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Issues of Non-Steroidal Anti-Inflammatory Drugs in Aquatic Environments: A Review Study †

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Abstract: The quality of wastewater greatly affects the aquatic environment. Currently, a significant amount of emerging pollutants are entering wastewater in the form of pharmaceutical contaminants, industrial chemicals, pesticides, toxins, etc. However, conventional wastewater treatment processes at WWTPs are not effective enough for these emerging pollutants. Therefore, emerging pollutants represent a significant source of wastewater pollution and associated pollution of surface water and even drinking water. The main sources of pharmaceutical contaminants are analgesics and anti-inflammatory drugs, and of these, the most common in wastewater are non-steroidal anti-inflammatory drugs (NSAIDs). The aim is to provide a comprehensive review of the available information on NSAIDs in the aquatic environment, i.e., their occurrence, effects on the environment, formation of main metabolites, and methods of NSAID removal, with a focus on current trends and possible directions for future research.

Keywords: non-steroidal anti-inflammatory drugs; aquatic environment; metabolites; ibuprofen; diclofenac; naproxen; ketoprofen

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1. Introduction

The issue of water quality in the aquatic environment (referring to wastewater, surface waters, and groundwater) is a widely discussed topic worldwide. These water sources commonly contain nitrates, heavy metals (e.g., Pb, Cd, Ni), persistent organic pollutants (such as PAHs, PCBs, $C_{10–40}$), etc. [1–5]. There is an European Pollutant Release and Transfer Register (E-PRTR), which includes a list of such substances totaling nearly one hundred. This register is established based on the regulations of the European Parliament and the Council (EU) and the implementing decisions of the Commission (EU). Its purpose is to control the quality of the environment [6].

Currently, in addition to the common pollution in the aquatic environment, there are so-called emerging contaminants. Emerging contaminants include personal care products, industrial chemicals, pharmaceutical residues, steroid hormones, endocrine-disrupting chemicals, microplastics, and others [7–9]. These emerging contaminants are not part of the E-PRTR, and their occurrence is not regulated by legislative measures. However, these contaminants have been repeatedly found in water sources. Their impact on the environment is not sufficiently known. Therefore, water quality experts are devoting significant efforts to researching the occurrence, adverse effects, and possible methods of removing emerging contaminants from the aquatic environment [8,9].

Among the frequently monitored emerging contaminants are pharmaceutical residues in the form of pharmaceuticals and personal care products (PPCPs) (e.g., carbamazepine, gabapentin, triclosan, furosemide, warfarin), nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, diclofenac, naproxen, ketoprofen, aspirin), medications affecting the central nervous system (e.g., paracetamol, tramadol, metoprolol, oxazepam, diazepam, caffeine), macrolide antibiotics (e.g., erythromycin, clarithromycin, azithromycin), and hormones (e.g., estrone, 17-β-estradiol, 17-α-ethinylestradiol) [10]. At the same time, NSAIDs are among the most frequently occurring contaminants in the aquatic environment [11,12]. This is mainly due to their high consumption, which ranks them among the most consumed medications [13]. The aim of this overview is to provide a comprehensive summary of available information on the issue of NSAIDs (non-steroidal anti-inflammatory drugs) in the aquatic environment, including their occurrence, environmental effects, formation of major metabolites, and methods of NSAID removal, focusing on current trends and potential directions for future research.

2. Selection and Characterization of NSAIDs

NSAIDs, with their effects, belong to analgesics (pain relievers), antipyretics (reduce fever), and anti-inflammatory agents. They are used for colds, flu, and arthritis; to alleviate headaches, toothaches, and muscle pain; during menstruation; and for sprains or strains. They act on the central nervous system similarly to steroids, but without their adverse effects. NSAIDs are typically available over the counter or prescribed by a doctor [11–15]. In the environment, they have been found not only in the aquatic environment but also in soil, sediments, and even in drinking water. Their typical concentrations range from ng/L to µg/L. Despite these low concentrations, they can have toxic effects on living organisms based on their high bioactivity [14,15].

