

## CRITICAL REVIEW

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## From prescription to pollution: environmental behavior and breakdown of fluoxetine

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Fluoxetine (FLX), a widely prescribed antidepressant and one of the most prevalent pharmaceuticals detected in the environment, has piqued significant interest recently due to its persistence and potential ecological effects. Despite its widespread detection, no comprehensive review currently exists that focuses specifically on FLX's environmental behaviour. As a polyfluorinated synthetic organic compound, FLX serves as an ideal model for understanding the broader challenges faced by fluorinated pharmaceuticals. This review presents a critical and integrative assessment of FLX, beginning with its molecular structure and the role of the C–F bond in enhancing the chemical stability and recalcitrance. The review then explores its environmental fate, including its behaviour towards hydrolysis, photolysis, partitioning, susceptibility to microbial attack, potential for bioaccumulation, and interactions and joint toxicity with other co-existing pollutants. This is followed by a comprehensive and critical discussion of existing advanced removal techniques currently investigated for FLX removal. Despite some promising approaches, challenges remain due to the inherent stability of the C–F bond, the toxicity of by-products, and the complexity of the matrix. The review proposes treatment chains, such as adsorption (AC, biochar, nano-adsorbents), followed by chemical (AOPs, electro-Fenton, UVC/solar irradiation) and biological (MBBR, biofilters) as recommendations for future studies. In addition, the review also aims to highlight the need for environmental management of FLX, not only to mitigate its ecological footprint but also to offer broader insights into the class of polyfluorinated pharmaceuticals.

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### Water impact

The persistence of fluoxetine (FLX), a polyfluorinated pharmaceutical, highlights the need for innovative and efficient removal strategies beyond conventional treatment. Despite some promising degradation approaches, the inherent stability of the C–F bond, the toxicity of by-products, and the complexity of the matrix pose challenges. This review aims to highlight the need for environmental management of contaminants like FLX and suggest future work to prioritize sustainable, scalable, and feasible integrative solutions for its remediation.

## 1. Introduction

Fluoxetine (FLX), sold as Prozac®, belongs to the second generation of the SSRI (selective serotonin reuptake inhibitor) class of antidepressants and is considered a breakthrough drug for depression. Following its discovery and FDA approval in 1987, FLX has become one of the most prescribed antidepressants globally.<sup>1</sup> This is primarily because of its safety, therapeutic efficiency for all genders and ages, and fewer adverse effects, withdrawal symptoms, and dropouts. It is considered a first line of treatment for mental disorders, including depression, anxiety, phobias, obsessive-compulsive disorders, and bulimia nervosa.<sup>1,2</sup> It acts on the central nervous system and inhibits the uptake of neurotransmitter

serotonin (5-hydroxytryptamine or 5-HT) by the presynaptic neuron by blocking the serotonin transporters (or SERT) in the neural membrane. The mechanism of action of FLX and its metabolism in the body is summarized in Text S1, Fig. S1 and S2 of the SI.

With increasing incidences of psychiatric and mental disorders, the prescription and consumption of FLX have increased over the years.<sup>3–7</sup> Fig. 1 displays the most recent data by the OECD on antidepressant consumption (the USA was not a part of this study).<sup>8</sup> However, as mentioned elsewhere, FLX was ranked 31 on the top 300 best-selling drugs in 2020, with 21.9 million prescriptions in the US in 2017. In 2019, 27.1 million prescriptions were filled for FLX, making it among the top 200 most prescribed drugs for the year at rank 20.<sup>9</sup> Similarly, Canada has seen a 26% increase in the use of antidepressants from 2019–2023 (as shown in Fig. 2), with over 2.5 billion units (tablets/capsules)

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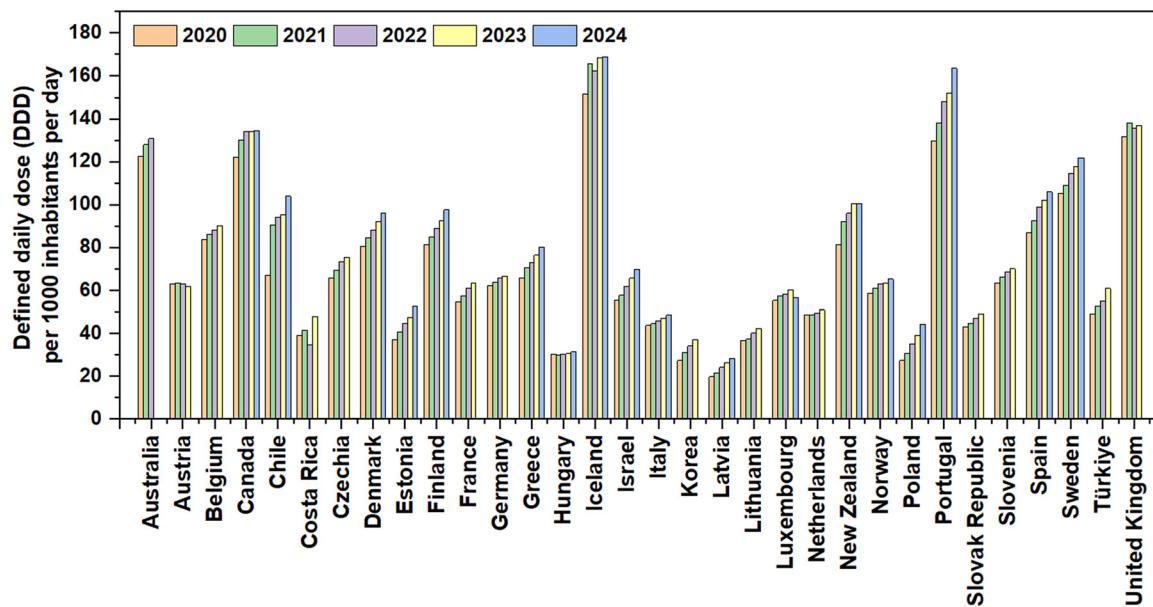


Fig. 1 Antidepressant consumption in OECD member countries (2020–2024).

dispensed in 2023.<sup>10</sup> In addition to North America, the use of SSRIs has also been on the rise in Europe. For instance, prescription data from Denmark show a gradual increase from 42.32 to 48.24 defined daily doses (DDD) per 1000

inhabitants between 2020 and 2024.<sup>11</sup> Similarly, data from Sweden and Spain indicate an increasing trend for FLX use for the same period, with DDD rising from 6.19 to 7.19, and from 7.06 to 8.08, respectively.<sup>11,12</sup> This increase in

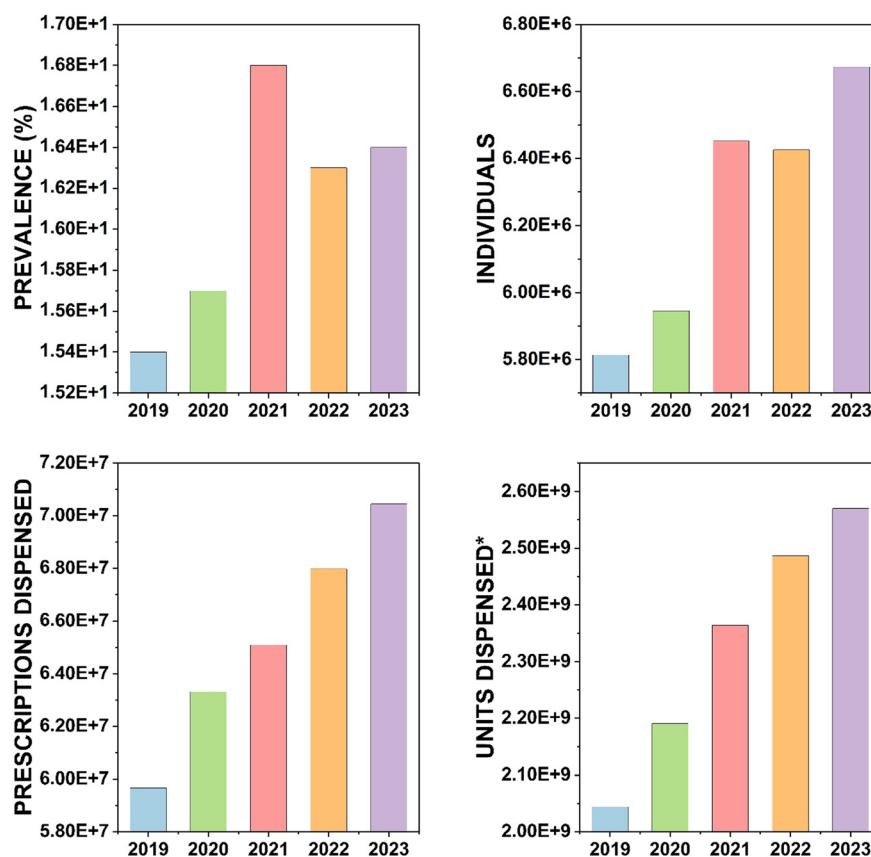


Fig. 2 Statistics on antidepressant use in Canada and variations (2019–2023).

consumption is well reflected in the concentrations and frequency of its detection in environmental matrices, such as wastewater, wastewater sludge, and surface water, *via* domestic and hospital effluents, industrial leaks, and poor disposal practices, as summarized in Table 1. Among environmental matrices, the highest FLX concentrations have been reported for wastewater treatment plant (WWTP) influents (reaching up to  $\sim 3.2 \mu\text{g L}^{-1}$ ), as WWTPs directly receive excreted drug residues from patients, and no chemical or biological methods of treatment have been applied to reduce their levels. In addition, the concentrations in Table 1 indicate highly variable removal efficiency for FLX during wastewater treatment. For instance, an analysis of grab samples collected from a WWTP in the UK by Evans *et al.* (2015) revealed an  $\sim 49\%$  efficiency, while another study by Paíga *et al.* (2019) in Portugal reported an efficiency of  $\sim 26\%$ .<sup>13,14</sup> In some cases, a negative removal efficiency was also observed. For example, for Canadian hospital wastewater monitoring, a removal efficiency ranging between and 171% and 40.2% was calculated based on the concentrations reported for the influent and effluent.<sup>15</sup> The negative values could indicate metabolite-back transformation, desorption, or sampling variability. Most of these samples are grab samples, which do not reflect the efficiency of the WWTP correctly. Despite this, an inconsistent, often incomplete removal of FLX has been reported during wastewater treatment.

