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# Comprehensive insights on the detection, occurrence and modelling of pharmaceuticals in surface water, groundwater, and drinking water treatment plants

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ABSTRACT

Pharmaceuticals have received extensive scientific and socio-economic attention worldwide due to their acute and chronic toxic effects on plants, animals, and human health. However, the geographical distribution and seasonal variability of pharmaceutical mixtures in aquatic environments remain underexplored, especially in resource-deficient countries. The present review provides an in-depth analysis of the seasonal occurrence of pharmaceuticals, particularly antibiotics detected over the last five years in surface water, groundwater, and drinking water. The effectiveness of the conventional and advanced drinking water treatment processes is discussed with a focus on the adsorption and ozonation processes, commonly employed at drinking water treatment plants (DWTPs). Findings reveal median concentrations of antibiotics and other pharmaceuticals in drinking water worldwide, often exceeding their levels in groundwater. This underscores the urgent need for global-scale, long-term monitoring of antibiotics in aquatic systems, especially in DWTPs. Beyond targeted analysis, non-targeted analysis (NTA) should be integrated into routine water quality monitoring at DWTPs to identify novel contaminants, including fluorinated pharmaceuticals. Finally, this review provides an overview concerning the process-based and data-driven modelling of pharmaceutical occurrence, fate, and transport as a complementary approach to sampling and lab-scaled experiments, especially in resource-limited settings. Strengthening long-term monitoring, expanding treatment solutions, integrating modelling tools, and promoting green chemistry innovations are crucial to mitigating risks and safeguarding water quality.

## 1. Introduction

Scientific concerns about pharmaceuticals presence in the environment have increased due to their negative effects on human and ecosystem health, as well as their role in promoting antimicrobial resistance (Menon et al., 2020; Pal et al., 2010, 2014). Among pharmaceuticals, the global market for antibiotics beta-lactam and beta-lactamase inhibitors is forecasted to reach a value of 34.2 billion U.S. dollars in 2030 from its market value of 27.5 billion U.S. dollars reported for 2019 (Statista, 2023). The Annual Epidemiological Report on antimicrobial consumption in the EU/EEA (ESAC—Net) estimated the average total consumption of antibacterials for systemic use (ATC group J01) at 19.4 (Fig. 1) defined daily doses (DDD) per 1000 individuals per day, with notable variations across countries (ECDPC, 2023). The highest consumption was reported for Greece, followed by Romania, whereas the lowest was reported for The Netherlands.

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With rising antibiotic use, environmental contamination is an inevitable consequence. Several studies have reported the presence of pharmaceuticals in various water matrices, including wastewater (Houtmanet al., 2014; Mohapatra et al., 2021, 2018; Nag et al., 2021), groundwater (García-Gil et al., 2018; Wu et al., 2020b), surface water (Cao et al., 2020, Liu et al., 2020), as well as in treated drinking water (Fu et al., 2019b; Kim and Homan, 2020; Yang et al., 2017b). Pharmaceuticals can reach the aquatic environment through wastewater discharges from houses and hospitals, pharmaceutical manufacturing industries, and landfill leachate, with municipal wastewater treatment plant (WWTP) effluents serving as the major point-source contributors (Fernandes et al., 2020; Yang et al., 2021). Conventional WWTPs often exhibit ineffective removal of pharmaceuticals, with studies reporting negative removal efficiencies (≥100 %) due to complex conjugation-deconjugation mechanisms, WWTP design, and transformation processes (Eregowda and Mohapatra, 2020; Kumar et al., 2022). Moreover, the occurrence of pharmaceuticals at the WWTPs follows seasonal variations, influenced by seasonal consumption patterns and environmental factors such as rainfall, runoff, and dry and wet weather flows, ultimately contaminating the surface water and groundwater. Therefore, focusing solely on WWTPs could be considered a "blind spot", as environmental factors may contribute to pharmaceutical pollution in surface water and groundwater, ultimately contaminating drinking water treatment plants (DWTPs) and drinking water supplies. The extent of contamination at DWTPs is also expected to vary globally due to differences in treatment techniques and operational factors, as discussed in Section 4.

Detecting pharmaceuticals in aquatic environments, especially in drinking water, poses additional challenges due to their low to ultra-low concentrations (pg/L to ng/L) (Priyanka and Mohapatra, 2020; Rusiniak et al., 2021; Zini and Gutterres, 2021). For reliable and precise quantification of pharmaceuticals at ultra-low levels, the water sample volume, choice of cartridges for concentration, and finally, type of analytical instruments become critical. Traditional field sampling campaigns, which collect data across multiple time points and locations, remain the primary method for assessing pharmaceutical contamination

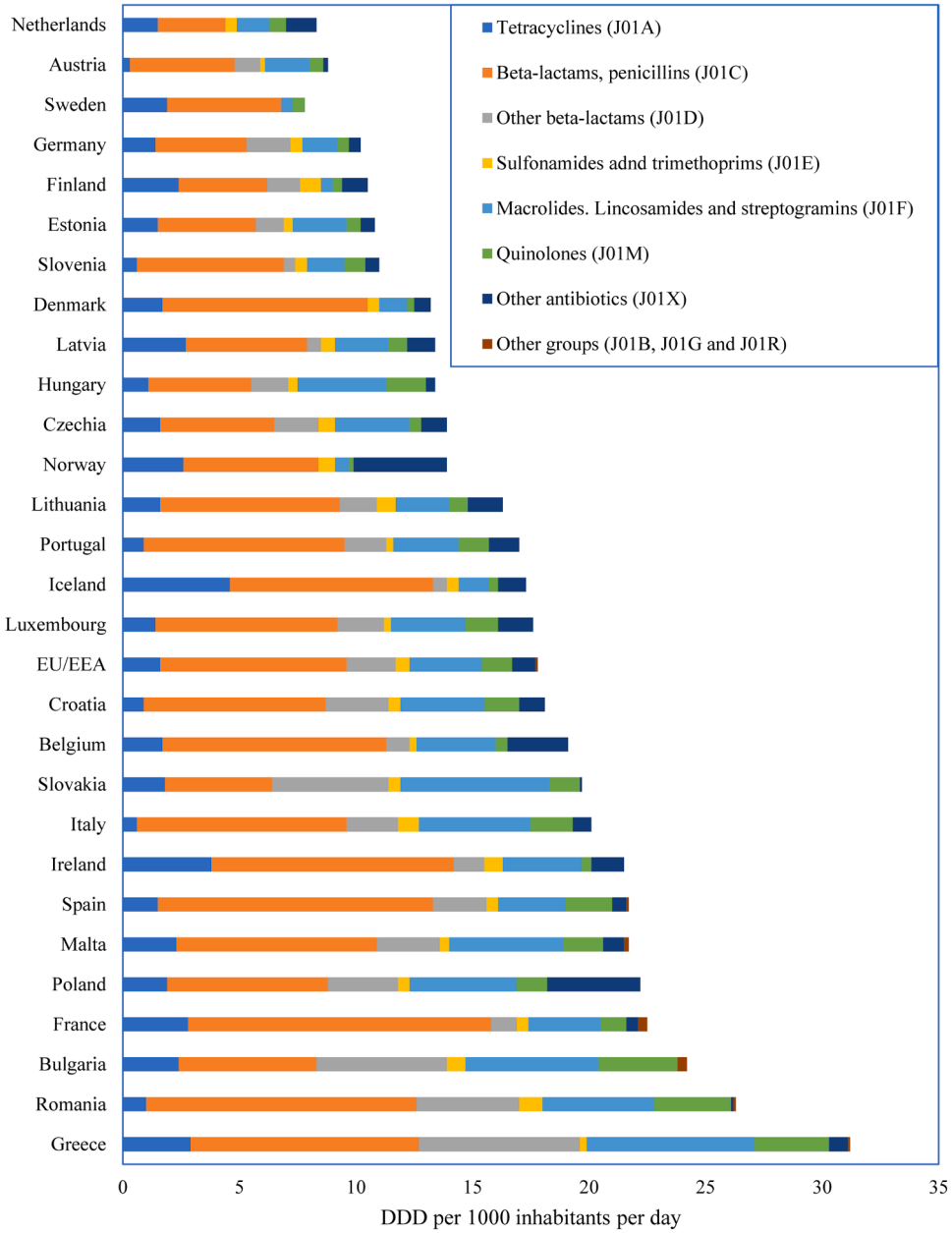


**Fig. 1.** Antibiotics consumption for systemic use (ATC group J01) at ATC level 3 subgroup, EU/EEA countries in 2022 (ECDPC, 2023).

in the environment; however, they are resource-intensive and time-consuming (Ramírez-Malule et al., 2020). To complement these efforts, machine learning-based models offer an innovative approach for real-time monitoring of pharmaceutical occurrence and fate. Furthermore, numerical modelling can provide a more comprehensive understanding of the pharmaceutical occurrence, transport, and fate, in the water cycle (Pal et al., 2014), yet modeling approaches received less attention than field sampling-based studies (Tong et al., 2022a).

