004) A radio frequency electric current enhances antibiotic efficacy against bacterial biofilms. Antimicrob Agents Chemother 48:4662–4664

Cecconet D, Devecseri M, Callegari A, Capodaglio AG (2018) Effects of process operating conditions on the autotrophic denitrification of nitrate-contaminated groundwater using bioelectrochemical systems. Sci Total Environ 613–614:663–671

Chakraborty I, Sathe SM, Khuman CN, Ghangrekar MM (2020) Bioelectrochemically powered remediation of xenobiotic compounds and heavy metal toxicity using microbial fuel cell and microbial electrolysis cell. Mater Sci Technol 3:104–115

Chatterjee P, Dessi P, Kokko M, Lakaniemi AM, Lens P (2019) Selective enrichment of biocatalysts for bioelectrochemical systems: a critical review. Renew Sustain Energy Rev 109:10–23

Chaturvedi P, Giri BS, Shukla P, Gupta P (2021) Recent advancement in remediation of synthetic organic antibiotics from environmental matrices: challenges and perspective. Bioresour Technol 319:124161

Chen M, Xu J, Dai R, Wu Z, Liu M, Wang Z (2019) Development of a moving-bed electrochemical membrane bioreactor to enhance removal of low-concentration antibiotic from wastewater. Bioresour Technol 293:122022

Cheng Z, Hu X, Sun Z (2016) Microbial community distribution and species analysis in the bio-electrochemical system treating low concentration cefuroxime. J Chem Eng 303:137–144

Cho S-H, Shim J, Moon S-H (2009) Detoxification of simulated textile wastewater using a membraneless electrochemical reactor with immobilized peroxidase. J Hazard Mater 162(2–3):1014–1018

Chung TH, Meshref MNA, Hai FI, Al-Mamun A, Dhar BR (2020) Microbial electrochemical systems for hydrogen peroxide synthesis: critical review of process optimization, prospective environmental applications, and challenges. Bioresour Technol 313:123727

Deutzmann JS, Sahin M, Spormann AM (2015) Extracellular enzymes facilitate electron uptake in biocorrosion and bioelectrosynthesis. Mbio 6(2):e0049615

Dogan A, Płotka-Wasylka J, Kempińska-Kupczyk D, Namieśnik J, Kot-Wasik A (2020) Detection, identification and determination of chiral pharmaceutical residues in wastewater: problems and challenges. Trends Analyt Chem 122:115710

Eibes G, Debernardi G, Feijoo G, Moreira MT, Lema JM (2011) Oxidation of pharmaceutically active compounds by a ligninolytic fungal peroxidase. Biodegradation 22:539–550

Fatta-Kassinos D, Meric S, Nikolaou A (2011) Pharmaceutical residues in environmental waters and wastewater: current state of knowledge and future research. Anal Bioanal Chem 399:251–275

Feng L, van Hullebusch ED, Rodrigo MA, Esposito G, Oturan MA (2013) Removal of residual anti-inflammatory and analgesic pharmaceuticals from aqueous systems by electrochemical advanced oxidation processes. A review. Chem Eng J 228:944–964

Fernando EY, Keshavarz T, Kyazze G (2019) The use of bioelectrochemical systems in environmental remediation of xenobiotic: a review. J Chem Technol Biotechnol 94:2070–2080

Freguia S, Virdis B, Harnisch F, Keller J (2012) Bioelectrochemical systems: microbial versus enzymatic catalysis. Electrochim Acta 82:165–174

Gadkari S, Gu S, Sadhukhanb J (2018) Towards automated design of bioelectrochemical systems: a comprehensive review of mathematical models. Chem Eng Sci 343:303–316

Ghangrekar MM, Sathe SM, Chakraborty I (2020) In situ bioremediation techniques for the removal of emerging contaminants and heavy metals using hybrid microbial electrochemical technologies. Emerging technologies in environmental bioremediation. Elsevier, Amsterdam, pp 233–255

Githinji LJM, Musey MK, Ankumah RO (2011) Evaluation of the fate of ciprofloxacin and amoxicillin in domestic wastewater. Water Air Soil Pollut 219:191–201

Graffius GC, Jocher BM, Zewge D, Halsey HM, Lee G et al (2017) Generic gas chromatography-flame ionization detection method for quantitation of volatile amines in pharmaceutical drugs and synthetic intermediates. J Chromatogr A 1518:70–77