Due to its poor degradation along the treatment chain and its relatively high lipophilicity, FLX persists beyond the influent stage, resulting in frequent detection in wastewater sludge and effluent, which can further carry FLX to surface water. Its frequent detection, persistence and toxicity in these environmental matrices instigate several concerns in aquatic and terrestrial ecosystems.<sup>13,15-18</sup> For instance, FLX uptake in fish has been reported to have consequences on growth and behavior, reproductive axis, metabolism, accumulation, and gene expression.<sup>19-22</sup> Similarly, wild European starlings (also known as songbirds), after exposure to FLX (2.7  $\mu\text{g}$  per day), displayed altered physiological and behavioral changes, such as higher aggression towards partners, poor courtship behavior, and reduced female attractiveness.<sup>23</sup> The hydrophobic and lipophilic nature of FLX allows its adsorption on biological membranes, resulting in its uptake, and bioaccumulation. The lipophilic nature of the drug also allows it to readily distribute into cells, including central nervous systems in the human body, and cross the blood-brain barrier (BBB) by passive lipophilic diffusion. This also poses a risk of neural disruptions by targeting serotonin pathways in non-target organisms, altered reproductive, growth, and physiological behaviors, including prey-predator dynamics, which can result in the disruption of the food web.<sup>24-26</sup> Further, in regard to its environmental presence, previous reports have indicated that the drug is stable towards hydrolysis, photolysis, and facile microbial

**Table 1** Summary of the occurrence of FLX in wastewater and wastewater sludge

Year	Matrix	Location	Concentration of FLX ( $\text{ng L}^{-1}$ )	Detection method	Ref.
2010	Raw influent	Douro River estuary (Portugal)	0.80–3.20 $\mu\text{g L}^{-1}$	HPLC-DAD	122
2011	Hydro matrix	Scotland (WWTPs)	<10	LC-MS	123
2012	Raw influent	5 STPs in Canada	9–26	LC-MS	124
2012	Final effluent				
2012	Effluent	Waterloo, Canada	5	LC-MS	22
2012	—	Italy	55–190	—	125
			10–63		
2013	Influent	UK	4.9–175.9	—	126
	Effluent		5.6–44.9		
2015	Influent	UK WWTP	51 $\pm$ 4.3	LC-MS	13
	Effluent		26		
2017	Influent	UK	36–436.5	—	127
	Effluent		33–66.5		
2019	Influent	WWTPs in Portugal	78	LC-MS/MS	14
	Effluent		57.5		
2019	Influent	Spain	77–207	LC-MS/MS	128
	Effluent		63–72		
2019	Raw influent	4 WTPs in Belgium	7.5–70	RPLC-MS/MS	16
2020	Raw influent	WWTP London, UK	50–58	LC-MS/MS	129
2022	Influent	Hospital wastewater, Canada	3.51	LC-MS/MS	15
	Effluent		2.1–9.5		
Year	Matrix	Location	Concentration of FLX ( $\text{ng g}^{-1}$ )	Detection method	Ref.
2011	Treated sludge and sediments	WWTP, Scotland	<10	LC-MS	18
2012	Treated sludge	WWTP, Sweden	144 $\pm$ 45	HF-LPME	130
2012	Primary sludge	STP, Canada	339	LC-MS	124
	Secondary sludge		94		
	Biosolids		74		
2015	Digested sludge	STP, Canada	85.6 $\pm$ 9.4	LC-MS	13
2019	Sewage sludge	STP, Brazil	90	LC-MS/MS	17



degradation, making it environmentally persistent.<sup>27–29</sup> This constant presence of FLX in both aqueous and solid matrices, along with its persistence and toxicity to non-target organisms, has rightly garnered attention recently. The number of publications addressing FLX in aquatic environments has increased markedly since 2010, as shown in Fig. 3, reflecting growing recognition of its importance, although significant research gaps remain in its treatment approaches. The drug has been identified as an emerging contaminant and demands immediate attention concerning its monitoring and degradation strategies.

Various researchers have investigated physical and chemical methods to tackle FLX-polluted waters; however, no method currently identified is sustainable, promising, and effective for potentially retrofitting treatment chains of current wastewater treatment plants (WWTPs). In order to overcome these challenges and present a low-energy, green, and economically feasible approach, several attempts have been made recently to degrade the recalcitrant FLX biologically. However, owing to the drug's low biodegradability, biodegradation attempts with microalgae, fungi, and bacteria (isolated and consortia) have displayed subpar results.<sup>30–33</sup> Previous reports have suggested that the current knowledge of bioremediation systems cannot handle polyfluorinated compounds due to evolutionary constraints.<sup>34–36</sup> While C–F bond cleaving enzymes are not rare, microbial intolerance to high concentrations of intracellular fluoride ions poses this limitation. Intracellular fluoride can deactivate enzymes, mimic phosphate in harmful ways, and disrupts cell's energy balance by collapsing the proton gradient across membranes. Due to this, very low concentrations of intracellular fluoride, as little as 70  $\mu$ M, are reported to be toxic to prokaryotic cells and

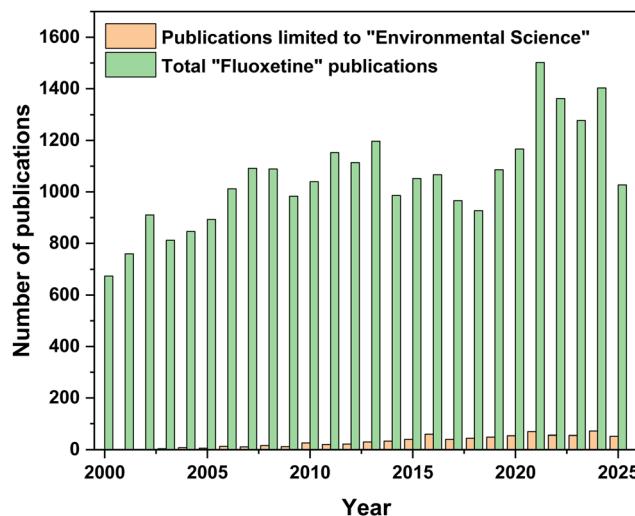
can result in cell death.<sup>36,37</sup> So, if a cell can defluorinate, it will generate fluoride ions, thereby causing cell death and putting a constraint on both microbial degradation and evolution. The same principle also makes the enrichment culturing an 'unpromising' method.<sup>36</sup> It is irrefutable that the efficiency of the employed removal technique depends on the structure of the pollutant, and its fate in the environment provides more insight into its behavior and breakdown profile. In this regard, the present review aims to (i) delineate the structural features of FLX, including fluorocarbon chemistry, which makes it persistent in the environment, (ii) elaborate on the fate of the drug in the environment, and (iii) comprehensively and critically discuss the existing removal methods for FLX, identify the challenges, and present prospects in the research area.

## 2. Structural features of FLX and fluorocarbon chemistry

The molecular structure of FLX contains two aromatic rings, one phenyl ring and one trifluoromethyl-substituted phenyl ring, connected by a substituted methoxy group (Fig. 4). The aliphatic side chains comprise a secondary amine functionality and a chiral carbon (giving rise to (*R*) and (*S*)-enantiomers of FLX). Although the two enantiomers have similar efficiency in blocking serotonin reuptake, their metabolism, half-life, renal clearance from the human body, and environmental behavior vary slightly.<sup>38,39</sup> For instance, the clearance and half-life of *R*-FLX are four times greater than those of *S*-FLX, as reported elsewhere.<sup>39</sup> Given its slower clearance and longer half-life, *R*-FLX is expected to be excreted and consequently released into the environment in greater quantities than the *S*-enantiomer. In addition, the stereoselective biodegradation in WWTPs often favours the transformation of *S*-FLX, leading to further enrichment of the more persistent and ecotoxicologically more relevant *R*-FLX in effluents.<sup>38</sup> However, at least one study has demonstrated preferential degradation of *R*-FLX under specific microbial conditions, indicating that enantioselective outcomes may vary with the microbial community and operational context.<sup>40</sup>

The structural features of FLX hinder facile microbial degradation and define its environmental persistence. To begin with, the presence of the secondary amine group ( $pK_a \sim 9.8\text{--}10.3$ ) indicates that FLX is a weak base and exists predominantly in its protonated or ionized form at circumneutral pH.<sup>30,41</sup> This not only improves the solubility of the drug at environmental pH but also stabilizes it against the nucleophilic attack.

Also, it is evident from the structure that the nitrogen heteroatom, which acts as an electron donor or Lewis base, is spatially well separated from the aromatic rings, suggesting that it does not significantly affect the  $\pi$ -electron delocalization of the rings.<sup>42</sup> The aromatic rings make the drug more hydrophobic and confer high affinity for sorption, thereby limiting its bioavailability. Further, the presence of



**Fig. 3** Annual number of publications on FLX for 2000–2025. Data retrieved from Scopus using relevant keywords (\*search strings used: (TITLE-ABS-KEY (fluoxetine) AND TITLE-ABS-KEY (wastewater OR aquatic OR river OR environment OR effluent OR lake) for studies limited to environmental science. For total FLX publications: (TITLE-ABS-KEY (fluoxetine))).



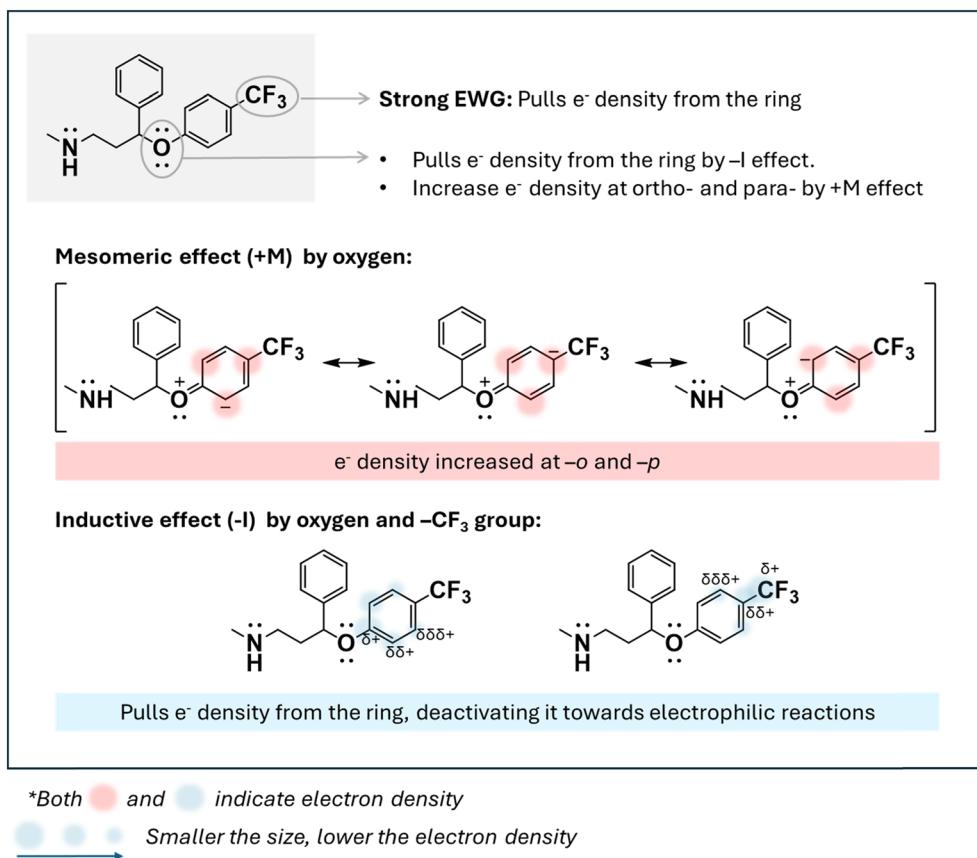


Fig. 4 Substituent effects on the trifluoromethyl-benzyl group in FLX.

an oxygen atom (in the phenoxy group, or ether linkage) and  $-CF_3$  substitution at the *para* position introduces some interesting effects. To begin with, fluorine has the highest electronegativity of all elements, and having three fluorine atoms attached to a single carbon unit makes the  $-CF_3$  a strong electron-withdrawing group (EWG). The fluorine atoms tend to pull electron density from the adjacent C, and the aromatic ring. This strong  $-I$  (negative inductive effect) of the trifluoromethyl group makes the ring less nucleophilic, thereby deactivating it towards electrophilic aromatic substitution reactions (EASR). This reduces the susceptibility of the drug to oxidative metabolism and confers metabolic stability in the environment. This also means that FLX is resistant to environmental breakdown processes, like those mediated by sunlight and radicals, in addition to microbes, as they proceed *via* electrophilic attack on the aromatic ring. This resistance keeps the aromatic rings intact, and FLX persists in the environment with long half-lives.