Given these challenges and knowledge gaps, a literature review is needed to establish a baseline for understanding the occurrence of pharmaceuticals in different aquatic environmental matrices, especially in wastewater, surface water, and groundwater, their removal at the DWTPs, and current trends in the sample preparation, detection techniques, and numerical modeling. The novelty of the present review over other contemporary literature lies in the global assessment of pharmaceuticals, including antibiotics occurrence, on a global scale, with a focus on drinking water sources. Additionally, it provides quantitative insights into the efficacy of various conventional and advanced DWTP treatment techniques, assessing both removal rates and complete degradation of pharmaceuticals.

## 2. Methodology

In this review, a bibliometric search was implemented using the PRISMA guidelines in three stages: identification, screening, and eligibility. Scopus was used to search for published materials from 2016 as part of the identification process. For this review, the following keywords were used: pharmaceuticals, antibiotics, occurrence, seasonal variations, and water treatment plants (similar keywords were separated by "OR"/ "AND" Boolean operators to obtain relevant results). The search criteria included the following: (1) Abstract, title, or keyword contains "pharmaceuticals, AND antibiotics AND occurrence AND in AND water AND water AND treatment AND plant" (2) English is the main language, and (3) articles published between 2016 and 2023 under environmental science domain. Keywords from the RIS file were the basis for illustrating the co-occurrence map using VOS viewer (version 1.6.17) (Fig. 2). Upon close inspection, it was found that antibiotics, including azithromycin, clarithromycin, ciprofloxacin, and other pharmaceuticals such as acetaminophen, caffeine and environmental monitoring and liquid chromatography were grouped under one cluster, highlighting their close association in the water environment.

Therefore, the present review is organised into four sections with the following objectives: a) to analyze and provide the overview of pharmaceuticals, including antibiotics concentrations with seasonal effects in all water sources such as surface water, reservoir, groundwater, tap water, treated and untreated drinking water, highlighting the dominant pharmaceuticals/antibiotics in developing and developed nations in the recent years (Section 3); b) to broadly review and focus on the efficiency of removal techniques/treatments commonly used at the DWTPs (Section 4); c) to compare and assess/validate available sample preparation and detection techniques that can detect pharmaceutical in pg/L-ng/L range (Section 5); and d) to review the numerical modelling techniques which have been used to study the occurrence, fate, and transport of pharmaceuticals (Section 6).

## 3. Concentrations of pharmaceuticals in the aquatic environment

Pharmaceuticals such as antibiotics are now frequently detected in a range of water environments (Fig. 3), such as surface water (Table S1), groundwater (Table S2), and drinking water (Table S3 and S4) worldwide (Garg et al., 2023a, b). The median concentrations of antibiotics and other pharmaceuticals remain consistently high. Surprisingly, median concentrations in drinking water exceeded those in groundwater, raising concerns about their persistence and potential accumulation at DWTPs.

A global comparison of median pharmaceutical concentrations in surface water (Fig. 4) reveals a geographical trend: Africa > North America> Europe > South America > Asia. The notably high median concentration in Africa aligns with a surge in antibiotic consumption, particularly in North Africa, where usage rose by 111 %, from 11.2 [9.2–13.7] DDD per 1000 individuals per day in 2000 to 23.6 [20.4–27.5] DDD in 2018 (Browne et al., 2021). In addition to antibiotics, high consumption of diclofenac, caffeine, and naproxen may have contributed to their elevated median concentration in Africa, as reported by Ebele et al. (2020), where levels exceeded 135 ng/L in Lagos during the dry season. In contrast, Europe exhibits a moderate decline in the median concentration of pharmaceuticals, primarily due to a major reduction in the EU population-weighted mean consumption over the past decade (ECDPC, 2023). The EU population-weighted mean

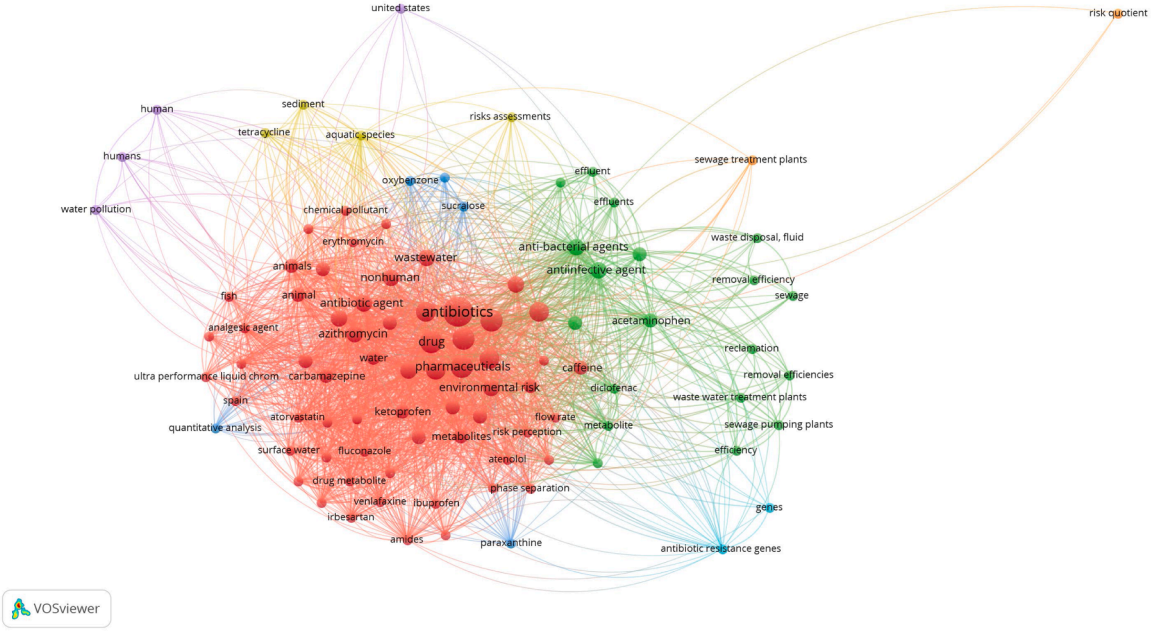


**Fig. 2.** Network analysis of literature using the data from 2016 to 2023.

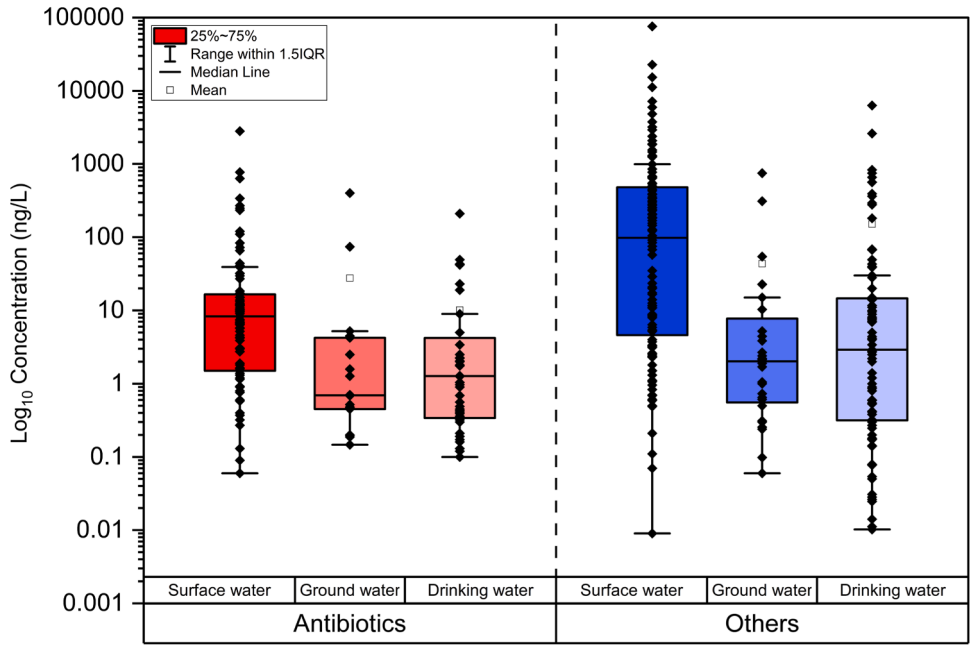


**Fig. 3.** Overview of antibiotics and other pharmaceuticals distribution form 2016 to 2023 in surface water, groundwater, and drinking water.