Among the representatives of NSAIDs most commonly found in the environment, there are diclofenac, ibuprofen, naproxen, and ketoprofen [12,13,15–17]. Diclofenac (DICL) is a widely used analgesic for both human and veterinary purposes worldwide. It is used to alleviate all kinds of pain, and its consumption amounts to several thousand tons per year. Diclofenac can accumulate in various environmental components due to its low biodegradability. In addition to being found in water bodies, it has been detected in soil, sediments, and even in drinking water [11]. In 2015, DICL was included in the list of monitored substances based on the Commission Implementing Decision (EU), but it was subsequently removed from the list in 2018 [18]. However, studies, e.g., [12,13,19], have reported its presence in the aquatic environment at concentrations higher than 0.1 µg/L (the proposed threshold by the European Framework Directive for Water) [20]. Therefore, it is still important to gather information not only about its occurrence but also about its potential effects on the environment. Ketoprofen (KET) is utilized for its analgesic and antipyretic effects, while ibuprofen (IBU) and naproxen (NAP) are also used for their anti-inflammatory effects (IBU has short-term effects, while NAP has long-term effects) [11]. Similar to DICL, their global annual consumption is estimated to be several thousand tons. These medications can enter the aquatic environment through industrial and domestic wastewater. These NSAIDs can negatively impact water quality and have chronic effects on living organisms. Therefore, it is essential to investigate the fate of NSAIDs in the aquatic environment [21].

3. Occurrence of NSAIDs in the Aquatic Environment

NSAIDs are usually over-the-counter drugs, and, therefore, they are easily accessible. These medications belong to the group of drugs with high daily dosages, and after passing through the human body, these NSAIDs become a significant source of pollution in the wastewater system (in their unchanged form or as metabolites). Another contribution to wastewater pollution by NSAIDs can come from residues from their production, hospital waste, or agriculture. Through this contamination, wastewater can become contaminated, leading to the pollution of surface waters and, occasionally, underground and drinking water as well.In other words, the production, consumption, disposal, and application of NSAIDs have an impact on overall water pollution [22].

From the data presented in the review study [22], Figure 1 was created by the authors, illustrating the extent of NSAID wastewater pollution worldwide. In South America and

Asia, lower concentrations of NSAIDs (hundreds of ng/L) were observed, while significantly higher concentrations (thousands of ng/L or µg/L) were found in Australia, Africa, North America, and Europe. This varying occurrence of NSAIDs in wastewater can be influenced by population density, the number of hospital facilities connected to the sewage system, the pharmaceutical industry, agriculture, aquaculture, the treatment processes of specific wastewater treatment plants (WWTPs), or relevant legislative regulations [22].

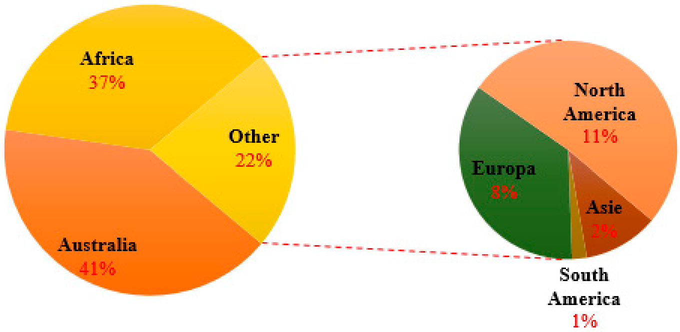

Figure 1. Level of global pollution of wastewater by NSAIDs.

Table 1 presents the results of global studies focusing on the presence of NSAIDs in aquatic environments. Frequently observed concentrations of NSAIDs range from 0.7 to 420 ng/L in Asia [11,23], 9 to 328 ng/L in South America [24,25], 23 to 1830 ng/L in Europe [11,13,18], 5 to 4880 ng/L in North America [23,26], 147 to 9585 ng/L in Africa [11,12,19], and 80 to 11,165 ng/L in Australia [27,28] in aquatic environments. In the case of monitoring lower concentrations, the study focused on surface water, groundwater, or drinking water [11,24,27], whereas inflows of municipal wastewater exhibited higher concentrations of NSAIDs [18,19].This is also evidenced, for example, by studies on wastewater [23] and drinking water [11] in China or studies on effluent [19] and influent [12] from WWTPs in Algeria, where there is an order of magnitude difference in NSAID concentrations.

Table 1. Occurrence of NSAIDs in aquatic environments worldwide.