In addition, oxygen, being electronegative, exhibits a  $-I$  effect, while also exerting a positive mesomeric effect ( $+M$ ) *via* resonance. This means that oxygen tends to pull the electron density through the  $\sigma$  bond *via* an inductive component, while donating a pair of electrons into the  $\pi$  system (resonance) (Fig. 3). Generally, for oxygen directly attached to an aromatic ring, the  $+M$  effect is stronger than the  $-I$  effect, which suggests that oxygen increases the

electron density at the *ortho* and *para* positions of the ring, making it more reactive towards EASR. However, the  $-I$  of the  $CF_3$  substituent at the *para* position often dominates the  $+M$  of the oxygen atom and, overall, deactivates the ring by making it electron deficient. This indicates low reactivity of the aromatic ring and greater chemical stability of the drug. The presence of ether also makes it relatively resistant to hydrolysis under ambient conditions that further limit microbial cleavage.

It is noteworthy that the molecular structure of FLX possesses 3 C-F bonds, which is known to have the highest bond dissociation energy (BDE) among all C-X bonds. To strengthen, the BDE of the C-F bond usually ranges between 105 and 130 kcal mol $^{-1}$  (*i.e.*, 4.53–5.59 eV), compared to 81 kcal mol $^{-1}$  for C-Cl and 46 kcal mol $^{-1}$  for C-Br bonds.<sup>43</sup> As mentioned elsewhere, the C-F bond in trifluoromethyl ( $CF_3H$ ) has a BDE of 114.6 kcal mol $^{-1}$ .<sup>44</sup> In FLX, the proton in the trifluoromethyl group has been substituted by an aromatic ring (phenyl), which stabilizes the structure by inductive and resonance effects, thereby increasing the BDE of C-F in aromatic structures, and supporting the high chemical stability of FLX under environmental and treatment conditions.

Owing to these highly stable fluorinated bonds, FLX has been identified as a per- and poly-fluoroalkyl substance (PFAS), commonly referred to as a 'forever chemical', in line

with the OECD guidelines.<sup>34</sup> Overall, this lipophilic and stable chemical structure of FLX contributes to its environmental persistence, underscoring the need to understand its fate in real systems.

### 3. Environmental persistence and fate of FLX

Once released into the wastewater, the pharmaceutical residues can undergo physical, chemical, and biological transformations, determining their fate in the environment. Understanding the fate of the analyte is crucial for determining its behavior and toxicity, and aids in devising suitable methods for its degradation. This section, in this regard, outlines different courses, such as hydrolysis, photolysis, sorption and partition, microbial susceptibility, interactions with co-existing pollutants, and their single and combined toxicity, which could influence the occurrence, persistence, and toxicity of FLX. It is, however, important to note that in the 'real' world, these do not operate in isolation but work in integration to define the environmental behavior of any pollutant, including FLX. The different courses highlighted in this section aim to summarize the existing literature and provide a fundamental understanding of how these processes influence FLX's fate and transformation in environmental matrices with a water–sediment–biota continuum.

#### 3.1 Hydrolysis and photolysis

To understand the fate of the antidepressant FLX, Lam *et al.* (2005) investigated the direct and indirect photolysis of the drug in simulated sunlit waters ( $\sim 300$ –800 nm) at pH 6, 8 and 10. An aqueous solution of FLX (10  $\mu$ M) (pH 8) was observed to be susceptible to direct photolysis with a half-life of  $7 \pm 1$  days ( $55.2 \pm 3.6$  h) with a pseudo-first-order rate constant of  $0.0126 \pm 0.001$   $\text{h}^{-1}$ . Negligible degradation in controls stored in the dark confirms the contribution of only base-catalyzed direct photolysis (<5%) and no effect of thermal or hydrolytic degradation of the drug was found.<sup>45</sup> The thermal stability of the drug at pH > 2.5, with  $\geq 95\%$  of initial FLX for 8 weeks at temperatures of 5 and 30 °C, was also reported previously by Peterson *et al.* (1994).<sup>27</sup>

Although the study by Lam *et al.* (2005)<sup>45</sup> did not provide degradation rates for pH 6 and 10, degradation is expected to be faster at alkaline pH (pH 10) due to the prevalence of more neutral/anionic species that are more photoreactive, compared to slightly acidic pH. However, this must be viewed as a comparative trend, and it must be noted that FLX has demonstrated stability towards base, heat, humidity, and oxidative conditions and displayed degradation only under highly acidic conditions (pH < 1), which is not environmentally relevant.<sup>46,47</sup> Another study by Kwon and Armbrust (2006) conducted laboratory-scale studies to investigate the persistence of FLX in aquatic systems, including aqueous solutions (buffered solution pH 7,

synthetic humic water, and lake water), water/sediment systems and activated sludge media. The study reported that the drug was hydrolytically and photolytically stable for a period of 30 days.<sup>28</sup> Similarly, a more recent study by ref. 29 observed low photolysis rates for the degradation of FLX and FLX-SO<sub>4</sub> by hydrolysis in pure water and natural pH and under simulated sunlight.

Also, it must be noted that hydrolysis and photolysis frequently overlap in aquatic environments, as hydrolytic reactions may occur under irradiation and photolytic pathways are typically studied in aqueous systems; these processes should not be considered entirely isolated, particularly in the environmental context.

#### 3.2 Sorption and partition in water/sediment systems

The physicochemical properties of FLX allow for the prediction of its environmental fate, including biodegradability and partition in water/sediment systems. For instance, the octanol–water partition coefficient, or hydrophobic descriptor, represented by  $\log K_{\text{ow}}$ , defines its uptake in biological wastewater treatment processes. A  $\log K_{\text{ow}} < 2.5$  indicates low sorption potential,  $2.5 < \log K_{\text{ow}} < 4$  indicates medium sorption potential, while  $\log K_{\text{ow}} > 4$  indicates high sorption potential.<sup>30,48</sup> Additionally, the solid–water distribution coefficient ( $K_d$ ) is defined as the partition of a compound between the sludge and the water phase at equilibrium. For compounds with  $K_d > 300 \text{ L kg}^{-1}$  (*i.e.*  $\log K_d > 2.48$ ), sorption onto sludge is considered significant.<sup>49</sup> However, factors such as functional groups, their speciation with pH, organic matter, cation exchange capacity, ions, and clay also play crucial roles.<sup>50,51</sup>

FLX has a  $\log K_d = 2.76$ –3.78 ( $\log K_d > 2.7$ ) and  $\log K_{\text{ow}} > 4$  at circumneutral pH (pH 6–8), which indicates that the drug is lipophilic and predicts its high adsorption potential.<sup>30,31,52</sup> This suggests that FLX tends to adsorb onto solids, indicating its elimination by activated sludge processes (ASP) during the treatment train at WWTPs. The study by Kwon and Armbrust (2006) also revealed that FLX rapidly partitions in water/sediment systems, with adsorption to sediments, and this distribution is unaffected by light/dark cycles.<sup>28</sup> Although this partitioning to sediments and natural organic matter (NOM) *via* adsorption or complexation, and salinity does not affect the concentration of FLX, it alters the bioavailability of the drug and uptake by organisms.<sup>53</sup> Recent studies have shown that (i) FLX is stable in soil for up to 270 days, which is sufficiently long period for plant uptake, if any, and (ii) the presence of FLX in soil significantly affects both the pH of the soil and internal pH of earthworm *Eisenia fetida*, which are the key terrestrial invertebrates.<sup>54,55</sup>

It is worth mentioning that although there is a significant knowledge gap concerning the fate of FLX in soil systems, it is known that organic matter in the soil, and thus the soil types, influence the sorption and bioavailability of FLX; however, they do not influence the stability and persistence



of the drug residues.<sup>54,55</sup> Long-term stability of FLX in soil coupled with the land application of FLX-containing sludge and biosolids as a fertilizer to the soil can provide a route of entry for the drug into the soil and agricultural fields. A previously reported preliminary study has reported the uptake of FLX into *Brassicaceae* tissues (cauliflower stems and leaves); however, more studies are required, especially for crops commonly grown on sewage-sludge amended soils, such as corn, potato, lettuce, and cabbage.<sup>56</sup>

It has also been reported that nucleophilic –NH of FLX reacts with electrophilic chlorine of hypochlorite during chlorination to rapidly (<2 minutes) form *N*-chloramine.<sup>57</sup> It is noteworthy that the presence of amine-containing organics, such as FLX, creates a high 'chlorine demand' but results in lower disinfection efficiency. The release of *N*-chloramines is also concerning because of (i) increased hydrophobicity and (ii) they act as an active chlorine carrier. Under neutral conditions, FLX exists in protonated form. However, the replacement of H by Cl makes it neutral or unprotonated, making it more hydrophobic than the parent FLX. This increased hydrophobicity can result in a greater tendency to adsorb on organic surfaces such as sediment, soil, and biological membranes.<sup>57,58</sup> *N*-Chlorofluoxetine can also serve as a carrier for 'active chlorine' and transfer its chlorine to other reductants or assimilate in biological cells post uptake.<sup>57</sup>

### 3.3 Microbial susceptibility and bioaccumulation potential

The  $K_{biol}$  for FLX ranges from 0.03 to 9.0, demonstrating poor to significant biodegradability, depending heavily upon conditions;<sup>30</sup> the antidepressant was found to be resistant to microbial degradation in WWTPs.<sup>28,59</sup> Ultrasonication has been explored as a pretreatment to improve the biodegradability of FLX.<sup>59</sup>