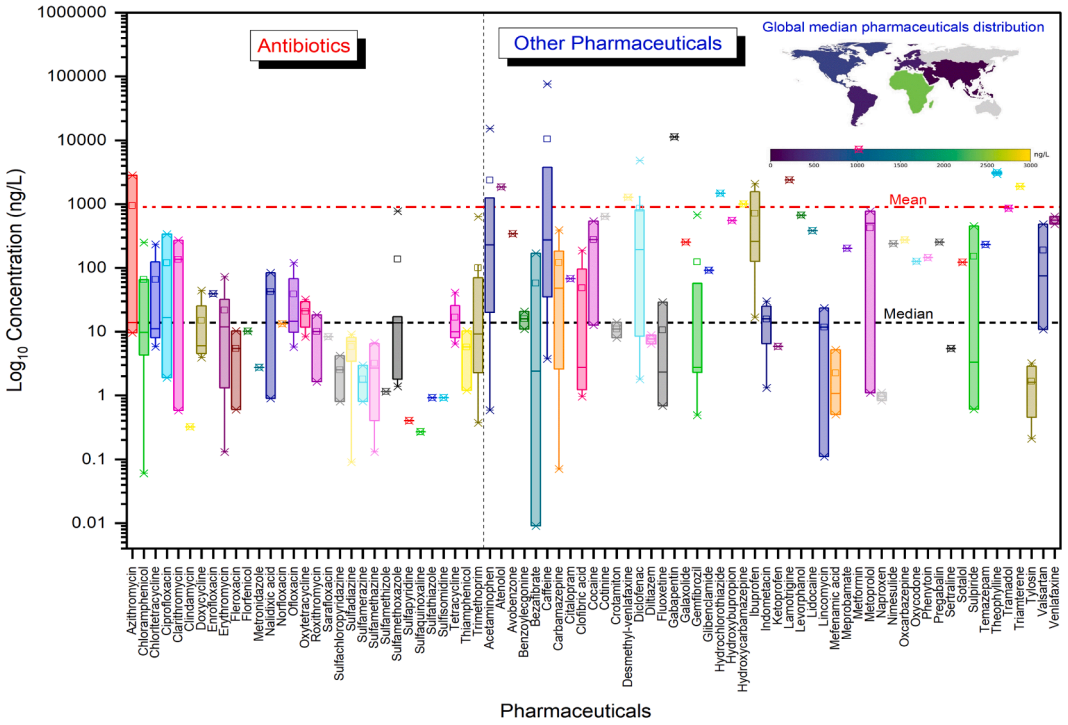


**Fig. 4.** Global distribution of antibiotics and other pharmaceuticals in surface water.
This global distribution map was prepared based on the data reported in Table S1. The global map within the graph represents the median distribution of pharmaceuticals, including antibiotics, in surface water of Asia, Europe, North America, and South America.

consumption of antibacterials for systemic use decreased by 2.5 % between 2019 and 2022, indicating slow but measurable progress toward the EU's 2030 target reduction of 20 % (ECDPC, 2023).

Among the pharmaceuticals, caffeine, followed by acetaminophen, gabapentin, and metformin, was detected at high concentrations (Fig. 4). Among antibiotics, high concentrations were reported for azithromycin and sulfamethoxazole. The demand for antibiotics such as azithromycin surged during the COVID-19 pandemic, leading to increased pharmaceutical production and, consequently, heightened their contamination. Given the dynamic nature of pharmaceutical consumption and their subsequent release into the environment, continuous monitoring is critical. To provide a more detailed understanding, the following sections explore global pharmaceutical occurrence in surface water, groundwater, and drinking water, with a particular focus on antibiotics.

### 3.1. Surface water

#### 3.1.1. Asia

China, which is considered one of the world's largest producers of pharmaceuticals, also takes the lead in the consumption of antibiotics. The studies conducted by Cao et al. (2020) and Liu et al. (2020) found that the most problematic concentrations of pharmaceuticals in surface waters (e.g., Yangtze river delta, Liao river, Ziya river, Daling river, Yellow river) are located in Beijing, China, where the industrial hub for the production of pharmaceuticals is located. In a few other studies conducted in Beijing, the mean antibiotic, non-antibiotic, and personal care products (PCPs) concentrations were reported to be 95.8 ng/L, 108.8 ng/L, and 84.7 ng/L, respectively (Su et al., 2020; Wang et al., 2021, 2021). Sulfonamides and macrolides were found with low concentrations in many sample sites, whereas tetracyclines were detected with relatively high concentrations (Lu et al., 2019). A similar observation was reported in another study conducted in China, where the highest levels of tetracyclines (1322 ng/L) followed by sulfonamides (851 ng/L) were determined in surface water (Zhang et al., 2023). In addition to sulfonamides and tetracyclines, Yu et al. (2023)reported the mean concentrations of fluoroquinolones such as norfloxacin and enrofloxacin as 43.47 ng/L and 27.35 ng/L, respectively in Yellow River, China. Macrolides at a concentration ranging from 30.9 to 237.49 ng/L were also reported in the surface water receiving effluent from pharmaceutical manufacturing industries in China (Liu et al., 2023). Although these studies highlighted the impact of pharmaceutical industry discharge on surface water, a study by Tran et al. (2014) in Singapore emphasized the impact of sewage pollution on surface water sources. Tran et al. (2014) suggested that carbamazepine, salicylic acid, and acetaminophen in surface water could be chemical markers of wastewater contamination. The concentrations of these pharmaceuticals may vary along the river stretch. For example, the study conducted by You et al. (2015) on 15 pharmaceuticals and personal care products (PPCPs) and endocrine-disrupting compounds (EDCs) in the tropical catchment of Singapore observed the difference in pharmaceutical concentrations between the downstream reservoir and upstream tributaries. The maximum concentrations of each pharmaceutical (≥300–900 ng/L) were found in upstream tributaries along with their highest frequency of detection (>90–95 %). Similar observations have been reported in other Asian countries, particularly regarding high concentrations of nonsteroidal anti-inflammatory drugs (NSAIDs) (Nozaki et al., 2023). For instance, NSAIDs such as ibuprofen, diclofenac, and mefenamic acid were detected in significant quantities (100–2000 ng/L) in the Vrishabhavathi River and Reservoir in Bengaluru, India (Nozaki et al., 2023). Comparable levels of NSAIDs were also found in the Sunter River, Jakarta, Indonesia (Dsikowitzky et al., 2014). Besides NSAIDs, a study on the Ganges River in India reported elevated concentrations of caffeine, ketoprofen, and carbamazepine, along with other contaminants, ranging from 15 to 200 ng/L (Sharma et al., 2019). In Japan, pharmaceutical residues, including indomethacin, crotamiton, bezafibrate, ampicillin, gliclazide, oseltamivir, and trimethoprim, were detected in spring and groundwater in Tokyo, with concentrations ranging from 0.30 to 87 ng/L (Kuroda and Kobayashi, 2021).

Caffeine and its products are highly in demand in China, resulting in high concentrations of caffeine in the Beiyun river water, with a concentration of 5.3–4690 ng/L in surface water and 1–54.5 ng/L in riverside groundwater samples (Yang et al., 2017a; Zheng et al., 2020). In these studies, the total amount of pharmaceuticals in the river was much higher (4x) than the riverside groundwater, indicating the importance of riverbed sand filtration. Similarly, among all the pharmaceuticals analysed, the highest concentration of caffeine (130–718 ng/L) was reported in Danshuei River in Taiwan (Fang et al., 2019). In addition to caffeine, a study in the Northern Taiwan Strait located between Taiwan island and Southeast Mainland China reported the presence of commonly used acetaminophen, carbamazepine, erythromycin, gemfibrozil, ketoprofen, naproxen, and some antibiotics such as sulfadiazine, sulfamethoxazole, sulfathiazole (Chen et al., 2022).

Being the world's 2nd largest producer of acetaminophen, high concentrations (155–302 ng/L) of this compound were also detected in the surface waters of China. Moreover, high pharmaceutical concentrations observed in the study area were primarily attributed to anthropogenic activities and sewage discharge (Zhang et al., 2018). On the contrary, a slightly different trend for dominant pharmaceuticals was seen in the sediment and water samples taken from the North Canal and Beiyun River of Beijing during the dry season, highlighting the seasonal impacts (Yang et al., 2017a; Pei et al., 2022).