Where/When		**Concentration NSAID [ng/L]**				**Ref.**
		IBU	**DICL**	**NAP**	**KET**	
Europe	Spain/2016, 2018	- 179	344 65	96 -	106 357	[13] [11]
	Greece/2022	-	119–620	40	23	[18]
	Finland/2016	1830	-	1687	-	[11]
Asia	China/2005, 2019	420 0.7	- 40	30 5	- 2	[23] [11]
	Korea/2009	414	-	-	-	[23]
Africa	South Africa/2016	3870–8500	-	<1500–5340	1200–9220	[19]
	Algeria/2014 Algeria/2016	340–430 1608	1615–2710 2319	333 9585	1035 -	[12] [19]
	Morocco/2022	274	147	197	198	[11]
North America	Canada/2006	5–8	-	-	-	[23]
	Mexico/2018	231–1106	283–1209	33–4880	-	[26]
South America	Columbia/2017	9–32	-	-	-	[24]
	Brazil/2020	<100–320	<100–328	-	-	[27]

Table 1. *Cont.*

Where/When		Concentration NSAID [ng/L]				Ref.
		IBU	DICL	NAP	KET	
Australia	Sydney/2020	80–150	-	-	-	[27]
	New Zealand/2019	3149–11,165	142–245	414–7976	-	[28]

4. Effects of NSAIDs on the Environment

NSAIDs occur in trace amounts in environmental compartments (water, soil, sediments). While their primary purpose is the treatment of diseases and the recovery of humans and animals, their presence in the environment can cause adverse effects on non-target organisms [29–31]. It has been demonstrated that NSAID representatives pose a health risk to birds, freshwater fish, mollusks, plants, algae, and bacteria due to their effects [20,29–36]. Another issue is the potential formation of metabolites from the original drug form. For example, it has been proven that IBU and DICL metabolites can occur in higher concentrations in water environments. Such metabolites can be more persistent and pose a more severe risk to non-target organisms [37,38].

The specific effects of IBU include toxicity to phytoplankton [31], algae, and bacteria [36]; kidney and gill damage in freshwater fish [31,35]; effects on bone development, aerobic respiration, and immune functions in freshwater fish [35]; chronic effects on aquatic organisms (reduced sperm motility and hatching) [29]; impact on the immune system; genotoxic effects [33]; and induction of morphological and ultrastructural changes in algal cells [35]. For DICL, the proven negative effects include extreme toxicity to vultures [30]; toxicity to phytoplankton [31], river biofilm communities [29], and broilers [35]; damage to the kidneys, liver, gills, testes, brain, and DNA in fish [20,31]; cardiac anomalies and cardiovascular defects in freshwater fish [34]; chronic effects on fish (reduced hatching, delayed hatching, reduced growth in the egg stage); cytological changes and tissue damage in freshwater fish [29]; and impact on the immune system and genotoxic effects [33]. Similarly to IBU, NAP also acts toxically on phytoplankton [31] and causes damage to the kidneys, liver, and gills in freshwater fish [20,31], additionally affecting the growth and photosynthetic processes of plants [32]. KET, like IBU and DICL, causes cardiac anomalies and cardiovascular defects in freshwater fish, affects the immune system, and has genotoxic effects [33,34,36].

From the studies conducted so far, it can be said that IBU and DICL pose a high eco-toxicological risk, while NAP and KET pose a moderate eco-toxicological risk to non-target organisms [36].

5. Main Metabolites of NSAIDs

During metabolism in living organisms, IBU undergoes oxidation and subsequent conjugation with glucuronic acid. The original form of IBU is transformed into two main metabolites: hydroxy-ibuprofen (OH-IBU) and carboxy-ibuprofen (CA-IBU). Approximately 15% of IBU is excreted unchanged after the metabolic process, while CA-IBU accounts for 43% and OH-IBU for 26% of the total IBU ingested [39]. In the case of DICL, metabolism involves hydroxylation of the methyl group, resulting in the formation of 4′-hydroxydiclofenac (4′OH-DICL). Only 6% of the total amount of DICL ingested is excreted in its original form, while 16% is excreted as 4′OH-DICL [40]. NAP is mainly metabolized into naproxen glucuronide and O-desmethyl-naproxen [11], and KET is transformed into ketoprofen glucuronide through metabolism [41].