Griffith DR (2013) Natural and synthetic estrogens in wastewater treatment plant effluent and the coastal ocean [dissertation]. Massachusetts Institute of Technology and Woods Hole Oceanographic Institution

Guo X, Yan Z, Zhang Y, Kong X, Kong D, Shan Z, Wang N (2017) Removal mechanisms for extremely high-level fluoroquinolone antibiotics in pharmaceutical wastewater treatment plants. Environ Sci Pollut Res 24:8769–8777

Guo R, Xu X, Sun Z, Hu X (2022) Performance and bacterial community of bio-electrochemical system treating simulated domestic wastewater containing low concentration of cephalosporin antibiotics. Environ Technol 43(6):893–906

Harnisch F, Gimkiewicz C, Bogunovic B, Kreuzig R, Schröder U (2013) On the removal of sulfonamides using microbial bioelectrochemical systems. Electrochem Commun 26:77–80

Haroune L, Saibi S, Cabana H, Bellenger J-P (2017) Intracellular enzymes contribution to the biocatalytic removal of pharmaceuticals by Trametes hirsute. Environ Sci Technol 51(2):897–904

Hartl M, García-Galan MJ, Matamoros V, Fernandez-Gatell M, Rousseau PLD, Du Laing G et al (2021) Constructed wetlands operated as bioelectrochemical systems for the removal of organic micropollutants. Chemosphere 271:129593

Hassan M, Zhu G, Lu Y, Al-Falahi AH, Lu Y, Huang S, Wan Z (2021) Removal of antibiotics from wastewater and its problematic effects on microbial communities by bioelectrochemical technology: current knowledge and future perspectives. Environ Eng Res 26(1):190405

Hernando MD, Mezcua M, Fern'andez-Alba AR, Barcel'o D (2006) Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments. Talanta 69:334–342

Hey-Mogensen M, Goncalves RLS, Orr AL, Brand MD (2014) Production of superoxide/H_2O_2 by dihydroorotate dehydrogenase in rat skeletal muscle mitochondria. Radic Biol 72:149–155

Hoseinzadeh E, Rezaee A, Farzadkia M (2018) Nitrate removal from pharmaceutical wastewater using microbial electrochemical system supplied through low frequency-low voltage alternating electric current. Bioelectrochemistry 120:49–56

Hu D, Min H, Chen Z, Zhao Y, Cui Y, Zou X, Wu P et al (2019) Performance improvement and model of a bio-electrochemical system built-in up-flow anaerobic sludge blanket for treating b-lactams pharmaceutical wastewater under different hydraulic retention time. Water Res 164:114915

Hu D, Min H, Wang H, Zhao Y, Cui Y et al (2020) Performance of an up-flow anaerobic bio-electrochemical system (UBES) for treating sulfamethoxazole (SMX) antibiotic wastewater. Bioresour Technol 305:123070

Huang L, Cheng S, Chen G (2011) Bioelectrochemical systems for efficient recalcitrant wastes treatment. J Chem Technol Biotechnol 86:481–491

Huang A, Yan M, Lin J, Xu L, Gong H, Gong H (2021) A review of processes for removing antibiotics from breeding wastewater. Int J Environ Res Public Health 18:4909

Ismail ZZ, Habeeb AA (2017) Experimental and modeling study of simultaneous power generation and pharmaceutical wastewater treatment in microbial fuel cell based on mobilized biofilm bearers. Renew Energy 101:1256–1265

Jin S, Yang F, Liao T, Hui Y, Xu Y (2008) Seasonal variations of estrogenic compounds and their estrogenicities in influent and effluent from a municipal sewage treatment plant in China. Environ Toxicol Chem 27(1):146–153

Karthikeyan KG, Meyer MT (2006) Occurrence of antibiotics in wastewater treatment facilities in Wisconsin, USA. Sci Total Environ 361:196–207

Khan W, Nam J-Y, Woo H, Ryu H, Kim S, Maeng SK, Kim H-C (2019) A proof of concept study for wastewater reuse using bioelectrochemical processes combined with complementary post-treatment technologies. Environ Sci Water Res Technol 5(8):1489–1498

Kong D, Liang B, Lee D-J, Wang A, Ren N (2014) Effect of temperature switchover on the degradation of antibiotic chloramphenicol by biocathode bioelectrochemical system. Science Direct 26:1689–1697