To understand the seasonal effects, several studies were conducted in both dry and wet seasons in six urban rivers of Guangzhou, China, i.e. Shijing River, Liuxi River, Chebei River, Sha River, Zhujiang River and Liede River for 17 pharmaceuticals, as shown in Table S1 (Peng et al., 2017; Ebele et al., 2020). In the dry season, the concentrations of pharmaceuticals were relatively high, with a maximum concentration of 0.83 ng/L noticed for naproxen. In the wet season, the concentration of all pharmaceuticals dropped drastically due to dilution caused by heavy rainfall. A similar effect was also observed in Dongting Lake in China, where several pharmaceuticals were detected in surface water during a rainstorm (Wang et al., 2019, 2022). The quantified concentrations of the detected antibiotics were between 0.15 and 214.75 ng/L. The authors argued that rainstorms in Dongting Lake have a strong effect, which usually causes high dilution in surface waters; therefore, the concentration of pharmaceuticals detected in this lake was much lower than in the other rivers and lakes of China. Diclofenac was found in high concentration (>200 ng/L) compared to other antibiotics and insect repellent N,N-diethyl-meta-toluamide (DEET) (>100 ng/L).

In addition to seasonal effects, researchers have shown that inflow concentrations and wastewater removal efficiency play significant roles in the detection and occurrence of pharmaceuticals in natural waterways (Bavumiragira et al., 2022; You et al., 2015; Yuan et al., 2020; Ohoro et al., 2022). Commonly used antibiotics in poultry, aquaculture, and livestock, such as sulfamethoxazole, could contribute to their high concentrations in river water. Research on pharmaceuticals in Bangladesh and India has mainly focused on the Brahmaputra River, receiving wastewater discharges from wastewater treatment facilities with an emphasis on human and veterinary medicines and aquaculture facilities (Hossain et al., 2018; Horn et al., 2022; Chaves et al., 2022). Five different pharmaceutical groups (several antibiotics and one antiepileptic drug), i.e., sulfamethoxazole, sulfadiazine, sulfamethoxazole, trimethoprim, tylosin, erythromycin, metronidazole, and carbamazepine were screened in the river water (Hossain et al., 2018). Among the antibiotics, metronidazole, which was rarely monitored in other Asian countries, had the highest (>95 %) detection frequency, with concentrations ranging from 0.05 to 13.51 ng/L. Among other pharmaceuticals, sulfamethoxazole, trimethoprim, erythromycin-$H_2O$, and tylosin were distinctly found at high concentrations (>17.2 ng/L) in the aquaculture-fed areas. Among the different sources, antibiotics-fed aquaculture activities were found to be responsible for the preponderance of emerging pharmaceuticals in the river water. The authors argued that the presence of antibiotics and anticonvulsant drugs such as metronidazole and carbamazepine in the river was mainly attributed to the discharges from nursing homes, hospitals, poultry industries, sewage, and surface runoff from river watersheds. Similarly, the high concentration (>10.2 ng/L) of tylosin was mainly attributed to their large-scale application in the livestock and poultry industries. Both tylosin and sulfamethazine contamination were primarily due to livestock manure and poultry droppings (Hossain et al., 2018). In India, a few other studies have also reported the occurrence of pharmaceutical metabolites such as hydroxyl carbamazepine in river water (Biswas and Vellanki, 2021; Sengar and Vijayanandan, 2022), indicating the importance of metabolites monitoring.

#### 3.1.2. South and North America

Compared to China, only a few studies have reported pharmaceutical

occurrence in America during the review period. A study by River-a-Jaimes et al. (2018) reported around 35 pharmaceuticals in Cuernavaca's (México) surface water with a 100 % detection frequency. The observed trend for the pharmaceuticals was slightly different where the most abundant pharmaceuticals in surface water were the non-steroidal anti-inflammatory drugs which were found up to a level of 4880 ng/L (naproxen), followed by the lipid regulator, bezafibrate (286–2100 ng/L), diclofenac (258–1398 ng/L), and the analgesic drug such as acetaminophen (354–4460 ng/L). The study suggested that the detected concentrations of pharmaceuticals differ significantly from those in other parts of the world due to differences in consumption patterns. However, acetaminophen was found at a high concentration, consistent with studies reported in Asia. Another study conducted by Cipriani-Avila et al. (2023) on the coastal province of Ecuador before and during the COVID-19 pandemic reported that the occurrence of caffeine and diclofenac decreased during lockdown from 100 % to 4.2 % and 25 % to 0 %, respectively due to lack of tourism. Similar to China, high concentrations of caffeine were reported in Brazil's raw water, i.e. 1385 ng/L (Riva et al., 2018; Zini and Gutterres, 2021), showing Brazil as one of the largest consumers of caffeine in the world after India, with reported mean concentrations of 35–22,733 ng/L and 5.3–4690 ng/L in Guwahati, India, and Baiyun River, China (Kumar et al., 2019; Yang et al., 2017a). Similar observations were recorded for river water samples collected (upstream and downstream) from different parts of South Africa, Turkey, and the Czech Republic (Horn et al., 2022; Datel and Hrabankova, 2020; Okoye et al., 2022; Mhuka et al., 2020; Üstün-Odabaşı et al., 2020).

Large-scale monitoring has been conducted by Mu et al. (2017) in Missouri, USA, to study the occurrence and fate of pharmaceutical compounds in drinking water sources, 13 DWTPs, and in finished drinking water over four different months, i.e., in February, May, August, and November, and over a period of a year (Mu et al., 2017). It was found that pharmaceutical concentrations (cotinine, cephapirin, ciprofloxacin, enrofloxacin, azithromycin, and diphenhydramine) were more than twice as high in surface water than in groundwater, with a total pharmaceutical concentration of <35 ng/L for all Missouri sites. Meanwhile, in China, the concentration of pharmaceuticals in surface water was four times higher than in groundwater, indicating efficient riverbed filtration in the USA. High concentrations were generally observed during the winter when various water sources were analyzed at the Missouri water treatment facility, drawing water from rivers, lakes, reservoirs, unconsolidated wells, and deep wells. This might be due to reduced flows and con-current differences in degradation kinetics. The slow biological and chemical degradation of pharmaceuticals for levofloxacin, tetracycline, amoxicillin, fluoxetine, and gemfibrozil in surface water at low temperatures resulted in their higher concentrations in the winter season. In contrast, several pharmaceuticals (e.g., ibuprofen, naproxen, acetaminophen, azithromycin, tamoxifen) were detected at lower concentrations during warm seasons because of high chemical and biological degradation rates and more dilutions (2–3 times more). This high dilution was mainly caused by the increase in snow melting during the early summer and spring seasons, resulting in increased flow in the streams and causing the dilution of pharmaceuticals.

#### 3.1.3. Europe

Although several studies have previously reported the occurrence of pharmaceuticals in Europe, Fernandes et al. (2020) for the first time reported the occurrence of antibiotics and psychiatric drugs in the Douro and Leça rivers of Portugal. Leça River showed a high concentration of pharmaceuticals; 27 PPCPs were detected, while six compounds were antibiotics. On the other hand, no antibiotic was detected in the Douro and Leça Rivers, North Portugal region, but several psychiatric drugs (fluoxetine, venlafaxine, trazodone, citalopram, diazepam, sertraline, carbamazepine) were found. The concentration of antibiotics was between 5.4 and 2819 ng/L, and the azithromycin level was surprisingly the highest (>2800 ng/L) among the others, which collaborates with the high antibiotics consumption data in the country. Portugal is among the top 15 countries with high antibiotic consumption in the EU (Fig. 1).

In summary, China, a major pharmaceutical producer, showed high levels of antibiotic consumption and problematic concentrations of pharmaceuticals in Beijing. Similar occurrences were observed in the Northern Taiwan Strait and Taihu Lake. Sediment and water samples in Beijing's North Canal and Beiyun River revealed high concentrations of pharmaceuticals, with caffeine being the most abundant compound. Caffeine is considered one of the most widely used compounds in the world, and it has a high concentration (>20,000 ng/L). In natural water, dilution and degradation were found to be the natural attenuation mechanisms responsible for reducing the concentrations of pharmaceuticals on the surface.

### 3.2. Groundwater

Compared to surface water, only a few studies have reported the occurrence of pharmaceuticals in groundwater with a lower median antibiotic concentration than pharmaceuticals, as shown in Fig. 5. Among them, the highest concentration was found for non-steroidal diclofenac and antibiotics tetracycline, followed by oxfendazole and caffeine. As mentioned previously, riverside groundwater samples taken from the Beiyun River in Beijing, China, showed high concentrations of caffeine with a mean concentration ranging from 1–55 ng/L (Yang et al. 2017a). Among the 15 PPCPs tested in the groundwater sample, the concentration of pharmaceuticals was high in the dry season. In the following year, another study conducted in the groundwater of Zaragoza (Spain) reported much higher levels (≥260 ng/L) of antibiotics due to their excessive usage (top 7 consumer, Fig. 1), with the highest detected antibiotics group being tetracycline (García-Gil et al., 2018). Among the physicochemical parameters analyzed, results showed that oxygen is the primary factor contributing to pharmaceutical attenuation compared to temperature. The input of oxygen from groundwater heat pump systems could indirectly raise the aerobic redox conditions, helping their degradation (García-Gil et al., 2018).