6. Methods of Removing NSAIDs from the Aquatic Environment

In the EU, the regular use of around three thousand drugs, including NSAIDs, is estimated. These substances end up in wastewater, and the current technologies for their treatment are not sufficiently effective because the original design of WWTPs did not consider them. As a result, surface waters and, in rare cases, even groundwater and drinking water become contaminated, i.e., the aquatic environment. Therefore, it is necessary to also study the possibilities of an additional treatment stage in WWTPs. This issue has been addressed in studies [13,42–44], where effective methods for treating NSAIDs have been confirmed, such as adsorption processes, membrane separations, advanced oxidation processes, or biodegradation/biotransformation. The adsorption technique is highly versatile, flexible, simple, fast, easily operable, and does not result in sludge formation, unlike membrane separation [45]. The key to adsorption is the selection of a suitable adsorbent, which can be activated carbon [42,43], sewage sludge [13,45], or agricultural/industrial/domestic waste [46]. On the other hand, membrane separation utilizes membranes ((non)porous, with various shapes, made of polymeric, ceramic, or mixed matrices, charged/neutral, etc.). Based on the pore size in membranes, we distinguish reverse osmosis, nanofiltration [13], microfiltration, and ultrafiltration [45]. As the pore size decreases, the efficiency of contaminant elimination increases, but it also leads to higher operational and financial demands [13]. Advanced oxidation processes include chemical [44], electrochemical, or photochemical [13,44,47] methods. However, advanced oxidation processes often result in the formation of intermediate products that are more toxic than the original micropollutants. To improve efficiency, combined techniques are utilized, such as combining advanced oxidation processes with membrane separation or biological processes [48]. The method of biodegradation/biotransformation is based solely on biological processes. In this method, plants assist in the elimination of contaminants [13,42] through the process of microbial degradation, which occurs through adsorption, absorption, and the process of metabolism.

The conducted studies on the elimination of NSAIDs, along with the effectiveness of the selected elimination process, are presented in Table 2. In the case of IBU elimination, high efficiency was achieved through adsorption [43,46], membrane separation (nanofiltration) [13], biodegradation/biotransformation [42], or with the help of combined techniques (adsorption + ozonation [29], adsorption + solid-phase extraction [49], adsorption + membrane separation [44]). Similar results were obtained for DICL and NAP. Successful solutions were also found with the use of a membrane bioreactor, which achieved an elimination efficiency of >90% for IBU, DICL, NAP, and KET [44].

Table 2. Implemented elimination processes of individual NSAIDs and their percentage effectiveness.

PROCESS	IBU	DICL	NAP	KET
ADSORPTION (activated carbon, biochar, or activated sludge)	90–96% [43,46]	89–95% [43]	88–94% [13,42]	-
MEMBRANE SEPARATION	86–99% (nanofiltration) [13]	90–99% (nanofiltration) [45]	95% (reverse osmosis) [13]	-
ADVANCED OXIDATION PROCESSES (AOP)	81% [47]	85–87 [13,47]	83–90% [44]	-
BIODEGRADATION/BIOTRANSFORMATION	90–99% [42]	90–99% [13]	68.6–90% [42]	-
ADSORPTION (activated carbon) + ozonation	>93% [29]	-	-	-
ADSORPTION (magnetic activated carbon) + magnetic solid-phase extraction + UV radiation	-	94% [49]	82% [49]	93% [49]
ADSORPTION and solid-phase microextraction	77–96% [49]	-	-	77–96% [49]
ADSORPTION (metal-organic frameworks) + magnetic solid-phase extraction	84–110% [49]			
ADSORPTION (activated sludge) + MEMBRANE SEPARATION, the so-called membrane bioreactor	95% [44]	95% [44]	98% [44]	90% [44]

7. Future Research

This overview is a comprehensive summary of the available information on the issue of NSAIDs in the aquatic environment. It evaluates the occurrence of NSAIDs, their effects on the environment, metabolic byproducts, and potential elimination from wastewater. The main gaps regarding the issue of NSAIDs in the water environment include the following:

- Unspecified requirements for potential tertiary treatment of wastewater from WWTPs;
- Non-existent threshold concentrations of NSAIDs in aquatic environments;
- Lack of information on the occurrence of metabolic byproducts of NSAIDs.