K'oreje KO, Vergeynst L, Ombaka D, De Wispelaere P, Okoth M, Van Langenhove H, Demeestere K (2016) Occurrence patterns of pharmaceutical residues in wastewater, surface water and groundwater of Nairobi and Kisumu city, Kenya. Chemosphere 149:238–244

Kumar AK, Reddy MV, Chandrasekhar K, Srikanth S, Mohan SV (2012) Endocrine disruptive estrogens role in electron transfer: bio electrochemical remediation with microbial mediated electrogenesis. Bioresour Technol 104:547–556

Kumar Thalla A, Shree Vannarath A (2020) Occurrence and environmental risks of nonsteroidal anti-inflammatory drugs in urban wastewater in the southwest monsoon region of India. Environ Monit Assess 192:193

Li H, Zhang S, Yang X-L, Yang Y-L, Xu H et al (2019) Enhanced degradation of bisphenol A and ibuprofen by an up-flow microbial fuel cell-coupled constructed wetland and analysis of bacterial community structure. Chemosphere 217:599–608

Li N, Zhang X, Zhao M, Zhang Y, Yuan Y, Lu X et al (2020) Integrating solar photovoltaic capacitor into algal-bacterial photo-bioelectrochemical system towards all-weather synchronous enhanced antibiotic and nitrogen removal from wastewater. J Clean Prod 272:122661

Li Z, Dai R, Yang B, Chen M, Wang X, Wang Z (2021) An electrochemical membrane biofilm reactor for removing sulfonamides from wastewater and suppressing antibiotic resistance development: performance and mechanisms. J Hazard Mater 404:124198

Liu H, Hu Q, Chen N, Feng C (2021) Effects of trace elements and current densities on denitrification, microbe growth, ATP generation and enzyme activity in a bio-electrochemical reactor. Int J Electrochem Sci 16:1–16

Lloret L, Eibes G, Lu-Chau TA, Moreira MT, Feijoo G, Lema JM (2010) Laccase-catalyzed degradation of anti-inflammatories and estrogens. Biochem Eng J 51(3):124–131

Lloret L, Eibes G, Moreira MT, Feijoo G, Lema JM (2013) On the use of a high-redox potential laccase as an alternative for the transformation of nonsteroidal anti-inflammatory drugs (NSAIDs). J Mol Catal B Enzym 97:233–242

Martz M (2012) Effective wastewater treatment in the pharmaceutical industry. Pharm Eng 32(6):48–62

Matongo S, Birungi G, Moodley B, Ndungu P (2015) Pharmaceutical residues in water and sediment of Msunduzi River, KwaZulu-Natal, South Africa. Chemosphere 134:133–140

Miran W, Nawaz M, Jang J, Lee DS (2017) Chlorinated phenol treatment and in situ hydrogen peroxide production in a sulfate-reducing bacteria enriched bioelectrochemical system. Water Res 117:198–206

Moghiseh Z, Rezaee A (2021) Removal of aspirin from aqueous solution using electro-active bacteria induced by alternating current. Environ Sci Pollut Res 28:25327–25338

Moghiseh Z, Rezaee A, Ghanati F, Esrafili A (2019a) Metabolic activity and pathway study of aspirin biodegradation using a microbial electrochemical system supplied by an alternating current. Chemosphere 232:35–44

Moghiseh Z, Rezaee A, Dehghani S, Esrafili A (2019b) Microbial electrochemical system for the phenol degradation using alternating current: metabolic pathway study. Bioelectrochemistry 130:107230

Moghiseh Z, Rezaee A, Dehghani S (2020) Minimization of hazardous sludge production using a bioelectrochemical system supplied by an alternating current electric field. Bioelectrochemistry 132:107446

Mook WT, Aroua MKT, Chakrabarti MH, Noor IM, Irfan MF, Low CTJ (2013) A review on the effect of bio-electrodes on denitrification and organic matter removal processes in bio-electrochemical systems. J Ind Eng Chem 19(1):1–13

Murdoch K (2015) Pharmaceutical pollution in the environment: Issues for Australia, New Zealand and Pacific Island countries. National Toxics Network. 1–36

Nadais H, Li X, Alves N, Couras C, Andersen HR, Angelidaki I, Zhang Y (2018) Bio-Electro-Fenton process for the degradation of nonsteroidal anti-inflammatory drugs in wastewater. Chem Eng J 338:401–410

Nakada N, Nyunoya H, Nakamura M, Hara A, Iguchi T, Takada H (2004) Identification of estrogenic compounds in wastewater effluent. Environ Toxicol Chem 23(12):2807–2815