In addition to microbial persistence, FLX has been studied to accumulate in aquatic organisms and transfer *via* the food chain, exhibiting the potential to bioaccumulate and biomagnify at all trophic levels.<sup>60–62</sup> For instance, after exposure to 75 ng L<sup>-1</sup> FLX for 15 days, mussel *M. galloprovincialis* showed signs of accumulation of both FLX and norfluoxetine, increasing from 2.53 and 3.06 ng g<sup>-1</sup> dry weight on day 3 to 9.31 and 11.65 ng g<sup>-1</sup> on day 15, respectively.<sup>63</sup> The SSRI has also been studied to accumulate in *Spirostomum ambiguum*, ciliated protozoa commonly found in activated sludge in WWTPs and surface waters.<sup>58</sup> Since protozoa have a critical role in controlling bacterial populations and dynamics, promoting floc formation, and improving sludge settling, FLX accumulation in them can potentially (i) affect their mobility and growth, (ii) cause a shift in bacterial communities, and (iii) impair sludge settleability, affecting nutrient removal and WWTP performance. Although previous studies have reported consequences on growth and behaviour, reproductive axis, metabolism, accumulation, and gene expression due to accumulation of FLX in the brain, liver, and muscles of zebrafish (*Danio rerio*) and goldfish

(*Carassius auratus*), reports on the accumulation of FLX in protozoa and its potential effects are lacking.<sup>2,19–21,53</sup>

### 3.4 Interactions with co-existing pollutants and combined toxicity

Owing to its structural features and physicochemical parameters, FLX can interact with co-existing pollutants and has been the center of a few studies, as summarized in Table 2. The drug has been studied to interact, directly or indirectly, with organic matters such as co-existing pharmaceutical residues, microplastics, and inorganic entities like metals and engineered nanomaterials.<sup>64–68</sup> For instance, the co-occurrence of FLX and sertraline (SER) has been studied to affect the growth, photosynthetic activity, and antioxidant system of the microalga *Chlorella pyrenoidosa*. Although both FLX and SER strongly inhibit microalgal growth, with 96 hour EC<sub>50</sub> values of 493 and 61.1 µg L<sup>-1</sup>, respectively. However, the combined effect is additive and causes more significant photosynthetic damage and oxidative stress than either compound alone. The microalgae *C. pyrenoidosa* can efficiently remove FLX by biodegradation and SER by both biodegradation and bioaccumulation, but their co-existence lowers the biodegradation rate and subsequent removal for both drugs.<sup>68</sup> A similar effect on the antioxidant system and inhibition of Ca(II)-ATPase was observed in *Daphnia magna* on simultaneous sub-chronic (7 days) and acute exposure (48 h) to FLX and Zn(II).<sup>64</sup> The presence of FLX has also been reported to affect the functioning of intracellular Ca(II) channels in cells, thereby inhibiting the respiratory chain and disrupting ATP production.<sup>69–71</sup>

Likewise, the co-existence of FLX and ketoprofen, an analgesic, induces greater disruptions in nitrogen and phosphorus cycles and micro-eukaryotic communities, including physicochemical and biological variations, compared to either pharmaceutical alone.<sup>66</sup> This can be partially owed to its potential to influence the antibacterial activity of several co-occurring antibiotics against both standard and multi-drug-resistant strains.<sup>65,72</sup> For instance, FLX is effective against Gram-positive bacteria, with limited activity against Gram-negative bacteria. Although it does not interfere with the antibacterial activity of antibiotics directly, it interferes with the bacterial resistance mechanism, such as inhibition of efflux pumps, to exhibit both antagonistic and synergistic effects.<sup>65</sup> It can also alter the behaviour of *Asellus aquaticus*, a benthic micro invertebrate and a decomposer, resulting in a slower rate of microbial decomposition of plants that remain near the sediment.<sup>67</sup>

A recent study by Yan *et al.* (2019) highlighted the increased FLX uptake and accumulation in fish in the presence of multi-walled carbon nanotubes (MWCNTs).<sup>53</sup> Similar results were observed with mussels (*Mytilus galloprovincialis*).<sup>63</sup> It is considered that nanomaterials, like MWCNTs, serve as adsorbents for FLX, form adducts,



Table 2 Summary of interactions between FLX and other environmental co-pollutants

Co-pollutant/condition	Interaction nature	Observed effects	Environmental relevance	Ref.
Sertraline	Additive	<ul style="list-style-type: none"> <li>- FLX with sertraline showed additive toxicity to microalgal growth</li> <li>- Damaged antioxidant systems and photosynthesis</li> </ul>	<ul style="list-style-type: none"> <li>- Presence of SSRIs can affect microalgae-based bioremediation</li> </ul>	68
Ketoprofen	Additive	<ul style="list-style-type: none"> <li>- Induced greater disruptions in nitrogen and phosphorus cycles</li> <li>- Reduced <i>D. magna</i> brood rate; inhibited <i>Lemna</i> growth</li> <li>- Changed the composition of micro-eukaryotic communities</li> </ul>	<ul style="list-style-type: none"> <li>- Can affect ecosystem communities and their functional processes</li> <li>- May affect ecological risk estimations due to over/underestimation</li> </ul>	66
Microplastics (polystyrene)	Synergistic	<ul style="list-style-type: none"> <li>- Disruption of gene expression and oxidative pathways</li> <li>- Increased malformations, mortality, and delayed embryonic development</li> <li>- Microplastics enhance FLX toxicity and tissue accumulation</li> </ul>	<ul style="list-style-type: none"> <li>- Interfere with fundamental biological processes; cause direct and indirect toxic effects</li> </ul>	131
Microplastics (polystyrene)	Mixed	<ul style="list-style-type: none"> <li>- Microplastics reduced trophic transfer of FLX along the food chain and mitigated the neurotransmission biotoxicity in fish induced by FLX</li> <li>- Enhanced oxidative stress, apoptosis, immune responses in zebra fish</li> </ul>	<ul style="list-style-type: none"> <li>- Carrier effects of microplastics can affect trophic transfer of FLX and biotoxicity in environmental matrices</li> <li>- Relevant in matrices containing both entities</li> </ul>	132
Microplastics (polystyrene)	Complex	<ul style="list-style-type: none"> <li>- Combination of FLX and microplastics influence phytoplankton biomass, zooplankton abundance, and microbial decomposition rate of plants</li> </ul>	<ul style="list-style-type: none"> <li>- Microplastics can reshape dose-response outcomes for FLX at ecosystem levels</li> </ul>	67
Azoles	Synergistic	<ul style="list-style-type: none"> <li>- Combination of FLX with fluconazole diminishes the virulence of <i>C. albicans</i> by downregulation of gene expression and weakening of extracellular phospholipase activity</li> </ul>	<ul style="list-style-type: none"> <li>- FLX in the presence of azoles can be used as a potential therapeutic strategy against resistant <i>C. albicans</i> infections</li> </ul>	133
Zinc ( $Zn^{2+}$ )	Antagonistic	<ul style="list-style-type: none"> <li>- Reduced FLX toxicity on <i>D. magna</i>, along with antioxidant suppression and Ca(II)-ATPase-inhibition</li> </ul>	Oxidative stress	64
Carbon nanotubes (MWCNTs)	Synergistic	<ul style="list-style-type: none"> <li>- MWCNTs play as a 'carrier', increasing bioavailability, uptake and accumulation in fish</li> <li>- NOM alleviated, and salinity reversed the carrier effect of MWCNTs</li> </ul>	<ul style="list-style-type: none"> <li>- NOM and salinity affect the interactions between FLX and engineered nanostructures; can cause uncertainty in risk assessment of FLX</li> </ul>	53

increase uptake, and promote accumulation in aquatic organisms.<sup>53</sup>

All these studies highlight that combined exposure of FLX with other pollutants may instigate harmful impacts on ecosystem levels, including aquatic microcosms and bacterial communities. This has encouraged researchers to devise effective removal techniques for FLX from aqueous matrices, including physical, chemical, and biological degradation, as discussed in the next section.

## 4. Removal technology bottlenecks

### 4.1 Physical methods

**4.1.1 Adsorption.** The physicochemical properties of FLX indicate its high tendency for surface adsorption, and this capacity has been utilized to remove FLX from aqueous solutions *via* adsorption. Various adsorbents, including but not limited to commercial adsorbents, biosorbents, and metal-based nanoparticles, have been employed for this purpose, as summarized in Table 3.

(i) *Waste-derived adsorbents.* The principles of waste valorization, zero-waste and circular economy have promoted

the utilization of waste, such as lignocellulosic and agri-food waste, to prepare high-capacity adsorbents to combat pharmaceutical pollution. For instance, Silva *et al.* (2020) utilized spent coffee grounds, pine bark and cork waste to produce biosorbents with maximum adsorption capacity between 4.74 mg g<sup>-1</sup> and 14.31 mg g<sup>-1</sup>.<sup>73</sup> Nkana *et al.* (2024) prepared a series of adsorbents using different ratios of polyethylene glycol (PEG 2000) and carboxymethyl chitosan derivatives (O-CMCs and N,O-CMCs; 0.03 g mL<sup>-1</sup>) (denoted as PHB1, PHB2, PHB3, PHB4, and PHB5, with a surface area of 19.84, 29.81, 37.50, 3.69, and 25.93 m<sup>2</sup> g<sup>-1</sup>, respectively), and used them to remove FLX *via* physisorption. The maximum absorption capacity observed for the materials ranged from 90.6 to 112.6 mg g<sup>-1</sup>.<sup>74</sup> Similarly, adsorbents prepared by chemical activation of primary paper sludge with KOH, NaOH, and ZnCl<sub>2</sub>, followed by pyrolysis (PS800-10KOH, PS800-10NaOH, and PS800-10ZnCl<sub>2</sub>) achieved a maximum adsorption capacity of 191.6 ± 4.8, 136.6 ± 9.6, and 28.4 ± 0.3 mg g<sup>-1</sup>, respectively.<sup>75</sup>

Naturally occurring fibres, such as xylan, pectin, and lignin, have also been exploited to produce efficient adsorbents. For instance, Farghal *et al.* (2023) used xylan and



Table 3 Summary of removal of FLX by adsorption using different adsorbents in previous studies

	$q_{\max}$ (mg g <sup>-1</sup> )	pH	Initial concentration (mg L <sup>-1</sup> )	Temperature (°C)	Ref.
Commercial adsorbents					
Activated carbon PBFG4	96.2	—	10	25	75
Granular activated carbon (GAC)	233.5	9	5	25	73
NQ40	125.24	7–7.5	1000	—	82
Biosorbents					
PS800-10KOH	191.6	—	10	25	75
PS800-10NaOH	136.6	—	10	25	75
PS800-10ZnCl <sub>2</sub>	28.4	—	10	25	75
Fish bone char	55.87	—	100	—	79
Eucalyptus biochar	6.41	6.5	20	RT	78
Nanofiber AL:PVA 50:50	29	—	50	—	77
Biochar	—	7.1	50	RT	81
Nanocomposite XCM	90.9	7.35	25	28	76
Nanocomposite PCM	114.9	7.35	25	28	76
Alperujo hydrochar	4.63, 5.95	6.4	30	RT	134
PHB4 (PEG/O-CMCs, 3:3)	112.6	8.5	50	30	74
PHB5(PEG/N,O-CMCs 0:3)	109.3	8.5	50	30	74
Modified pine bark	0.652	—	5	25	83
Synthetic adsorbents					
RuFeO <sub>3</sub> nanoparticles	683.5	7	—	25	42
CeFeO <sub>3</sub> nanoparticles	729.6	—	—	—	—

pectin-coated activated-carbon-based magnetite adsorbents to remove FLX. These nanocomposites – xylan/AC/magnetite (XCM) and pectin/AC/magnetite (PCM) – displayed adsorption capacities of 90.9 mg g<sup>-1</sup> and 114.9 mg g<sup>-1</sup>, respectively. The xylan and pectin-modified nanocomposites displayed enhanced regeneration, reusability, and stability compared to the AC/magnetite (CM) nanocomposite.<sup>76</sup> Similarly, Camiré *et al.* (2020) transformed lignin into anionic nanofibrous adsorbents *via* electrospinning, using poly(vinyl alcohol) (PVA) as a co-polymer. Nanofibers containing different ratios of lignin and PVA were prepared, and the nanofibers with a lignin:PVA ratio of 50:50 exhibited the best performance, with a maximum adsorption capacity of 29 mg g<sup>-1</sup>.<sup>77</sup>