Future research should, therefore, focus on exploring possibilities for improving wastewater treatment using affordable, effective, and sustainable technologies. Additionally, studying the long-term effects of NSAIDs on ecosystems and human health is crucial in order to establish permissible concentrations of NSAIDs in the aquatic environment that do not burden the environment. It is also necessary to investigate the presence of metabolic byproducts from the original form of NSAIDs and their potential adverse effects on the environment.

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References

1. Foltová, P.; Heviankova, S.; Chromikova, J.; Kasparkova, A. Increased concentrations of nitrates in groundwater in selected localities of the Moravian–Silesian and Olo-mouc Regions in the Czech Republic. *Inz. Miner.* **2018**, *2018*, 35–38.
2. Fei, Y.; Hu, Y.H. Recent progress in removal of heavy metals from wastewater: A comprehensive review. *Chemosphere* **2023**, *335*, 139077. [CrossRef]
3. Kotalova, I.; Calabkova, K.; Drabinova, S.; Heviankova, S. Contribution to the study of selected heavy metals in urban wastewaters using ICP-MS method. *IOP Conf. Ser. Earth Environ. Sci.* **2020**, *444*, 012028. [CrossRef]
4. Vojtková, H.; Maslanová, I.; Sedlácek, I.; Svanová, P.; Janulková, R. Removal of heavy metals from wastewater by a *Rhodococcus* sp. Bacterial strain. In Proceedings of the 12th International Multidisciplinary Scientific Geoconference & Expo, Albena, Bulgaria, 17–23 June 2012.
5. Rosińska, A. The influence of UV irradiation on PAHs in wastewater. *J. Environ. Manag.* **2021**, *293*, 112760. [CrossRef] [PubMed]
6. European Pollutant Releases and Transfer Register—E-PRTR. Integrovaný Registr Znečišťování Životního Prostředí [Online]. 2021. Available online: www.irz.cz/registry-znecistovani/evropsky-registr-uniku-a-prenosu-znecistujicich-latek-e-prtr (accessed on 30 July 2023).
7. Chen, Y.; Lin, M.; Zhuang, D. Wastewater treatment and emerging contaminants: Bibliometric analysis. *Chemosphere* **2022**, *297*, 133932. [CrossRef] [PubMed]
8. Kumar, R.; Qureshi, M.; Vishwakarma, D.K.; Al-Ansari, N.; Kuriqi, A.; Elbeltagi, A.; Saraswat, A. A review on emerging water contaminants and the application of sustainable removal technologies. *Case Stud. Chem. Environ. Eng.* **2022**, *6*, 100219. [CrossRef]
9. Halfar, J.; Brožová, K.; Čabanová, K.; Heviánková, S.; Kašpárková, A.; Olšovská, E. Disparities in Methods Used to Determine Microplastics in the Aquatic Environment: A Review of Legislation, Sampling Process and Instrumental Analysis. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7608. [CrossRef] [PubMed]
10. Morin-Crini, N.; Lichtfouse, E.; Liu, G.; Balaram, V.; Ribeiro, A.R.L.; Lu, Z.; Stock, F.; Carmona, E.; Teixeira, M.R.; Picos-Corrales, L.A.; et al. Worldwide cases of water pollution by emerging contaminants: A review. *Environ. Chem. Lett.* **2022**, *20*, 2311–2338. [CrossRef]
11. Hawash, H.B.; Moneer, A.A.; Galhoum, A.A.; Elgarahy, A.M.; Mohamed, W.A.; Samy, M.; El-Seedi, H.R.; Gaballah, M.S.; Mubarak, M.F.; Attia, N.F. Occurrence and spatial distribution of pharmaceuticals and personal care products (PPCPs) in the aquatic environment, their characteristics, and adopted legislations. *J. Water Process. Eng.* **2023**, *52*, 103490. [CrossRef]