Nikhil GN, Suman P, Mohan SV, Swamy YV (2017) Energy-positive nitrogen removal of pharmaceutical wastewater by coupling heterotrophic nitrification and electrotrophic denitrification. Chem Eng Sci 326:715–720

Ouarda Y, Tiwari B, Azaïs A, Vaudreuil MA, Ndiaye SD, Drogui P et al (2018) Synthetic hospital wastewater treatment by coupling

submerged membrane bioreactor and electrochemical advanced oxidation process: kinetic study and toxicity assessment. Chemosphere 193:160–169

Patel M, Kumar R, Kishor K, Mlsna T, Pittman UC Jr, Mohan D (2019) Pharmaceuticals of emerging concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chem Rev 119:3510–3673

Peng Xh, Cao J, Xie B, Duan M, Zhao J (2020) Evaluation of degradation behavior over tetracycline hydrochloride by microbial electrochemical technology: performance, kinetics, and microbial communities. Ecotoxicol Environ Saf 188:109869

Praveenkumarreddy Y, Vimalkumar K, Rajendran Ramaswamy B, Kumar V, Kumar Singhal R, Basu H, Mallappa Gopal C et al (2021) Assessment of nonsteroidal anti-inflammatory drugs from selected wastewater treatment plants of Southwestern India. Emerg Contam 7:43–51

Pun A, Boltes K, Leton P, Esteve-Nunez A (2019) Detoxification of wastewater containing pharmaceuticals using horizontal flow bioelectrochemical filter. Bioresour Technol 7:100296

Pylypchuk IV, Daniel G, Kessler VG, Seisenbaeva GA (2020) Removal of diclofenac, paracetamol, and carbamazepine from model aqueous solutions by magnetic sol-gel encapsulated horseradish peroxidase and lignin peroxidase composites. Nanomaterials 10(2):282

Qin S, Hou Y, Yuan G, Yu Z, Tu L, Yan Y, Chen S, Sun J et al (2020) Different refractory organic substances degradation and microbial community shift in the single-chamber bio-photoelectrochemical system. Bioresour Technol 307:123176

Qiu B, Hu Y, Tang C, Chen Y, Cheng J (2022) Degradation of diclofenac via sequential reduction-oxidation by Ru/Fe modified biocathode dual-chamber bioelectrochemical system: performance, pathways and degradation mechanisms. Chemosphere 291:132881

Quejigo JR, Tejedor-Sanz S, Schroll R, Esteve-Núñez A (2019) Electrodes boost microbial metabolism to mineralize antibiotics in manure. Bioelectrochemistry 128:283–290

Ramírez-Vargas CA, Prado A, Arias CA, Carvalho PN, Esteve-Núñez A, Brix H (2018) Microbial electrochemical technologies for wastewater treatment: principles and evolution from microbial fuel cells to bioelectrochemical-based constructed wetlands. Water 10(9):1128

Ratanapongleka K, Punbut S (2018) Removal of acetaminophen in water by laccase immobilized in barium alginate. Environ Technol 39(3):336–345

Reddy MV, Srikanth S, Mohan SV, Sarma PN (2010) Phosphatase and dehydrogenase activities in anodic chamber of single chamber microbial fuel cell (MFC) at variable substrate loading conditions. Bioelectrochemistry 77(2):125–132

Ren L, Chen M, Zheng J, Li Z, Tian C, Wang Q, Wang Z (2021) Efficacy of a novel electrochemical membrane-aerated biofilm reactor for removal of antibiotics from micro-polluted surface water and suppression of antibiotic resistance genes. Bioresour Technol 338:125527

Rivera-Utrilla J, Sanchez-Polo M, Angeles Ferro-Garcia M, Prados-Joya G, Ocampo-Pérez R (2013) Pharmaceuticals as emerging contaminants and their removal from water. A review. Chemosphere 93(7):1268–1287

Rodriguez-Mozaz S, Vaz-Moreira I, Varela Della Giustina S, Llorca M, Barceló D, Schubert S, Berendonk TU, Michael-Kordatou I et al (2020) Antibiotic residues in final effluents of European wastewater treatment plants and their impact on the aquatic environment. Environ Int 140:105733

Sacher F, Ehmann M, Gabriel S, Graf C, Brauch HJ (2008) Pharmaceutical residues in the river Rhine—results of a one-decade monitoring programme. J Environ Monit 10(5):664–670