In 2019, a study consisting of a wide range of PPCPs (31compounds) was performed in South Korea (Lee et al., 2019), where 15 antibiotics, four anthelmintics, seven other different PPCPs (antipyretic drugs, nerve stimulants, β-blockers, scabicide, personal care products), 4 artificial sweeteners, and one pesticide were detected in groundwater. Again, caffeine was detected at the highest concentration (~15 ng/L). While it was expected to find high levels of the insecticide carbofuran, high levels of antibiotics such as sulfathiazole, sulfamethoxazole, and oxfendazole in agricultural groundwater were surprising. Hence, it was concluded that sewage leakage could be another factor contributing to groundwater contamination, which might be a risk factor when considering groundwater as a prime drinking water source (Lee et al., 2019; Beltrán et al., 2020).

Some researchers have discussed that groundwater showed little seasonal change compared to surface water, where increased concentrations of pharmaceuticals were found in the groundwater samples during the fall and winter seasons (Peng et al., 2014; Rusiniak et al., 2021; Kibuye et al., 2019). Minimal seasonal fluctuations in groundwater might be attributed to various factors such as vadose zone transport, groundwater residence duration of the substance, and dilution, which can have a direct influence on the pharmaceutical concentrations. On the other hand, Kibuye et al. (2019) reported that preferential flow paths, high precipitation, and freeze-thaw cycles (during winter) in the groundwater environment led to increased (i.e., ≥1–10 μg/L) mean groundwater concentrations for naproxen, acetaminophen, and caffeine.

In summary, groundwater studies have reported lower pharmaceutical concentrations than surface water. Studies conducted in different locations, such as Beijing and Zaragoza, analysed the presence of pharmaceuticals in groundwater and found elevated levels of antibiotics. Diclofenac, trimethoprim, sulphonamides, oxfendazole, and

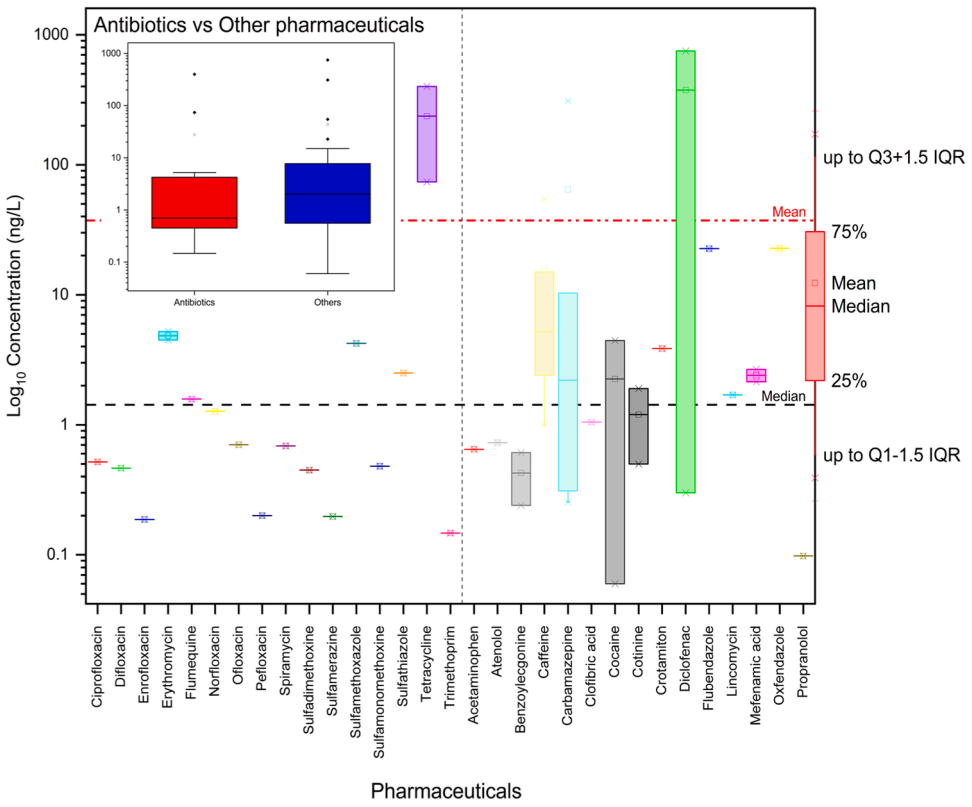


**Fig. 5.** Concentration of antibiotics and other pharmaceuticals in groundwater.
This concentration profile was prepared based on the data reported in Table S2. The box plot within the graph represents the distribution of antibiotics vs pharmaceuticals. The box plot indicates a median lower concentration of antibiotics than other pharmaceuticals in groundwater.

caffeine were found to have the highest concentrations in groundwater. While oxygen level was identified as a major factor influencing the degradation of pharmaceuticals in groundwater, sewage leakage was suggested as a potential contributor to groundwater contamination.

### 3.3. Raw and treated drinking water

The variation in the concentrations of pharmaceuticals at DWTPs in the influent and effluent streams is shown in Fig. 6. Among pharmaceuticals, the highest concentrations were detected for rarely reported pharmaceuticals such as betamethasone and prednisone in the influent and effluent, respectively. Similarly, among antibiotics, enoxacin and norfloxacin were detected at a high concentration in the influent and effluent, respectively. A more detailed discussion of their occurrence continent-wise is provided below.

#### 3.3.1. Asia and Europe

Among several studies reported on drinking water, the highest number of studies were from China, with high levels of pharmaceuticals in drinking water. A study was published in 2016 reporting the concentrations of antibiotics in advanced drinking water treatment plants (ADWTPs) around Taihu Lake in China (Lin et al., 2016). The study analyzed 39 PPCPs, of which 13 compounds were detected in the raw water influent stream. Even after advanced treatment at the ADWTPs, some antibiotics (sulfamethoxazole), nerve stimulants (caffeine), and anti-inflammatory/antipyretic (indomethacin) were found in the treated effluent. However, the authors argued that the detected pharmaceuticals in the treated water posed an insignificant ecotoxicological and human health risk due to their risk quotient (RQ) index of <1 (Lin et al., 2016). Sulfamethoxazole was also found in drinking water samples in China and Malaysia, with a high concentration in China, i.e., between 0.56–33.78 ng/L (W. Fu et al., 2019; Wu, 2020a), while that in Malaysia was just 0.16 ng/L (Praveena et al., 2019). Consistently high concentrations of pharmaceuticals were also reported in Shanghai, China, when samples were compared to Hanoi, Vietnam, and Metro Manila, Philippines, covering 35 treatment plants (Gu et al., 2019; Van et al., 2021). Methyl testosterone, a type of hormone, was found at very low concentration (≤0.052 ng/L) (Gu et al., 2019). However, dicyclohexylamine, an enzyme inhibitor, was detected at a concentration of 11.8 ng/L in the drinking water of Shanghai, but it was present in minimal amounts compared to other studies (Shi et al., 2022; Pontius, 2021). The highly toxic antitumor drug cyclophosphamide was also detected at a high concentration, i.e., 3.72 ng/L.

Compared to Asia, slightly different trends in pharmaceutical occurrence were noticed in Europe. For example, in the Gulf of Gdańsk, caffeine was detected with the highest frequency (>70 %) and concentration (>49 ng/L) in both treated and untreated water (Kot-Wasik et al., 2016). Ibuprofen was the second highest in untreated water samples, with a concentration of 49.5 ng/L and 39 ng/L in the untreated and treated water, respectively. Some polar compounds like metformin were also found to have very high concentration levels of up to 8100 ng/L in raw wastewater, contributing to drinking water contamination. The concentration was higher in winter than in summer, possibly due to slower degradation kinetics associated with lower temperature and sunlight intensity. To assess the impact of industrial activity, drinking water samples were taken from about 21 wells and five DWTPs in the most industrialized and inhabited area of Italy, Milan (Riva et al., 2018). While the PPCP bisphenol-A was detected with the highest concentration, i.e. 9.72–683 ng/L, among all the samples, pharmaceuticals were found in low concentrations in the drinking water.