A study by Fernandes *et al.* (2019), on the other hand, utilized agri-food waste to produce twelve biochars and explored their potential to absorb and remove FLX. The biochar prepared by pyrolysis of eucalyptus proved to be the most promising, with a surface area of 335 m<sup>2</sup> g<sup>-1</sup> and an adsorption capacity of 6.41 mg g<sup>-1</sup>.<sup>78</sup>

(ii) *Inorganic adsorbents.* Both waste-derived mineral-based and synthetic metal-based adsorbents have been employed for FLX removal from aqueous solutions. For example, Piccirillo *et al.* (2017) prepared biphasic apatite-carbon bone-char from cod fish bones by pyrolysis at different temperatures (200, 400, 600, 700, 800, 900, and 1000 °C) and used it to remove 60% of FLX from an initial concentration of 200 mg L<sup>-1</sup> in aqueous solutions.<sup>79</sup>

On the other hand, Narayanan *et al.* (2021) synthesized and utilized mesoporous ferrite nanoparticles of RuFeO<sub>3</sub> (80–100 nm) and CeFeO<sub>3</sub> (20–30 nm) for effective FLX removal (>99% for initial FLX concentrations of 20 mg L<sup>-1</sup>), with

maximum adsorption capacities of 683.5 mg g<sup>-1</sup> and 729.6 mg g<sup>-1</sup>, respectively.<sup>42</sup> A nanocomposite of ternary ZnCoAl layered double hydroxide, supported on activated carbon (LAC), was recently synthesized and used for FLX removal by Mahgoub *et al.* (2024), thereby reaching a maximum adsorption capacity of 450.92 mg g<sup>-1</sup> for an FLX concentration of 50 µg mL<sup>-1</sup>. However, this adsorption capacity was achieved at pH 10, which is unsuitable for environmental applications.<sup>80</sup>

(iii) *Commercial adsorbents.* A few studies have also investigated the potential of commercially available adsorbents for FLX removal, which have been summarized here for reference. A recent study by Silva *et al.* (2020) reported the adsorption capacity ranging between 21.86 and 233.5 mg g<sup>-1</sup> for commercial adsorbents – granular activated carbon (GAC), zeolite 13X and zeolite 4A.<sup>73</sup> Similarly, a report by Escudero-Curiel *et al.* (2021) utilized low-cost commercial biochar, with an adsorption capacity of 6.57 mg g<sup>-1</sup>, to remove FLX *via* adsorption at room temperature and pH 7.1.<sup>81</sup> Another study by the same authors employed commercial carbon aerogel (NANOLIT 3D monolith NQ40 honeycomb premium (CO<sub>2</sub> activated); specific surface area of 790 m<sup>2</sup> g<sup>-1</sup>) as a high-capacity adsorbent to remove high concentrations of FLX *via* chemisorption, with an adsorption capacity of 125.24 mg g<sup>-1</sup> at pH 7–7.5.<sup>82</sup> However, after regeneration with Fenton's process, about 87% of the surface area was lost due to the collapse of the pores, which might not be well-suited for biochar removing FLX *via* pore-filling.<sup>82</sup> For biochar operating by other forces such as electrostatic, hydrophobic-hydrophobic, or π-π interactions, solvent desorption and thermal methods of regeneration have been reported to be effective.<sup>76,78,83</sup>



**4.1.2 Membrane technology.** Membrane processes have gained immense attention recently, both as a method of separation and remediation technique of pharmaceutical wastewater. Membranes of varying pore size, retention characteristics, composition and membrane material, and configuration (hollow fibre, flat sheet, tubular) have been employed recently. However, these techniques have not been explored for FLX removal, and only three studies have been reported.

Dalbosco *et al.* (2023) observed an FLX removal efficiency of 50–60% and >98% for polymeric nanofiltration (NF) and reverse osmosis (RO) membranes,

respectively.<sup>84</sup> These commercial membranes comprised a polyamide (PA) layer on a polysulfone (PS) support for mechanical strength. The NF membrane was operated at 600 kPa, and the permeate flux decreased from 41 to 34 L m<sup>-2</sup> h<sup>-1</sup> after 1 h of operation when FLX concentrations were increased from 1 to 50 mg L<sup>-1</sup>. Similarly, RO membranes displayed a high dependence on operating pressure and FLX concentrations. The RO membrane achieved a permeability of about 29 L m<sup>-2</sup> h<sup>-1</sup> with a rejection efficiency of 98.8% for an FLX concentration of 20 mg L<sup>-1</sup> at a pressure of 1500 kPa, which makes it highly energy intensive.<sup>84</sup>

**Table 4** Summary of FLX removal via advanced oxidation processes (AOPs)

AOP method	Dosage and operating conditions	Removal efficiency	Insights/comments	Ref.
Ozone/H <sub>2</sub> O <sub>2</sub>	30 mg L <sup>-1</sup> ozone, 0.02 mM H <sub>2</sub> O <sub>2</sub> , 20 minutes, 50 mg L <sup>-1</sup> FLX	86.14% removal		86
Ozonation and ozone/activated carbon	1 mM FLX, 2 g of activated carbon, 20 g N m <sup>-3</sup> O <sub>3</sub> , flow rate 0.06 Nm <sup>3</sup> h <sup>-1</sup> ; pH 3–9	~100% removal within 20 minutes (pH 7 and 9)	- Degradation slower under acidic conditions - FLX highly reactive with HO <sup>·</sup> but not with O <sub>3</sub> – indirect oxidation primary route	98 87
Catalytic ozonation with a nano- $\gamma$ -alumina catalyst	30 mg L <sup>-1</sup> ozone, 1 g L <sup>-1</sup> catalyst	96.14% of 28.56 mg L <sup>-1</sup> FLX in 30 minutes		100
Photocatalysis with TiO <sub>2</sub> P25 and g-C <sub>3</sub> N <sub>4</sub> photocatalysts	Ultrapure water (lab); 5 mg L <sup>-1</sup> FLX, 100 mg L <sup>-1</sup> catalyst; <i>I</i> = 500 W m <sup>-2</sup>	~100% in 120 minutes using TiO <sub>2</sub> ( <i>t</i> <sub>1/2</sub> = 18 minutes) ~91% removal using g-C <sub>3</sub> N <sub>4</sub> ( <i>t</i> <sub>1/2</sub> = 69 minutes) ~100% in 120 minutes using TiO <sub>2</sub> ( <i>t</i> <sub>1/2</sub> = 34 minutes) ~90% removal using g-C <sub>3</sub> N <sub>4</sub> ( <i>t</i> <sub>1/2</sub> = 65 minutes)	- Half life of 87 minutes was calculated for FLX under simulated solar radiation ( <i>I</i> = 500 W m <sup>-2</sup> ) - TiO <sub>2</sub> found superior to g-C <sub>3</sub> N <sub>4</sub>	88
	Real secondary hospital wastewater (pilot scale); 5 mg L <sup>-1</sup> FLX, 100 mg L <sup>-1</sup> catalyst; <i>I</i> = 500 W m <sup>-2</sup>	~100% removal in 120 minutes using TiO <sub>2</sub> ( <i>t</i> <sub>1/2</sub> = 34 minutes) ~90% removal using g-C <sub>3</sub> N <sub>4</sub> ( <i>t</i> <sub>1/2</sub> = 65 minutes)		
Photocatalysis with the hybrid heterojunction photocatalyst Fe <sub>3</sub> O <sub>4</sub> –BiVO <sub>4</sub> /Cr <sub>2</sub> V <sub>4</sub> O <sub>13</sub> (FBC)	10 mg L <sup>-1</sup> FLX, 30 mg catalyst, 500 W Xe lamp (280 mW cm <sup>2</sup> )	~99.2% removal in 60 minutes	- ·OH and ·O <sub>2</sub> <sup>·</sup> identified as dominant species - Charge transfer mediated by Fe <sub>3</sub> O <sub>4</sub>	99
Photocatalysis with a molecularly imprinted catalyst (MI-BiOCl)	Municipal wastewater, 20 mg L <sup>-1</sup> FLX, 20 mg (in <i>V</i> = 50 mL) catalyst; simulated solar irradiation (500 W)	99.3% removal in 150 minutes		91
Catalytic ozonation	0.11 mM FLX, 60 minutes, pH 11, 0.050 g L <sup>-1</sup> TiO <sub>2</sub>	UV/TiO <sub>2</sub> : ~100% removal in 60 minutes with 50% mineralization UV/O <sub>3</sub> /H <sub>2</sub> O <sub>2</sub> : ~100% in 10 minutes, ~97% mineralization	- Strong pH dependence on adsorption of FLX on TiO <sub>2</sub>	89
FeO/sulphite (S(IV)) FeO/PMS FeO/PDS	Real wastewater	84.4% 56.4% 30.7% in 17.5 minutes 14.4%	- Photolysis of FLX only under alkaline conditions - Peroxide enhances the removal of dissolved organic carbon - Surface passivation of FeO with operation results in lower removal - Inhibitory effects of Cl, HCO <sub>3</sub> <sup>-</sup> , and NOM - Removal efficiency directly influenced by doses of PMS, Fe(II), and citric acid	95
PMS/Fe(II) (with and without citric acid)	50 mg L <sup>-1</sup> FLX	~100% in 5 minutes		81
Electrogenerated peroxide (AO-H <sub>2</sub> O <sub>2</sub> ) Electro-Fenton (EF)	BDD anode for PEF	94% in 300 minutes	- In situ generation of hydroxy radicals results in FLX oxidation	102
Photoelectro-Fenton (PEF) Heterogeneous EF with an FeS <sub>2</sub> /C nano-catalyst	IrO <sub>2</sub> /air diffusion cell 50 mA with 0.4 g L <sup>-1</sup> catalyst	~100% in 60 minutes		103



In another study, Rad *et al.* (2024) prepared Ti-based MOF-modified electrospun PS/PEG nanofiber membranes (PSf/PEG/NH<sub>2</sub>-MIL-125(Ti)) to achieve a maximum flux and removal efficiency of 148.3 L m<sup>-2</sup> h and 84.5% at pH 8 and a loading of 1.5% w/w in continuous mode and a maximum adsorption capacity of 21.6 mg g<sup>-1</sup> for an FLX concentration of 2 mg L<sup>-1</sup> in batch mode.<sup>85</sup> It is also worth mentioning that membrane technology is a separation technique, and when applied to treat FLX-contaminated wastewater, it produces a secondary stream loaded with the pollutant, thereby underlining the need for complementary degradation technologies.