12. Kermia, A.E.B.; Fouial-Djebbar, D.; Trari, M. Occurrence, fate and removal efficiencies of pharmaceuticals in wastewater treatment plants (WWTPs) discharging in the coastal environment of Algiers. *Comptes Rendus Chim.* **2016**, *19*, 963–970. [CrossRef]
13. Sapingi, M.S.M.; Khasawneh, O.F.S.; Palaniandy, P.; Aziz, H.A. Analytical techniques for the detection of pharmaceuticals in the environment. In *The Treatment of Pharmaceutical Wastewater*; Elsevier: Amsterdam, The Netherlands, 2023; pp. 149–177, ISBN 9780323991605. [CrossRef]
14. Samal, K.; Mahapatra, S.; Ali, H. Pharmaceutical wastewater as Emerging Contaminants (EC): Treatment technologies, impact on environment and human health. *Energy Nexus* **2022**, *6*, 100076. [CrossRef]
15. Bankole, D.T.; Oluyori, A.P.; Inyinbor, A.A. The removal of pharmaceutical pollutants from aqueous solution by Agro-waste. *Arab. J. Chem.* **2023**, *16*, 104699. [CrossRef]
16. Oluwalana, A.E.; Musvuugwa, T.; Sikwila, S.T.; Sefadi, J.S.; Whata, A.; Nindi, M.M.; Chaukura, N. The screening of emerging micropollutants in wastewater in Sol Plaatje Municipality, Northern Cape, South Africa. *Environ. Pollut.* **2022**, *314*, 120275. [CrossRef] [PubMed]
17. Dubey, M.; Vellanki, B.P.; Kazmi, A.A. Fate of emerging contaminants in a sequencing batch reactor and potential of biological activated carbon as tertiary treatment for the removal of persisting contaminants. *J. Environ. Manag.* **2023**, *338*, 117802. [CrossRef] [PubMed]
18. Ofrydopoulou, A.; Nannou, C.; Evgenidou, E.; Christodoulou, A.; Lambropoulou, D. Assessment of a wide array of organic micropollutants of emerging concern in wastewater treatment plants in Greece: Occurrence, removals, mass loading and potential risks. *Sci. Total Environ.* **2022**, *802*, 149860. [CrossRef] [PubMed]
19. Waleng, N.J.; Nomngongo, P.N. Occurrence of pharmaceuticals in the environmental waters: African and Asian perspectives. *Environ. Chem. Ecotoxicol.* **2022**, *4*, 50–66. [CrossRef]
20. Näslund, J.; Asker, N.; Fick, J.; Larsson, D.J.; Norrgren, L. Naproxen affects multiple organs in fish but is still an environmentally better alternative to diclofenac. *Aquat. Toxicol.* **2020**, *227*, 105583. [CrossRef]
21. Letsoalo, M.R.; Sithole, T.; Mufamadi, S.; Mazhandu, Z.; Sillanpaa, M.; Kaushik, A.; Mashifana, T. Efficient detection and treatment of pharmaceutical contaminants to produce clean water for better health and environmental. *J. Clean. Prod.* **2023**, *387*, 135798. [CrossRef]
22. Adeleye, A.S.; Xue, J.; Zhao, Y.; Taylor, A.A.; Zenobio, J.E.; Sun, Y.; Han, Z.; Salawu, O.A.; Zhu, Y. Abundance, fate, and effects of pharmaceuticals and personal care products in aquatic environments. *J. Hazard. Mater.* **2022**, *424*, 127284. [CrossRef]
23. Kumar, M.; Sridharan, S.; Sawarkar, A.D.; Shakeel, A.; Anerao, P.; Mannina, G.; Sharma, P.; Pandey, A. Current research trends on emerging contaminants pharmaceutical and personal care products (PPCPs): A comprehensive review. *Sci. Total Environ.* **2023**, *859*, 160031. [CrossRef]