#### 3.3.2. South and north America

Compared to Asia and Europe, where antibiotics and caffeine were detected at high levels, in the tropical environment of South America,

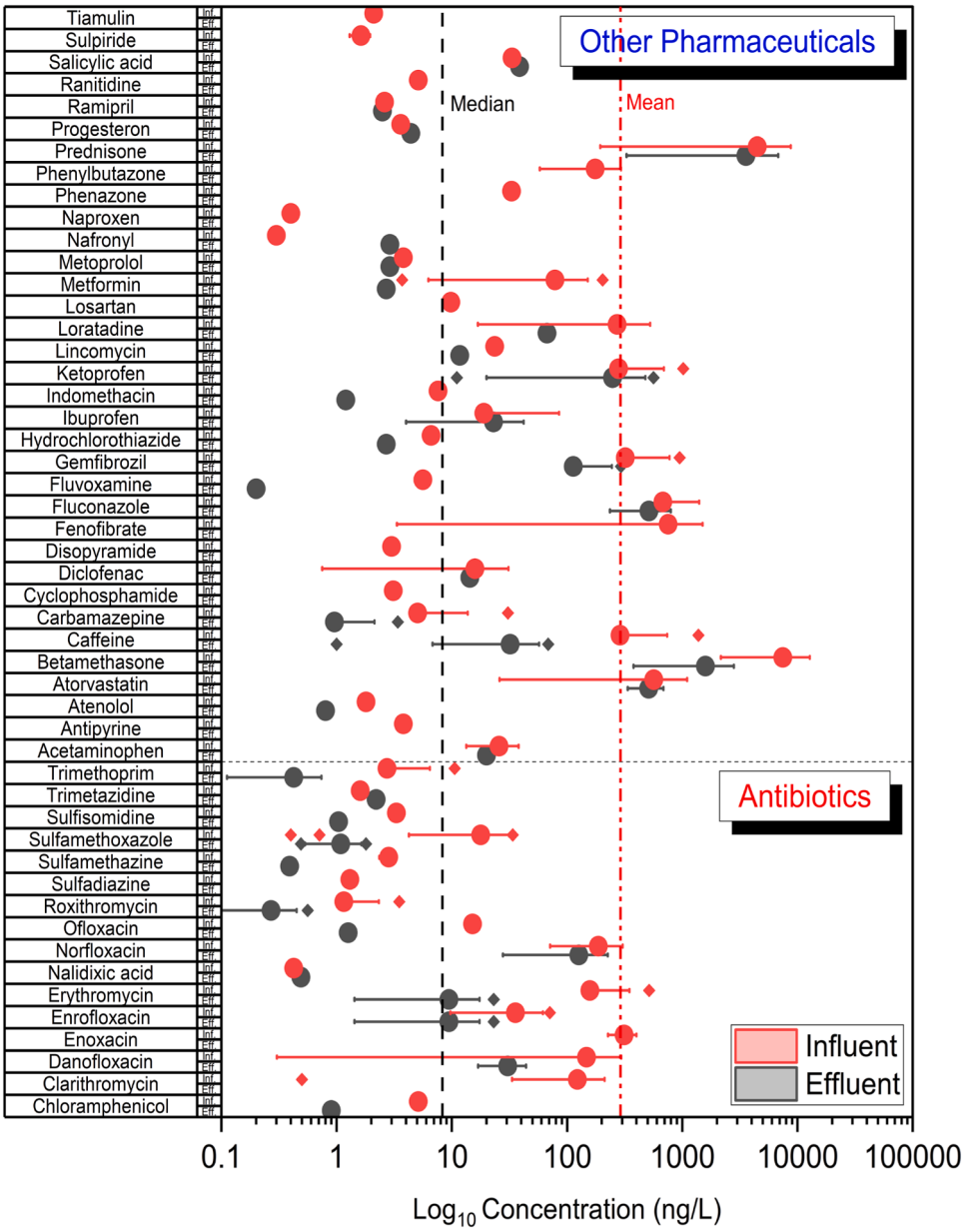


**Fig. 6.** Concentration of antibiotics and other pharmaceuticals in the influent and effluent streams of DWTPs (Table S3).

high concentrations of ultraviolet filters (UVFs) and corticosteroids were reported in the raw drinking water. For example, in 2017, besides pharmaceuticals, a study conducted in Colombia reported a high concentration of benzophenone (>36 ng/L) in the tributaries, their reservoirs La Fe and the Rio Grande, and the influent and effluent streams of two DWTPs (Aristizabal-Ciro et al., 2017). The detection frequency of some compounds (i.e., methylparaben, ibuprofen, UVFs) also showed that there was no efficient removal of these compounds from water, highlighting the ineffectiveness of the DWTPs in Colombia, which employed conventional treatment processes (flocculation, sedimentation, filtration, and coagulation) (Aristizabal-Ciro et al., 2017). Another year-long study was conducted by researchers in Minas Gerais (Brazil), in which 12 drinking water samples were tested before and after drinking water treatment (Reis et al., 2019). Out of 28 targeted compounds, 11 were detected at very high concentrations, depicting a significant amount of pharmaceutical contamination in Brazil compared to other parts of the world. The influent concentration ranged between 12 and 11,960 ng/L, in which corticosteroid betamethasone was found at the highest concentration. The study also showed that conventional DWTPs were ineffective enough in Brazil, as the treated water concentrations remained high (up to 6323 ng/L). Pharmaceuticals experiencing high concentrations were fluconazole, atorvastatin, and prednisone. Similarly, another study conducted in Brazil over 4 years on drinking water sampling reported 30 compounds with concentrations ranging between 181 and 290 ng/L (Caldas et al., 2019).

Similar to South America, in North America, several pharmaceuticals, such as acetaminophen, ampicillin, atrazine, caffeine, carbamazepine, cimetidine, ciprofloxacin, digoxin, gemfibrozil, ibuprofen, metformin, naproxen, simazine, sulfamethoxazole, sulfathiazole, and trimethoprim were reported in the drinking water sources (Kim and Homan, 2020). While the pharmaceuticals in raw water in Pennsylvania ranged between 0.2–125 ng/L, the concentration in the effluent stream was reduced by >50 % due to treatment by an ultrafiltration membrane system.

In summary, studies conducted worldwide in DWTPs reported the high concentrations of pharmaceuticals, including antibiotics, caffeine, and corticosteroids, in drinking water. The effectiveness of treatment processes in removing these compounds varied. Some studies showed

low concentrations of pharmaceuticals in treated water, while others reported high concentrations, suggesting the need for more effective treatment methods. Hence, the following section discusses the effectiveness of individual treatment processes commonly employed in those DWTPs, focusing on adsorption and ozonation.

## 4. Removal of pharmaceuticals at drinking water treatment plants (DWTPs)

At a typical full-scale DWTP receiving raw surface water, coagulation, sedimentation, filtration, activated carbon-based adsorption, and chlorination are commonly employed. In contrast, advanced oxidation-based treatment techniques, including ozonation, are employed at ADWTPs. Meanwhile, DWTPs relying on groundwater as their source primarily employ aeration and filtration as primary treatment units. The effectiveness of these treatment processes in removing pharmaceuticals, including antibiotics, varies significantly. Several studies have also researched hybrid systems (combinations of conventional and advanced technologies) in the past few years to examine their removal at lab and field scale (Polak et al., 2021; Vasagar et al., 2021; Wan et al., 2021).

### 4.1. Conventional treatment processes

Conventional treatment processes such as adsorption, coagulation, and flocculation are widely used in DWTPs to remove pharmaceuticals (Cao et al., 2022; Du et al., 2022). For example, a DWTP in Missouri demonstrated lower pharmaceutical concentrations in treated water compared to raw surface water due to integrated water treatment processes, such as prechlorination followed by sedimentation, disinfection, coagulation, and/or activated carbon sorption. Similar observations were also reported by Jiang et al. (2019), Wei et al. (2021) and Wang et al. (2018). However, removal efficiencies vary; for instance, benzophenone, methylparaben, and ibuprofen showed removal of 30–60 %, 20–60 %, and 0–50 %, respectively, across two DWTPs employing coagulation, flocculation, sedimentation, and filtration. These conventional methods were inefficient in removing highly polar compounds (Table 1). Furthermore, coagulation was least effective for fluorinated compounds (Kim et al., 2020), and even chlorination, while effective in some studies for fluoroquinolones, failed to remove them in others. Earlier studies across five DWTPs reported pharmaceutical removal efficiencies ranging from 72–95 %, with hydrophobic compounds exhibiting removal rates above 79 % (Reis et al., 2019; Cao et al., 2022; Du et al., 2022). Hence, in the following subsection, the removal of hydrophobic pharmaceuticals through adsorption-based treatment techniques is discussed in detail.