## 4.2 Chemical technologies

**4.2.1 Advanced oxidation processes (AOPs).** Reports on the degradation of micropollutants, including FLX, by ozonation and heterogeneous photocatalysis are not scarce (Table 4).<sup>86-91</sup> FLX is susceptible to the action of both oxidizing (·OH) and reducing agents (e<sub>aq</sub><sup>-</sup>).<sup>92,93</sup> They have been increasingly explored and reported to be highly efficient in removing contaminants by cyclo-addition and electrophilic reactions.

Ozone is an electrophile and can attack the secondary amine group in the FLX structure to aid its degradation *via* oxidation.<sup>94</sup> Hydroxylation, demethylation, carbonylation, and cleavage of benzene rings also contribute to the degradation of FLX *via* radical pathways.<sup>95,96</sup> As reported by Yu *et al.* (2015), FLX is photo-susceptible and can be effectively degraded by direct UVC photolysis (254 nm), with ~30% degradation observed at a UVC dose of 100 mJ cm<sup>-2</sup> in the absence of H<sub>2</sub>O<sub>2</sub>. The addition of H<sub>2</sub>O<sub>2</sub> (3–6 mg L<sup>-1</sup>) did not result in a significant increase in FLX degradation, suggesting that indirect photolysis, or ·OH-mediated oxidation, plays a minor role.<sup>97</sup> Nevertheless, various photosensitizers, including but not limited to ozone, hydrogen peroxide, and photocatalysts, have been recently investigated and reported to improve FLX degradation under UV irradiation.<sup>88,91,94,98</sup>

Chemical oxidation of FLX using sulphate-radicals (SO<sub>4</sub><sup>2-</sup>) *via* peroxymonosulphate (PMS), peroxydisulphate (PDS), or sulphite (S(iv)) activation has also shown promising results in previously reported studies.<sup>81,95</sup> For instance, Escudero-Curiel *et al.* (2021) reported almost complete FLX removal under 5 minutes of treatment with PMS/Fe(II) and PMS/Fe(II)/citric acid (CA) systems for different molar ratios. Meanwhile, the removal efficiency of FLX (50 mg L<sup>-1</sup>) was directly influenced by doses of PMS and Fe(II), as well as the presence of CA, and demanded a high molar ratio of chemical reagents.<sup>81</sup> A comparison of FeO/S(iv), FeO/PDS and FeO/PMS under the same conditions for FLX degradation, as reported by Chen (2022), showed removal efficiencies of 84.4, 56.4, and 30.7%, respectively, in 17.5 minutes. Both PMS and PDS have a high oxidizing capacity, and the possibility of surface passivation of FeO, resulting in lower removal of FLX, could not be eliminated.<sup>95</sup>

Also, despite the high removal efficiency of the FeO/S(iv) system in eliminating FLX under neutral conditions, the system could not degrade the pollutant satisfactorily (14.4% at pH 7) in real water because of the inhibitory effects of Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, and NOM. For instance, with an increase in concentration of Cl<sup>-</sup> from 0 to 8 mM, the FLX removal efficiency decreased from 84.4% to 32.9%. Similarly, in the presence of 4 mg L<sup>-1</sup> fulvic acid (used as a model NOM), FLX removal efficiency reduced by 61.1%. Both Cl<sup>-</sup> and NOM quench the free radicals, thereby inhibiting the degradation pathways, while bicarbonate, *via* the buffering effect, results in slow dissolution of Fe(II) and, thus, slower degradation. At circumneutral pH, iron can also precipitate as hydroxides, thereby retarding the S(iv) activation.<sup>95</sup> Also, despite the agent, AOPs necessitate the optimization of parameters to obtain desired results, which is not feasible in a dynamic setting such as wastewater.

Several nano-photocatalysts have also been fabricated and have demonstrated improved degradation for FLX in real wastewater systems. For instance, application of a hybrid heterojunction photocatalyst (Fe<sub>3</sub>O<sub>4</sub>-BiVO<sub>4</sub>/Cr<sub>2</sub>V<sub>4</sub>O<sub>13</sub> (FBC)) removed >99% FLX under 60 minutes of exposure to visible and solar radiation by the action of ·OH and ·O<sub>2</sub><sup>-</sup>.<sup>99</sup> Another study by Liu *et al.* (2025) employed a molecularly imprinted photocatalyst (MI-BiOCl) and removed 99.3% of FLX (C<sub>0</sub> 20 mg L<sup>-1</sup>) from municipal wastewater in 150 minutes.<sup>91</sup> In another study, catalytic ozonation using a nano-gamma-alumina catalyst degraded 96.14% of 28.56 mg L<sup>-1</sup> FLX in 30 minutes of reaction using 30 mg L<sup>-1</sup> ozone and 1 g L<sup>-1</sup> catalyst.<sup>100</sup> Similarly, Fotiou *et al.* (2024) investigated the removal of FLX (C<sub>0</sub> 5 mg L<sup>-1</sup>) using TiO<sub>2</sub> P25 and g-C<sub>3</sub>N<sub>4</sub> photocatalysts from both ultrapure water (lab scale) and real secondary treated hospital wastewater (HWW) (pilot scale).<sup>88</sup> It should be noted that although a much lower concentration of FLX was used in HWW (250 ng L<sup>-1</sup>) compared to ultrapure water (5 mg L<sup>-1</sup>), the degradation proceeded at a lower rate in HWW, with a *t*<sub>1/2</sub> of 34 min *vs.* 18 min in ultrapure water. This is primarily due to the complexity of the HWW, which contains dissolved organics and inorganic ions capable of scavenging the ROS and attenuating UV radiation. Overall, it is evident that inhibitory effects of Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, NOM, surface passivation, and pH dependency limit the use of AOPs in real systems. Therefore, further studies are necessary to understand the effect of real wastewater on the efficiency of AOPs and to enhance their applicability to WWTPs, without compromising the overall WWTP performance and nutrient removal.

It is also noteworthy that these AOPs can result in more toxic by-products, resulting in obstinate toxicity and limiting the application. Typically, toxicity has been reported to increase in the beginning due to the formation of free radicals, and then decrease with continued AOPs, which does not necessarily imply reduced toxicity. AOPs produce hydroxylated and dealkylated intermediates and transformation products, which often exhibit different environmental persistence, bioavailability, and toxicity.<sup>89,96,101</sup>



For instance, the demethylated product of FLX norfluoxetine (NFLX) has a longer half-life and higher bioaccumulation potential than the parent compound itself. In addition to dealkylation, the formation of smaller molecular products with functionalities, such as aldehydes, also contributes to the toxicity of the transformation products at the end of AOPs.<sup>96</sup> As reported, 'high degradation efficiency' of AOPs, which generally means the removal of parent compound only, does not necessarily imply reduced toxicity; therefore, future studies should include toxicity analysis of intermediate and transformation products formed by AOPs rather than reporting parent compound removal.

#### 4.3 Electrochemical methods

Some researchers have coupled AOPs with electrochemical methods to degrade FLX. For instance, Salazar *et al.* (2017) explored the potential of electrochemical methods (electrogenerated peroxide (AO-H<sub>2</sub>O<sub>2</sub>), electro-Fenton (EF) and photoelectron-Fenton (PEF)) to degrade the fluorinated antidepressant FLX.<sup>102</sup> The drug was oxidized, owing to the generation of hydroxy radicals by *in situ* peroxide production and Fenton's reaction, coupled with the photolytic action of UVA radiation. PEF with a boron-doped-diamond (BDD) anode was observed to be the most effective process, with 94% mineralization in 300 minutes.<sup>102</sup> Another study by Ye *et al.* (2020) studied the heterogeneous EF treatment for FLX degradation in spiked wastewater using an FeS<sub>2</sub>/C nanocatalyst. EF treatment with an IrO<sub>2</sub>/air diffusion cell ensured complete removal and mineralization of the drug (150 mL of 0.049 mM) at near neutral pH in 60 min at 50 mA with a 0.4 g L<sup>-1</sup> catalyst dose.<sup>103</sup> The electrochemical oxidation has also been coupled with adsorption to present a commercial solution, Nyex Rosalox, to FLX-contamination with an impressive ~92% removal efficiency for FLX (from 0.06 µg L<sup>-1</sup> to 0.0046 µg L<sup>-1</sup>).<sup>104</sup> Although very effective, these techniques can only be adapted to small-scale facilities, community-level water treatment systems, or modular installations, as a stand-alone or as a hybrid technology. The high energy demand and matrix complexity (including but not limited to competition for electrons, fouling electrode surface, and lower selectivity) hinder their application in rugged, high-volume settings such as WWTPs.

#### 4.4 Biological degradation

**4.4.1 Phytoremediation (microalgae).** Microalgae-mediated remediation, or phytoremediation, is an environmentally friendly, sustainable, and cost-effective approach for remediating pharmaceutical-contaminated water. This carbon-fixation-based, sunlight-driven approach primarily removes pollutants by abiotic (hydrolysis and photolysis) and biotic processes (bio-adsorption, bioaccumulation, and biodegradation).

Previous studies have shown that positively charged pharmaceuticals (or pK<sub>a</sub> >7) and higher lipophilicity (higher log K<sub>ow</sub>) exhibit enhanced elimination due to their adsorption

on the negatively charged surface of microalgae and their ability to penetrate the cell membrane.<sup>105-108</sup> With an acid dissociation constant of 9.80, FLX partially exists as a cationic species in the circumneutral pH (pH 6.5-8.5) environmental wastewater and surface waters. In addition, high lipophilicity (log K<sub>ow</sub> of 4.10) makes it adept at biosorption and accumulation.

A few researchers have investigated the potential of microalgae under free and immobilized conditions in the removal of FLX. A recent study assessed the ecotoxicological effects of FLX (10-1000 µg L<sup>-1</sup>) and its subsequent removal by a typical freshwater microalga *Chlorella pyrenoidosa* for 10 days. The study revealed that the presence of FLX at a concentration of ≥50 µg L<sup>-1</sup> inhibited the growth of *C. pyrenoidosa* and can be considered as 'very toxic' to the studied microalgae based on the EU-Directive 93/67/EEC (EC<sub>50</sub> 72 h or longer).<sup>107</sup> Similarly, FLX shows high toxicity to *Pseudokirchneriella subcapitata* and *Skeletonema marinoi* with 72 h EC<sub>50</sub> values of 0.2 and 0.043 mg L<sup>-1</sup>, respectively.<sup>109</sup> However, *C. pyrenoidosa* was able to recover its growth, along with photosynthetic and antioxidant functions, after exposure to FLX toxicity, with a removal efficiency of 100%, 97%, 77.4%, 58.6% and 41.2% for initial FLX concentrations of 10, 50, 200, 500, and 1000 µg L<sup>-1</sup>, respectively.