24. Aristizabal-Ciro, C.; Botero-Coy, A.M.; López, F.J.; Peñuela, G.A. Monitoring pharmaceuticals and personal care products in reservoir water used for drinking water supply. *Environ. Sci. Pollut. Res.* **2017**, *24*, 7335–7347. [CrossRef] [PubMed]
25. Chaves, M.d.J.S.; Barbosa, S.C.; Malinowski, M.d.M.; Volpato, D.; Castro, B.; Franco, T.C.R.d.S.; Primel, E.G. Pharmaceuticals and personal care products in a Brazilian wetland of international importance: Occurrence and environmental risk assessment. *Sci. Total Environ.* **2020**, *734*, 139374. [CrossRef] [PubMed]
26. Rivera-Jaimes, J.A.; Postigo, C.; Melgoza-Aleman, R.M.; Acena, J.; Barcelo, D.; Lopez de Alda, M. Study of pharmaceuticals in surface and wastewater from Cuernavaca, Morelos, Mexico: Occurrence and environmental risk assessment. *Sci. Total Environ.* **2018**, *613–614*, 1263–1274. [CrossRef] [PubMed]
27. McKenzie, T.; Holloway, C.; Dulai, H.; Tucker, J.P.; Sugimoto, R.; Nakajima, T.; Harada, K.; Santos, I.R. Submarine groundwater discharge: A previously undocumented source of contaminants of emerging concern to the coastal ocean (Sydney, Australia). *Mar. Pollut. Bull.* **2020**, *160*, 111519. [CrossRef]
28. Kumar, R.; Sarmah, A.K.; Padhye, L.P. Fate of pharmaceuticals and personal care products in a wastewater treatment plant with parallel secondary wastewater treatment train. *J. Environ. Manag.* **2019**, *233*, 649–659. [CrossRef]
29. Lonappan, L.; Brar, S.K.; Das, R.K.; Verma, M.; Surampalli, R.Y. Diclofenac and its transformation products: Environmental occurrence and toxicity—A review. *Environ. Int.* **2016**, *96*, 127–138. [CrossRef]
30. Okoye, C.O.; Okeke, E.S.; Okoye, K.C.; Echude, D.; Andong, F.A.; Chukwudozie, K.I.; Okoye, H.U.; Ezeonyejiaku, C.D. Occurrence and fate of pharmaceuticals, personal care products (PPCPs) and pesticides in African water systems: A need for timely intervention. *Heliyon* **2022**, *8*, e09143. [CrossRef]
31. Mohan, H.; Rajput, S.S.; Jadhav, E.B.; Sankhla, M.S.; Sonone, S.S.; Jadhav, S.; Kumar, R. Ecotoxicity, Occurrence, and Removal of Pharmaceuticals and Illicit Drugs from Aquatic Systems. *Biointerface Res. Appl. Chem.* **2021**, *11*, 12530–12546. [CrossRef]
32. Zezulka, Š.; Kummerová, M.; Šmeringai, J.; Babula, P.; Tříska, J. Ambiguous changes in photosynthetic parameters of Lemna minor L. after short-term exposure to naproxen and paracetamol: Can the risk be ignored? *Aquat. Toxicol.* **2023**, *259*, 106537. [CrossRef]
33. Mezzelani, M.; Gorbi, S.; Fattorini, D.; D'errico, G.; Consolandi, G.; Milan, M.; Bargelloni, L.; Regoli, F. Long-term exposure of Mytilus galloprovincialis to diclofenac, Ibuprofen and Ketoprofen: Insights into bioavailability, biomarkers and transcriptomic changes. *Chemosphere* **2018**, *198*, 238–248. [CrossRef]
34. Selderslaghs, I.W.; Blust, R.; Witters, H.E. Feasibility study of the zebrafish assay as an alternative method to screen for developmental toxicity and embryotoxicity using a training set of 27 compounds. *Reprod. Toxicol.* **2012**, *33*, 142–154. [CrossRef]