Sathe SM, Chakraborty I, Dubey BK, Ghangrekar MM (2022) Microbial fuel cell coupled Fenton oxidation for the cathodic degradation of emerging contaminants from wastewater: applications and challenges. Environ 204:112135

Schröder P, Helmreich B, Škrbić B, Carballa M, Papa M, Pastore C et al (2016) Status of hormones and painkillers in wastewater effluents across several European states considerations for the EU watch list concerning estradiols and diclofenac. Environ Sci Pollut Res 23:12835–12866

Shraim A, Diab A, Alsuhaimi A, Niazy E, Metwally M, Amad M et al (2017) Analysis of some pharmaceuticals in municipal wastewater of Almadinah Almunawarah. Arab J Chem 10(1):S719–S729

Siddiqui MR, AlOthman ZA, Rahman N (2017) Analytical techniques in pharmaceutical analysis: a review. Arab J Chem 10(1):S1409–S1421

Singh A, Saluja S (2021) Microbial degradation of antibiotics from effluents. Recent advances in microbial degradation. Springer, Singapore, pp 389–404

Song H-L, Lu Y-X, Yang X-L, Xu H, Singh RP, Du K-X, Yang Y-L (2020) Degradation of sulfamethoxazole in low-C/N ratio wastewater by a novel membrane bioelectrochemical reactor. Bioresour Technol 305:123029

Sun J, Xu W, Yang P, Li N, Yuan Y, Zhang H et al (2019) Enhanced oxytetracycline removal coupling with increased power generation using a self-sustained photo bioelectrochemical fuel cell. Chemosphere 221:21–29

Syed Z, Sogani M, Dongre A, Kumar A, Sonu K, Sharma G, Bhushan Gupta A (2021) Bioelectrochemical systems for environmental remediation of estrogens: a review and way forward. Sci Total Environ 780:146544

Tang T, Hou J, Ai S, Qiu Y, Ma Q, Han R (2010) Electroenzymatic oxidation of bisphenol A (BPA) based on the hemoglobin (Hb) film in a membraneless electrochemical reactor. J Hazard Mater 181(1–3):413–418

Tiwari B, Sellamuthu B, Ouarda Y, Drogui P, Tyagi DR, Buelna G (2017) Review on fate and mechanism of removal of pharmaceutical pollutants from wastewater using biological approach. Bioresour Technol 224:1–12

Tyumina EA, Bazhutin GA, Cartagena Gomez ADP, Ivshina IB (2020) Nonsteroidal anti-inflammatory drugs as emerging contaminants. Microbiology 89:148–163

Vasileva E, Parvanova-Mancheva T, Beschkov V, Alexieva Z, Gerginova M, Peneva N (2021) Effects of constant electric field on biodegradation of phenol by free and immobilized cells of *Bradyrhizobium japonicum* 273. Chem Engineering 5(4):1–13

Wang C, Zhang H, Ren D, Li Q, Zhang S, Feng T (2015a) Effect of direct-current electric field on enzymatic activity and the concentration of Laccase. Indian J Microbiol 55:278–284

Wang H, Luo H, H. Fallgren P, Jin S, Ren ZJ, (2015b) Bioelectrochemical system platform for sustainable environmental remediation and energy generation. Biotechnol Adv 33(3–4):317–334

Wang X, Wang Y, Zhang J, Duanmu P, Zheng L, Hasson SU, Baldwin A, Wong I, Zhao C (2021) Degradation of diclofenac in urine by electro-permanganate process driven by microbial fuel cells. Water 13:2047

Wen X, Jia Y, Li J (2010) Enzymatic degradation of tetracycline and oxytetracycline by crude manganese peroxidase prepared from Phanerochaete chrysosporium. J Hazard Mater 177(1–3):924–928

Wu YC, Fu HY, Wen H, Chen FD, Dai ZN, Yang AL (2019) Degradation of diclofenac sodium in microbial fuel cells. IOP Conf Ser Earth Environ Sci 369:012011

Wu D, Sun F, Chua FJD, Zhou Y (2020) Enhanced power generation in microbial fuel cell by an agonist of electro-active biofilm-sulfamethoxazole. Chem Eng Sci 384:123238

Xiao Y, Zhao F, Penuelas J, Huang Q, Zhu Y-G (2021) Super pathogens from environmental biotechnologies threaten global health. Natl Sci Rev 8(9):8nwab110