After 10 days of exposure, biodegradation was found to be the primary factor in removing FLX, accounting for 88.2-92.8% of the total removal. In contrast, bioaccumulation and biosorption contributed negligibly towards the removal, with ND-5.33% and 0.38-1.90%, respectively. The greater contribution of biodegradation also suggests that FLX absorbed by the microalgae was rapidly metabolized, leading to the release of transformation products (demethylation, O-dealkylation, hydroxylation, N-acylation) into the medium. Meanwhile a similar study with *Chlorella vulgaris* by Silva indicated biosorption as a leading contributor to the removal of FLX by the microalgae, followed by bioaccumulation and biodegradation in living algal medium. The maximum monolayer capacity (q<sub>mL</sub>) for living *C. vulgaris* (pH<sub>ZC</sub> 7.0) was only slightly better (1.9 ± 0.1 mg L<sup>-1</sup>) than the dead biomass (pH<sub>ZC</sub> 5.8) (1.6 ± 0.2 mg g<sup>-1</sup>).<sup>110</sup>

**4.4.2 Bacteria and bacterial consortia.** Many advances have been made recently to tackle pharmaceutical pollution using bacterial consortia, such as those found in municipal wastewater, sludge, leachate, or bacterial strains isolated from these contaminated and complex matrices. These autochthonous bacterial communities often develop tolerance to these pollutants and release enzymes under stress that can facilitate their biodegradation. Some of the recent studies are summarized in Table 5. For instance, a previous study by Khan and Murphy (2021) demonstrated the ability of common environmental bacteria, such as *B. subtilis*, *Comamonas testosteroni*, *P. aeruginosa*, *P. knackmussii*, and *P. putida*, to grow in the presence of FLX and use it as a sole carbon and energy source. Of these, *C. testosteroni* and *P. knackmussii* B-13 grew the best with 55% and 70% of glucose growth, respectively, whereas *E. coli* grew the least.<sup>111</sup> It was



Table 5 Overview of FLX biodegradation performance in biological systems

Biodegradation strategy	Organism/system	Conditions	Removal efficiency	By-products/insights	Ref.
Microalgae	<i>Chlorella pyrenoidosa</i>	25 °C, 12:12 h light-dark period	100–41.2% for $[C_0] = 10\text{--}1000 \mu\text{g L}^{-1}$ in 4–10 days	- Growth inhibition by FLX - Uptake and transformation of FLX by demethylation, O-dealkylation, hydroxylation, and N-acylation	107
	<i>Chlorella vulgaris</i> (living and non-living)	RT, real wastewater Biomass centrifuged, frozen, and free-dried	Maximum capacity 1.9 ± 0.1 mg g <sup>-1</sup> and 1.6 ± 0.2 mg g <sup>-1</sup> for living and non-living microalgae, respectively	- Significant contribution from adsorption by algae - Simultaneous removal of nutrients	110
Bacteria	<i>B. subtilis</i> , <i>C. testosteroni</i> , <i>P. aeruginosa</i> , <i>P. knackmussii</i> , and <i>P. putida</i>	Aerobic, 30 °C for 72 h, mineral salt media (MSM) with FLX as the only carbon source		- FLX hydrolysed to form 4-(trifluoromethyl) phenol (TFMP) and 3-(methylamino)-1-phenylpropan-1-ol, which is further catabolized via <i>meta</i> -cleavage to produce trifluoroacetate and fluoride ions	111
	Autochthonous aerobic community from a WWTP	Aerobic sludge (10% w/v) used as the inoculum, real wastewater, RT, 6 days (144 h)	~60%, 85%, and ≈89% of degradation after 48, 72, and 144 h, respectively (at 20 mg L <sup>-1</sup> FLX)	- <i>P. putida</i> , <i>Enterobacter ludwigii</i> , <i>Pseudomonas nitirreducens</i> , <i>Alcaligenes faecalis</i> , <i>P. aeruginosa</i> and <i>P. nitroreducens</i> could grow with FLX as the sole carbon source - <i>P. nitroreducens</i> showed the highest removal of 55% of 20 mg L <sup>-1</sup> FLX after 24 hours	32
	SRB consortia from WWTP's lagoon system (anaerobic pond)	SRB consortia (10% v/v) used as the inoculum; 20, 50, and 100 mg L <sup>-1</sup> of FLX in the presence of sulphate	28–69% removal for 20 mg L <sup>-1</sup> FLX after 5–31 days 66% removal for 50 mg L <sup>-1</sup> FLX after 31 days under sulfate reducing conditions 82.1% of 16 mg L <sup>-1</sup> FLX mainly by adsorption; biodegradation also occurred. – 504 hours (21 days)	- Initial enrichments were performed without the drug and in the presence of 5, 10 and 20 mg L <sup>-1</sup> of FLX - Observed a shift in bacterial community after addition of FLX (20 mg L <sup>-1</sup> and 50 mg L <sup>-1</sup> )	33
	<i>Micrococcus yunnanensis</i> strain (isolated from autochthonous marine organisms) <i>Labrys portucalensis</i> F11	28 °C at 150 rpm in the dark for 21 days in synthetic media (MSM)			31
Algae + bacteria	Algal-bacteria pond	Aerobic, 25 °C, 30 days, 0.6–2.8 mg L <sup>-1</sup> FLX as sole carbon; 1.2–27.5 mg L <sup>-1</sup> FLX when supplied with acetate	Sole C source: up to 97% (R) and 80% S in 55 days With acetate: complete removal up to 21 μM; ≥81% at 49–89 μM in 55 days	- Observed stereoselective degradation (degradation of R more than S-enantiomer)	113
		Pilot scale, continuous mode (6 days HRT)	66% removal	- Contribution from photo-oxidation, biodegradation, adsorption, not accounted	112
Fungi	<i>Pleurotus ostreatus</i> colonized lignocellulosic matrix White-rot fungi ( <i>Bjerkandera</i> sp. R1, <i>Bjerkandera adusta</i> , <i>Phanerochaete chrysosporium</i> )	Batch and continuous studies with 600 and 750 μg L <sup>-1</sup> FLX, resp.	Batch: ~83% Column: 70%	- Combined effect of biosorption (44.7%) and enzymatic activity (19.6%)	118
		30 °C, 14 days modified Kirk medium, 1 mg L <sup>-1</sup> FLX	Partial degradation (23–46%)		117

also proposed that the drug first undergoes hydrolysis to yield 4-(trifluoromethyl)phenol (TFMP) and 3-(methylamino)-1-phenylpropan-1-ol, which is further catabolized via *meta*-cleavage to produce trifluoroacetate and fluoride ions.<sup>111</sup> However, the final product, trifluoroacetate, is both toxic and recalcitrant.

Further, in a recent study, Luz Palma *et al.* (2021) could degrade >50% and ~89% of the 20 mg L<sup>-1</sup> drug after 48 h and 144 h (6 days), respectively, using autochthonous bacteria from municipal wastewater and aerobic sludge as an

inoculum. The study further isolated six bacterial strains – *Pseudomonas putida*, *Enterobacter ludwigii*, *P. nitirreducens*, *Alcaligenes faecalis*, *P. aeruginosa* and *P. nitroreducens*, out of which *P. nitroreducens* showed the highest removal of 55 ± 1% of 20 mg L<sup>-1</sup> FLX after 24 h.<sup>32</sup> The maximum removal efficiencies of 69% and 66% were observed using anaerobic sludge as an inoculum for FLX concentrations of 20 and 50 mg L<sup>-1</sup>, respectively.<sup>33</sup> The same authors also reported the removal of 82.1 ± 0.9% of 16 mg L<sup>-1</sup> FLX after 504 h (*i.e.*, 21 days) utilizing isolated strains from marine organisms:



*Micrococcus yunnanensis* strain TJPT4 from *Hymedesmia versicolor* and *Filograna implexa*.<sup>31</sup> However, both biosorption and biodegradation contributed to the drug's removal. The efficiency of the process was reported to be 82% with a rate of 0.0538 d<sup>-1</sup> ( $R^2 = 0.9562$ ) and  $t_{1/2}$  of 13 days, while the adsorption assay with a 10% inactivated inoculum presented a removal efficiency of 81 ± 8% after 504 h, corresponding to a rate of 0.0625 d<sup>-1</sup> and  $t_{1/2}$  of 11 days ( $R^2 = 0.9689$ ). The biosorption of FLX onto the inactivated inoculum followed a pseudo-second order kinetics with an  $R^2$  of 0.9954, an equilibrium sorption capacity ( $K$ ) of 0.048 ± 0.001 g mg<sup>-1</sup> and an experimental sorption capacity of equilibrium ( $q_{eq, exp}$ ) of 13.2 ± 0.6 mg g<sup>-1</sup>.<sup>31</sup> Other studies have reported similar findings, showing that sorption significantly contributes to FLX removal.<sup>30,112</sup>

Since FLX is chiral with one chiral-carbon, certain bacteria perform enantioselective biodegradation. For instance, a study by Moreira *et al.* (2014) used a bacterial strain, *Labrys portucalensis* F11, isolated from an industrially contaminated site to degrade 100%, 80%, and 67% of S-FLX; 100%, 97% and 89% of R-FLX at initial racemic-FLX concentrations varying from 2, 4, and 9  $\mu$ M (*i.e.*, 0.6, 1.2, and 2.8 mg L<sup>-1</sup>), respectively, after 30 days of treatment. The presence of supplementary organic carbon sources, such as acetate, can further aid FLX biodegradation by achieving higher removal efficiency in a shorter period.<sup>113</sup> The study surely reported high removal for FLX; however, the rate of removal is excessively slow-paced for application in fast, dynamic, and large-scale WWTPs.

**4.4.3 Mycoremediation.** In addition to microalgae and bacteria, fungal-based solutions have shown promising potential in removing wastewater organic contaminants, and their application for wastewater remediation has been extensively reviewed recently.<sup>114–116</sup> However, only two reports have employed fungal-based degradation methods for FLX removal, and that too with low rates of FLX removal by biodegradation. For example, a report by Rodarte-Morales *et al.* (2011) studied the degradation of the antidepressant (1 mg L<sup>-1</sup>) by three white-rot fungi: *Bjerkandera adjusta*, *Phanerochaeta chrysosporium*, and an anamorph of *Bjerkandera* sp. R1, and observed poor drug removal in all the cases (maximum 46% by anamorph of *Bjerkandera* sp. R1).<sup>117</sup> This could be owed to the concentration of FLX used for the study.