35. Jiang, L.; Li, Y.; Chen, Y.; Yao, B.; Chen, X.; Yu, Y.; Yang, J.; Zhou, Y. Pharmaceuticals and personal care products (PPCPs) in the aquatic environment: Biotoxicity, determination and electrochemical treatment. *J. Clean. Prod.* **2023**, *388*, 135923. [CrossRef]
36. Wojcieszyńska, D.; Guzik, H.; Guzik, U. Non-steroidal anti-inflammatory drugs in the era of the Covid-19 pandemic in the context of the human and the environment. *Sci. Total Environ.* **2022**, *834*, 155317. [CrossRef]
37. La Farré, M.; Pérez, S.; Kantiani, L.; Barceló, D. Fate and toxicity of emerging pollutants, their metabolites and transformation products in the aquatic environment. *TrAC Trends Anal. Chem.* **2008**, *27*, 991–1007. [CrossRef]
38. Leclercq, M.; Mathieu, O.; Gomez, E.; Casellas, C.; Fenet, H.; Hillaire-Buys, D. Presence and Fate of Carbamazepine, Oxcarbazepine, and Seven of Their Metabolites at Wastewater Treatment Plants. *Arch. Environ. Contam. Toxicol.* **2009**, *56*, 408–415. [CrossRef] [PubMed]
39. Tan, S.; Jackson, S.; Swift, C.; Hutt, A. Stereospecific analysis of the major metabolites of ibuprofen in urine by sequential achiral-chiral high-performance liquid chromatography. *J. Chromatogr. B Biomed. Sci. Appl.* **1997**, *701*, 53–63. [CrossRef] [PubMed]
40. Stülten, D.; Zühlke, S.; Lamshöft, M.; Spiteller, M. Occurrence of diclofenac and selected metabolites in sewage effluents. *Sci. Total Environ.* **2008**, *405*, 310–316. [CrossRef]
41. Drover, V.J.; Bottaro, C.S. Determination of pharmaceuticals in drinking water by CD-modified MEKC: Separation optimization using experimental design. *J. Sep. Sci.* **2008**, *31*, 3740–3748. [CrossRef]
42. AL Falahi, O.A.; Abdullah, S.R.S.; Abu Hasan, H.; Othman, A.R.; Ewadh, H.M.; Kurniawan, S.B.; Imron, M.F. Occurrence of pharmaceuticals and personal care products in domestic wastewater, available treatment technologies, and potential treatment using constructed wetland: A review. *Process Saf. Environ. Prot.* **2022**, *168*, 1067–1088. [CrossRef]
43. Liu, T.; Aniagor, C.O.; Ejimofor, M.I.; Menkiti, M.C.; Tang, K.H.D.; Chin, B.L.F.; Chan, Y.H.; Yiin, C.L.; Cheah, K.W.; Chai, Y.H.; et al. Technologies for removing pharmaceuticals and personal care products (PPCPs) from aqueous solutions: Recent advances, performances, challenges and recommendations for improvements. *J. Mol. Liq.* **2023**, *374*, 121144. [CrossRef]
44. Hossein, M.; Asha, R.; Bakari, R.; Islam, N.F.; Jiang, G.; Sarma, H. Exploring eco-friendly approaches for mitigating pharmaceutical and personal care products in aquatic ecosystems: A sustainability assessment. *Chemosphere* **2023**, *316*, 137715. [CrossRef] [PubMed]
45. Osuoha, J.O.; Anyanwu, B.O.; Ejileugha, C. Pharmaceuticals and personal care products as emerging contaminants: Need for combined treatment strategy. *J. Hazard. Mater. Adv.* **2023**, *9*, 100206. [CrossRef]
46. Ayati, A.; Tanhaei, B.; Beiki, H.; Krivoshapkin, P.; Krivoshapkina, E.; Tracey, C. Insight into the adsorptive removal of ibuprofen using porous carbonaceous materials: A review. *Chemosphere* **2023**, *323*, 138241. [CrossRef] [PubMed]
47. Javaid, A.; Latif, S.; Imran, M.; Hussain, N.; Rajoka, M.S.R.; Iqbal, H.M.; Bilal, M. Nanohybrids-assisted photocatalytic removal of pharmaceutical pollutants to abate their toxicological effects—A review. *Chemosphere* **2022**, *291*, 133056. [CrossRef]
48. Alessandretti, I.; Rigueto, C.V.T.; Nazari, M.T.; Rosseto, M.; Dettmer, A. Removal of diclofenac from wastewater: A comprehensive review of detection, characteristics and tertiary treatment techniques. *J. Environ. Chem. Eng.* **2021**, *9*, 106743. [CrossRef]
49. Yang, L.; Wang, S.; Xie, Z.; Xing, R.; Wang, R.; Chen, X.; Hu, S. Deep eutectic solvent-loaded Fe3O4@MIL-101(Cr) with core–shell structure for the magnetic solid phase extraction of non-steroidal anti-inflammatory drugs in environmental water samples. *Microchem. J.* **2023**, *184*, 108150. [CrossRef]