#### 4.1.1. Adsorption process

Activated carbon-based adsorption is a very common process for purifying water, demonstrating pharmaceutical removal efficiencies of up to 83 % (Kim et al., 2020). Notably, metformin removal reached 91 %, in one study (Choi et al., 2022). Researchers have also attempted several modifications to activated carbon for enhanced removal, including a granular activated carbon (GAC) sandwich slow sand filter, which achieved 98 % removal for acetaminophen, caffeine, and triclosan (Li et al., 2018). However, adsorption efficiency is influenced by system configurations; for instance, when GAC was combined with sand filtration, lower removal rates were reported by W. Fu et al. (2019). In a DWTP employing two-stage biofiltration, i.e., a sand/anthracite (SA) biofilter coupled with GAC, pharmaceuticals were removed up to 48 % through GAC compared to 54 % during biofiltration, highlighting the importance of biofiltration in removing these compounds (Fu et al., 2019a; Campinas et al., 2021). Pre-chlorination can further enhance the removal of pharmaceuticals, increasing total pharmaceutical elimination from 27.6 % to 47.2 %, with atenolol, ciprofloxacin, and cotinine removal reaching 80 %. Notably, GAC alone removed about 92.5 % of pharmaceuticals containing halo-nitroalkane and halo-nitriles, highlighting selective adsorption to nitrogenous compounds (Table 1).

Beyond GAC-based adsorption, alternative materials have been explored for pharmaceutical removal. Tian and Chowdhury (2019) and Krishnan et al. (2021) studied transition metal dichalcogenides (TMDCs), molybdenum disulfide ($MoS_2$) and tungsten disulfide ($WS_2$), which exhibited superior adsorption compared to activated carbon, particularly for erythromycin (antibiotic), 17β-estradiol, and triclosan in surface water. As adsorption is a surface phenomenon, $MoS_2$, with a smaller particle size than $WS_2$ experienced high adsorption (86.5–97.6 %). $MoS_2$ and $WS_2$ were more effective than activated carbon for triclosan removal due to their hundred times lower unit surface area. Erythromycin, an antibiotics, showed nearly tenfold higher adsorption on $MoS_2$ and $WS_2$ compared to 17β-estradiol and triclosan. Similarly, porous aromatic frameworks (PAFs) exhibited high adsorption capacities for ibuprofen, chloroxylenol, and DEET, with ibuprofen showing the highest affinity (Zhao et al., 2019). In a separate study, electrospun PAN fibre membranes experienced the highest adsorption capacities of 613.5 mg/g for ibuprofen, among the studied compounds (Zhao et al.,

**Table 1**
% Removal of PPCPs in during water treatment technologies.

| Experimental Conditions | List of PPCPs | % Removal | | | | | References |
|---|---|---|---|---|---|---|---|
| | | Coagulation | Filtration | Chlorination | Ozonation | Adsorption | |
| Lab study | PPCP | – | – | – | 95–100 % | 8. 1 % by Granular Activated Carbon (GAC) | (Ewadh et al., 2019) |
| Lab study | PPCP | – | 53.4 % removal by Biofiltration | – | – | – | (Fu et al., 2019a) |
| Lab study | Removal of PPCPs by MBR | Estriol (95 %), benzhabeite (88 %), caffeine (88 %) and atenolol (87 %). Lower removal is observed for carbamazepine (41 %) and metoprolol (47 %). | | | | | (Wang et al., 2018) |
| | Removal of PPCPs by MBR-RO/NF System | Overall removal rates are greater than 95 %, which means that additional removal of selected contaminants with RO and NF membrane is higher than 95 % and | | | | | |
| Nakdong River Basin | Caffeine, carbamazepine, crotamiton, | – | – | – | – | GAC: −1.4 % to 83 % | (Kim et al., 2020) |
| | Fenbendazole, metformin, and sulfamethoxazole | | – | – | – | | |
| | Metformin | (~50.8 % | −0. 9 % | | | GAC: 7.7 % | |
| | Crotamiton | | <1 % | 1 4 %–4 6 % | 53 %– 57 % (pre+post) | | |
| | Caffeine | – | – | – | 19–65 % (pre+post) | 72. 2 %–89. 5 % | |
| Lab study | Acetaminophen | – | 97.9 % | – | – | – | (Li et al., 2018) |
| | Caffeine | | 96. 2 % 95. 7 % | | | | |
| | Triclosan | | 97 .6 % | | | | |
| | DEET | | | | | | |
| Lab study | Atenolol Carbamazepine Ibuprofen | Nanofiltration membranes | | | | | (Tian and Chowdhury, 2019) |

2019). Further advancements in adsorption technologies include bio-MOF-derived highly porous carbons (BMDCs), which demonstrated over 67 % adsorption for basic atenolol and acidic clofibric acid, driven by electrostatic interactions and hydrogen bonding (Yu et al., 2022; Bhadra and Jhung, 2018). Additionally, metal-organic framework (MOF) MIL-101, functionalized with polar –OH and $–NH_2$ groups, achieved over 72 % adsorption of naproxen (Table 1), emphasizing the importance of surface chemistry and pH in adsorption efficiency (Seo et al., 2016).

#### 4.1.2. Biochar as a model adsorbent

The application of biochar as a carbonaceous adsorbent has gained increasing attention from the scientific community over the past decade. Researchers have demonstrated that biochar and biochar-based nanocomposites function effectively as "super sorbents" for removing pharmaceuticals from aquatic environments (Arora et al., 2025; Rani et al., 2024; Sudarsan et al., 2024; Kumar et al., 2023).

Liang et al. (2022) reported that high-temperature biochar (700 °C) exhibits strong adsorption capabilities for norfloxacin. Furthermore, modifying biochar has been shown to enhance its ability to adsorb pharmaceuticals. The pollutant sequestration properties of biochar largely depend on its synthesis process. For instance, Ahmad et al. (2019) found that nano zero-valent iron-modified biochar (nZVI-DBC) efficiently removed 98 % of chlortetracycline from aqueous solutions, outperforming zeolite-modified biochar (Z-DBC), silica-modified biochar (S-DBC), and unmodified biochar. This enhanced performance may be attributed to forming Fe-N covalent bonds between chlortetracycline's amino group and $Fe^{3+}/Fe^{2+}$, following the oxidation of $Fe^0$. Similarly, manganese dioxide-modified biochar (Mn-BC) demonstrated superior sorption capacity for organic contaminants due to its larger specific surface area, total pore volume, and pore diameter (Shen et al., 2020). MnCeOx-modified tea waste biochar (MnCeOx/TBC) further enhanced the aggregation of bimetallic oxides, accelerating tetracycline adsorption by >60 % in aquatic environments.

The adsorption properties of biochar are also influenced by the initial concentrations of both the adsorbate and the adsorbent, as well as the dosage of biochar. For example, the adsorption capacity of biochar decreased from 11 mg/g to 4 mg/g as the concentration of ofloxacin increased from 1 g/L to 4 g/L. At higher biochar concentrations, adsorption capacity remained constant due to the limited availability of binding sites, restricting pollutant transfer (Dong et al., 2023).

In a different approach, Chand et al. (2022) reported over 70 % removal of amoxicillin, ibuprofen, and caffeine in a vertical flow constructed wetland system filled with animal waste biochar and riverbed sand.

### 4.2. Advanced or hybrid treatment technologies

Due to the limitations of the conventional treatment processes, advanced DWTPs (ADWTPs) have integrated oxidation and biodegradation techniques to improve pharmaceutical removal (Lin et al., 2016; Alazaiza et al., 2022). Unlike conventional approaches, ADWTPs use advanced oxidation processes (AOPs) that generate highly reactive radicals, such as hydroxyl radicals and singlet oxygen ($^1O_2$) (Mohapatra et al., 2023, 2024). In one study, of 13 pharmaceuticals detected in the influent of an ADWTP, only three remained after treatment, demonstrating the efficacy of these processes (Lin et al., 2016). Acetaminophen concentration was reduced by 50 % from its initial concentration of 15.2 ng/L, while removal efficiencies for caffeine, indomethacin, and sulfamethoxazole reached 89 %, 84 %, and 92 %, respectively. Similar observations were reported by Aristizabal-Ciro et al. (2017) and Al-Baldawi et al. (2021) at two other ADWTPs. In another study, ozonation combined with chlorination contributed to >90 % pharmaceutical removal, except for metformin, which was below 70 % (Kim et al., 2020). Caffeine removal ranged from 72 % to 89 %, whereas pre- and post-ozonation eliminated up to 57 % of crotamiton, commonly used for scabies treatment. In the following subsection, recent advancements in the ozonation-based treatment technique are discussed in detail.