Xu H, Quan X, Xiao Z, Chen L (2018) Effect of anodes decoration with metal and metal oxides nanoparticles on pharmaceutically active compounds removal and power generation in microbial fuel cells. Chem Eng J 335:539–547

Xu L, Yu W, Graham N, Zhao Y, Qu J (2019) Application of integrated bioelectrochemical-wetland systems for future sustainable wastewater treatment. Environ Sci Technol 53(4):1741–1743

Xu P, Zheng D, Xie Z, He Q, Yu J (2020) The degradation of ibuprofen in a novel microbial fuel cell with PANi@CNTs/SS bio-anode and CuInS2 photo-catalytic cathode: property, efficiency and mechanism. J Clean Prod 265:121872

Xu W, Zou R, Jin B, Zhang G, Su Y, Zhang Y (2022) The ins and outs of pharmaceutical wastewater treatment by microbial electrochemical technologies. Sustain Horizons 1:100003

Yan W, Xiao Y, Yan W, Ding R, Wang S, Zhao F (2019) The effect of bioelectrochemical systems on antibiotics removal and antibiotic resistance genes: a review. Chem Eng J 358:1421–1437

Yang K, Ji M, Liang B, Zhao Y, Zhai S, Ma Z, Yang Z (2020) Bioelectrochemical degradation of monoaromatic compounds: current advances and challenges. J Hazard Mater 398:122892

Yeruva DK, Velvizhi G, Mohan SV (2016) Coupling of aerobic/anoxic and bioelectrogenic processes for treatment of pharmaceutical wastewater associated with bioelectricity generation. Renew Energy 98:171–177

Yuan H, He Z (2015) Integrating membrane filtration into bioelectrochemical systems as next generation energy-efficient wastewater treatment technologies for water reclamation: a review. Bioresour Technol 195:202–209

Zhang Y, GeiBen S-U (2010) In vitro degradation of carbamazepine and diclofenac by crude lignin peroxidase. J Hazard Mater 176(1–3):1089–1092

Zhang X, Feng H, Shan D, Shentu J, Wang M, Yin J et al (2014) The effect of electricity on 2–fluoroaniline removal in a bioelectrochemically assisted microbial system (BEAMS). Electrochim Acta 135:439–446

Zhang L, Yin X, Li SFY (2015) Bio-electrochemical degradation of paracetamol in a microbial fuel cell-Fenton system. Chem Eng Sci 276:185–192

Zhang S, Yang X-L, Li H, Song H-L, Wang R-C, Dai Z-Q (2017) Degradation of sulfamethoxazole in bioelectrochemical system with power supplied by constructed wetland-coupled microbial fuel cells. Bioresour Technol 244:345–352

Zhang G, Sui X, Xu Y, Jiao Y, Chang JS, Lee DJ (2022) Efficient removal of tetracycline using U-type continuous-flow bioelectrochemical system without ion exchange membrane or cathodic catalyst. Bioresour Technol 346:126677

Zhao Q, An J, Wang X, Li N (2021) In-situ hydrogen peroxide synthesis with environmental applications in bioelectrochemical systems: a state-of-the-art review. Int J Hydrog Energy 46(4):3204–3219

Zhou JL, Zhang ZL, Banks E, Grover D, Jiang JQ (2009) Pharmaceutical residues in wastewater treatment works effluents and their impact on receiving river water. J Hazard Mater 166(2–3):655–661

Zhou Y, Shi C, Fan M, Feng Y, Xu Y, Chen Y (2019) The efficient biodegradation of dimethyl phthalate using an anaerobic bioelectrochemical system. J Chem Technol Biotechnol 94(9):2935–2943

Zhou L, Jiang Q, Sun S, Wu Y, Li T, Gao Y et al (2022) Acetate stimulates tetracycline biodegradation pathways in bioelectrochemical system. Sep Purif Technol 286:120481

Zhu M, Zhang M, Yuan Y, Zhang P, Du S, Ya T et al (2021) Responses of microbial communities and their interactions to ibuprofen in a bio-electrochemical system. J Environ Manage 289:112473

Ziylan A, Ince NH (2011) The occurrence and fate of anti-inflammatory and analgesic pharmaceuticals in sewage and fresh water: treatability by conventional and non-conventional processes. J Hazard Mater 187:24–36

Zou R, Tang K, Angelidaki I, Andersen HR, Zhang Y (2020) An innovative microbial electrochemical ultraviolet photolysis cell (MEUC) for efficient degradation of carbamazepine. Water Res 187:116451