In another study conducted by Silva *et al.* (2022), a mushroom substrate (CMS) colonized by *Pleurotus ostreatus* and its crude enzyme extracts, specifically laccase, were used to remove 600  $\mu$ g L<sup>-1</sup> FLX from aqueous solutions, thereby achieving a removal efficiency of >83.1% and 19.6% in 10 minutes, respectively.<sup>118</sup> Although the authors reported a synergistic contribution of biosorption onto CMS and enzymatic degradation in the degradation of the contaminant, the contribution of biosorption was much greater than biodegradation. The oxidative catabolism of extracellular lignin-modifying enzymes (LMEs), such as laccase, depends highly on the structure of the substrate. It is

acknowledged that the presence of EWGs, such as amide, halogen, carboxylic, and nitro, makes the molecule less susceptible to enzymatic oxidation by generating electron deficiency, whereas electron-donating groups (EDGs), like amines, hydroxyl, alkyl, among others, make the substrate more prone to the electrophilic attack of enzymes, thereby exhibiting good removal efficiency. FLX, despite having methyl, ether, and secondary amines (EDGs), the presence of trifluoromethyl EWG hinders the laccase-based degradation.<sup>118</sup> A more recent article suggests that the role of laccase may be limited to acting as an adsorbent rather than a degrader, particularly in the removal of perfluorinated compounds.<sup>36,119</sup>

## 5. Challenges and future perspective

As discussed in previous sections, removal of FLX *via* physical, chemical, and biological systems has been extensively studied. However, after careful review, it is clear that these techniques have significant disadvantages (Table 6). Physical removal methods are based on adsorption and only work to remove the pollutant without degrading it. The disposal of generated secondary waste material, saturated with contaminants, is another challenge. Chemical treatment, such as advanced oxidation processes (AOPs) and electrochemical methods, has a high chemical and carbon footprint and requires the optimization of influencing parameters, limiting its application in real wastewater systems. These methods generally require high energy input, chemical requirements, and/or extreme operating conditions. Further, the presence of organic matter, nitrates, phosphates, and bicarbonates affects the action of free radicals.<sup>81,95,96</sup>

Although FLX is classified as a PFAS, its structure differs from that of a long-chain PFAS, such as PFOA. The structure of conventional PFASs consists of a fully fluorinated carbon chain, whereas FLX contains aromatic rings with one trifluoromethyl group. PFOA is extremely stable and resistant to most conventional chemical, biological, and photolytic degradation, with its removal dominated by physical separation methods. In contrast, FLX is stable in water and wastewater and resistant to biological methods but can be partially degraded by AOPs and removed by adsorbent-based strategies. However, newer technologies currently being explored for PFASs can inform approaches for FLX treatment. Some recently published reviews have also discussed the possibility of using mechanochemical degradation, sonolysis, gamma ray irradiation, electron beam (eBeam), sub- and supercritical treatment, vapor energy generator (VEG), and plasma for the degradation of PFAS, in addition to bioremediation and advanced oxidation/reduction processes.<sup>120,121</sup> However, research in the area has been lacking so far for FLX, and scalability and efficiency for real environmental samples remain a challenge. The current investigations for high-energy techniques, such as eBeam, gamma-ray, and plasma, are limited to a very small scale (<1 L) and their



Table 6 Comparative assessment of FLX removal methods: advantages and limitations

Treatment technology	Advantages	Limitations
Adsorption (e.g., biochar, GAC, nanoparticles)	<ul style="list-style-type: none"> <li>- Simple and cost effective</li> <li>- Scalable</li> <li>- Effective for low/trace concentrations</li> <li>- No toxic by-products</li> <li>- No chemical transformation</li> </ul>	<ul style="list-style-type: none"> <li>- Limited desorption/regeneration strategies</li> <li>- Competitive adsorption with co-contaminants</li> </ul>
Membrane filtration (e.g., NF, RO)		<ul style="list-style-type: none"> <li>- Energy and cost intensive</li> <li>- Membrane fouling</li> <li>- Concentrate disposal issue</li> </ul>
Advanced oxidation processes (AOPs) (e.g., UV/H <sub>2</sub> O <sub>2</sub> , Fenton, O <sub>3</sub> , photocatalysis)	<ul style="list-style-type: none"> <li>- High removal efficiency</li> <li>- Capable of mineralization of FLX</li> </ul>	<ul style="list-style-type: none"> <li>- Matrix effects</li> <li>- Optimization of all working parameters (dose, time, pH)</li> <li>- pH-sensitive performance</li> <li>- High energy/chemical costs</li> <li>- Toxic intermediate and/or by-products</li> </ul>
Electrochemical oxidation	<ul style="list-style-type: none"> <li>- Fast and effective for micropollutants</li> <li>- Reusable catalysts</li> <li>- No sludge production</li> <li>- Selective and tunable</li> <li>- High removal efficiency</li> </ul>	<ul style="list-style-type: none"> <li>- Electrode fouling</li> <li>- Optimization of parameters (pH, electrode distance, current, electrode material, electrolyte)</li> <li>- Limited full-scale studies</li> <li>- Low removal efficiency for FLX</li> </ul>
Biological treatment	<ul style="list-style-type: none"> <li>- Low cost</li> <li>- Can be integrated with any physical-chemical treatment technology</li> <li>- Environmentally friendly and sustainable</li> </ul>	<ul style="list-style-type: none"> <li>- Sorption to sludge</li> </ul>

implementation is expected to incur very high costs and energy, with challenging scale-up. Some of these advanced methods also require extreme working conditions, and optimization of all working parameters, which is practically not suitable for application in WWTPs. More research is needed to develop a treatment process that could effectively remove and degrade FLX (and other PFASs) at a reduced cost and under practical field conditions.

Although bioremediation is a generally inexpensive and reliable means to degrade low concentrations of distributed pollutants, it is not currently practical for polyfluorinated compounds, including FLX, given the present level of scientific understanding.

The biodegradation of FLX may appear promising based on the studies summarized in the previous section; however, a deeper analysis of the results reveals that: (i) there is a noticeable gap in enzyme-based solutions for FLX degradation, (ii) adsorption and absorption play crucial roles in the removal of FLX from biological systems, and (iii) these processes are time intensive. Most of the studies have shown that even under enriched consortia, the half-life of FLX varies from several days to weeks, while retention time in WWTPs is usually around a few hours to 1 day. It must also be noted that most of these studies were conducted at FLX concentrations significantly higher than those typically found in the environment (Table 1). At such elevated concentrations, the drug can act as a stressor, eliciting stress-induced responses from the microbial and micro-algal-systems. In contrast, in real systems, where the concentrations are much lower (ranging from ppt to a few ppb), these responses are neither expected nor observed. Moreover, the presence of easily degradable carbon sources in wastewater, like glucose and acetate, can compete with FLX for microbial activity,

reducing the FLX biodegradation, even if the microbes are capable of degrading it.

Nevertheless, the drug continues to be detected in final effluent and sludge, despite undergoing biological treatment in WWTPs and having prolonged sludge retention times. It would, therefore, be correct to say that FLX recalcitrance is not a function of the sludge retention time (SRT) of municipal WWTPs, but its resistance to microbial transformation and low biodegradability. This raises concerns regarding the pseudo-persistence of FLX and its potential acute and chronic effects across ecosystems. Despite extensive research, effective, safe, and sustainable methods of removal for perfluorinated compounds, including FLX, remain lacking.

Previous reviews have suggested three main constraints that limit biodegradation of polyfluorinated organic compounds: rarity of natural fluorine, low tolerance of microbes to intracellular fluoride, and fluorine chemistry that makes these compounds stable. There are only a few naturally occurring organo-monofluorinated compounds, such as fluoroacetone, fluorocitric acid, and fluorothreonine, in contrast to over a million synthetic commercial polyfluorinated compounds introduced in the last few decades. This surge has put microbes at an 'evolutionary disadvantage'. Some studies indicate that the C-F bond is stable and 'harder' to enzymatically cleave than other C-X bonds, while others claim that the C-F bond can be cleaved but it is the toxicity of fluoride that poses the constraint. Microbes have acquired the ability to tolerate high concentrations of extracellular fluoride by expelling the anion out of the cells using membrane export proteins. However, the cleavage of the C-F bond generates a much higher concentration of intracellular fluoride, which is toxic and makes them non-viable. That means if the microbe has the



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potential to cleave a C-F bond, it will toxify itself and die, thereby extinguishing the idea of evolutionary innovation.<sup>36</sup> This leaves the knowledge gap in the remediation of organofluorinated compounds unfilled.

Recent review articles suggest addressing this gap by developing 'fluorophiles' and engineering or identifying novel defluorinating enzymes using machine learning tools, adaptive laboratory evolution, and rational enzyme design. Meanwhile, further research is needed to validate these approaches experimentally and assess their feasibility in real environmental contexts.

As natural evolutionary processes continue to adapt and refine microbial capabilities to tackle polyfluorinated organic compounds, it is important that we persist in our efforts. Given current resources, a compelling path forward lies in employing hybrid techniques combining physical, chemical, and biological strategies as a treatment chain. To begin with, the strong tendency of polyfluorinated pharmaceuticals, FLX and NFLX, to adsorb can be exploited, which not only concentrates these widely distributed pollutants for further treatment but also lowers the energy demand of the entire process. For this, carbon-based adsorbents, such as activated carbon and biochar, ion-exchange resins, and synthetic porous carriers, can provide effective and sustainable solutions. The spent adsorbent used for physical removal can then be subjected to degradation *via* electrochemical, AOPs, or thermal methods. They are effective in treating FLX-concentrated, small-volume streams and will ensure no legacy problems by degradation rather than mere physical removal. A commercial solution, Nyex Rosalox, as mentioned earlier, has combined electrochemical oxidation with adsorption for effective removal of FLX. However, toxic by-products can form, which may need further treatment before environmental release. This highlights the need for combining chemical degradation with biological treatment, where the former fragments aromatic structures and the latter mineralizes the biodegradable residuals and intermediates. This also reduces total organic carbon (TOC) and toxicity and offers sustainability to the treatment chain. Catalytic ozonation, electro-Fenton, and UVC/solar irradiation, coupled with a moving bed biofilm reactor (MBBR) or biofilters, can be seen as a promising solution to FLX-contamination.

In some cases, two methods can be combined to reduce the steps in the treatment chain, thereby improving efficiency and reducing operational complexity. For instance, immobilization of the photocatalyst on porous carriers with UVC/solar irradiation can be directly followed by biological systems. Another example includes coupling of AOPs with biological activated carbon (BAC), combining biological (MBBR or biofilters) and physical methods. Such integrative technologies can enhance treatment efficiency and overcome the limitations of a single technique. While this can enhance treatment performance, the environmental footprint, sustainability, and resource efficiency must be evaluated using life cycle assessment (LCA). Future studies must

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quantify energy use, emissions, and potential secondary pollution across single and hybrid treatment stages to inform sustainable research in the area.

Beyond these hybrid approaches, source control and regulatory frameworks can also play a crucial role in mitigating FLX pollution. With the development of greener FLX analogues or the use of safer, more biodegradable FLX alternatives, environmental burden could potentially be controlled at the source. Further, by pairing scientific advances and 'control at source' strategies with thoughtful and practical policy, such as setting up discharge standards, monitoring guidelines, and ensuring compliance, sustainable pharmaceutical management can be achieved.

## Author contributions

Pratishtha Khurana: conceptualization, writing – original draft; Ratul Kumar Das: writing – review and editing; Satinder Kaur Brar: writing – review and editing, funding acquisition.

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Supplementary information is available. See DOI: <https://doi.org/10.1039/D5EW00636H>.

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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