### 4.3. Ozonation and advanced oxidation

The Ozonation-based treatment is optimized through key operational variables, i.e., pharmaceutical concentration, retention time, and pH. Even the removal up to 95–100 % was reported for the lowest contact time (<1 h) when the pH was 8.9. Among several pharmaceuticals, ibuprofen and ketoprofen were removed at a rate ranging from 67–100 % and 75–100 %, respectively (Table 1). The researchers concluded that pharmaceutical removal was greatly influenced by the pH, concentration of pharmaceuticals, and ozone contact time (Ewadh et al., 2019; Lou et al., 2020). Sulfamethoxazole was removed by 95 % by ozonation and GAC, while flocculation and sedimentation removed only 3.8 % for the same compound.

Pai and Wang (2022) found that $UV/H_2O_2$ could effectively (≥60–80 %) remove caffeine, diclofenac, benzophenone, carbamazepine, ibuprofen, oxybenzone, trimethoprim, and other estrogen compounds in ADWTPs through reactive hydroxyl radicals. The effectiveness of this process depends on the concentration of oxidants, reaction conditions, pH of the solution, and types of pharmaceuticals present in the treatment process. Similar observations were recorded by Borikar et al. (2015), who reported that $UV/H_2O_2$ effectively eliminated fluoxetine, ibuprofen, atorvastatin, and naproxen to levels of ≥80 %. Although the generation and scavenging of hydroxyl radicals/reactive oxygen species (ROS) through AOP can remove chlorophene, clofibric acid, nimesulide, and acetaminophen to levels of >85 %, the risks of production of transformation products cannot be ruled out (Jiao et al., 2022).

In summary, ADWTPs that use oxidation-based treatment technologies, such as ozonation have shown better removal efficiencies ( >85 %) compared to conventional treatment. However, removal efficiency is influenced by factors such as pH and ozone contact time. Adsorption using activated carbon has also been widely used and has shown high removal efficiencies for a few pharmaceuticals. While numerous lab-scale techniques have demonstrated effectiveness in pharmaceutical treatment, there is still a need for unified removal techniques that are user-friendly, cost-effective, energy-efficient, and minimize transformation product formation.

## 5. Sample preparation and analytical measurements

An overview of conventional and advanced analytical techniques of pharmaceutical measurement has been provided in this section by referring to extensive data presented in Table S5. Additionally, solid and liquid-phase-based microextraction approaches have been critically discussed, which may provide insights into the separation and preconcentration of pharmaceuticals.

### 5.1. Solid-phase extraction (SPE)

The solid-phase extraction (SPE) technique is usually used for a large range of samples, including environment, forensic, food, and pharmaceutical, because it is regarded as an efficient and convenient extraction method (Chen et al., 2022; Mohapatra et al., 2018;2022; Nitti et al., 2022). It can preconcentrate trace analytes and minimize the impact of the matrix effect by phase transferring (mobile phase to the solid phase) of target analytes. Compared to conventional liquid-liquid extraction (LLE), SPE demonstrates numerous advantages, i.e. low solvent consumption and a short extraction time. Furthermore, because of the large number of developed sorbents and the ease with which they can be automated, SPE has become popular in sample extraction techniques for liquid samples (Loganathan et al., 2020; Madikizela et al., 2022). Based on the review of the literature, it was found that Oasis HLB cartridges are commonly used to concentrate a wide range of acidic, basic, and neutral

pharmaceuticals in environmental samples, as highlighted in Table S5. Due to the water-wettable nature of the Oasis HLB sorbent, it can maintain its high retention capability and excellent recoveries even when it runs dry. As a result, samples up to 4000 mL were used to concentrate selected analytes with a recovery of up to 141 % (Liu et al., 2019). Three studies have also reported using Oasis MCX (Riva et al., 2018) and Strata-X (Fernandes et al., 2020; Pompei et al., 2019) SPE cartridges from Waters and Phenomenex, respectively. As pharmaceuticals are present in pg/L to ng/L in surface water, groundwater, and drinking water, most studies conducted on those samples, except for one reported by Ewadh et al. (2019), used a larger sample volume of >500 mL for SPE (Table S5). In most studies, methanol or methanol spiked with formic acid or ammonium solutions was used to elute the analyte. Lee et al. (2019), Peng et al. (2014), and Caldas et al. (2019) found ≥75 % and ≥78 % recoveries for sulphonamides, β-blockers, analgesic/antipyretic, enzyme inhibitors, and lipid-regulators in surface and groundwater samples of Southern China, Southern Brazil and South Korea (Table S5). A group of researchers in South America, Italy, Malaysia and Spain had observed analytical recovery of 78–112 % for 4, 4′-Dihydroxybenzophenone, 2-(2H-Benzotriazol-2-yl)-p-cresol, 4-p-aminobenzoic acid, sulfapyridine, succinyl-sulfathiazole, pipemidic acid, tylosin, oxytetracycline and trimethoprim (Aristizabal-Ciro et al., 2017; Sadutto et al., 2020 and 2021; García-Gil et al., 2018) (Table S5). Similarly, Fernandes et al. (2020) achieved analytical recovery of 74–85 % of pharmaceuticals (antibiotics and psychiatric drugs) in river waters from Douro and Leça rivers, Portugal (Fernandes et al., 2020). Wu et al. (2022); Pei et al. (2022), and Van et al. (2021) observed a similar recovery (≥72 %) for sertraline, ofloxacin, moxifloxacin, azithromycin, naproxen, sulfathiazole, and trimethoprim compounds. While SPE remains the gold standard for sample preparation, the loss of analytes, time consumption, and exhaustive solvent preparation during SPE (Okoye et al., 2022; Huang et al., 2022) has led to the development of other sample preparation techniques, which are discussed in detail here.

#### 5.1.1. Solid phase-based microextraction (SPME) and needle trap device (NTD)

SPME offers inherent advantages such as combined sampling, analyte isolation, single-step sample enrichment, and environmentally friendly expedited sample recovery. The SPME process uses a small amount of extraction phase and/or sample while maintaining sensitivity and minimising sample preparation steps, which also reduces intensive manpower and improves the overall analytical performance (Sadutto et al., 2020, 2021). SPME usually uses less solvent to obtain pure extracts of the analyte compared to the traditional SPE techniques, which also broaden the nature of both the target analytes and samples (Dao et al., 2020; Chaves et al., 2022). SPME's mechanism consists of two major steps: (a) adsorption of analytes from the sample matrix into the sorbent phase and (b) desorption of analytes into the appropriate mobile phase for instrumental analysis by liquid/gas chromatography coupled with mass spectrometry (LC/GC–MS). In this method, the most used adsorbents, such as divinyl benzene (DVB), polyethylene glycol (PEG), and Carbowax (CW), are supported on a solid fused silica matrix coated with a layer of polymer. New materials such as graphene and graphene oxide, carbon nanotubes, molecularly imprinted polymers (MIPs) and metallic nanoparticles have been synthesized to improve the efficiency and selectivity of isolation. Furthermore, SPME methods have received more attention than other analytical extraction techniques due to the principles of green analytical chemistry and the need for environmentally benign techniques (Ebele et al., 2020).

To overcome the limitations of the SPME methods, researchers have discussed a suite of needle-based devices/alternatives, i.e. needle trap device (NTD) (Wu et al., 2022; Pei et al., 2022). Usually, NTD is recognized as a solvent-free sample preparation method commonly designed for volatile target compounds and preconcentration of the target analytes (Zheng et al., 2020; Yang et al., 2021). NTD offers high sensitivity, simplicity, and efficient extraction time, avoiding solvents. Furthermore, NTD combines extraction, desorption, and analysis of ECs. NTD outperformed SPME in fiber brittleness, capacity, and active sampling (Ma et al., 2022; Liu et al., 2020).

#### 5.1.2. Stir bar sorptive dispersive microextraction (SBSE)

SBSE extraction is based on the sorptive method, in which target analytes are extracted from an aqueous sample into a stir bar coated with PDMS based on their octanol-water partitioning (Kow) coefficient. Such kinetically controlled methods are commonly applied for analyzing samples of varying complexity, different volumes, stir bar dimensions, and stirring speed, which also directly impact the extraction efficiency of the SBSE. Following sample extraction, thermal or liquid desorption of the residual analytes can also be carried out to enhance the recovery of polar samples. SBSE is also helpful in the multi-residue methods for the simultaneous pre-concentration and detection of emerging xenobiotics. However, extracting hydrophilic analytes using SBSE remains challenging. As a result, carbon-based materials, functional polymers, and metal-organic frameworks (MOFs) have become popular in the last decades (Van et al., 2021).

#### 5.1.3. Thin film microextraction (TFME)

The thin-film micro-extraction (TFME) technique was popularized to increase the sorbent's surface-to-volume ratio during the analytical extraction of PPCPs, which was also found suitable in terms of fast extraction kinetics, high analytical sensitivity, and improved contact with the sample surface. The widespread usage of cellulose films in conjunction with nanostructured sorbents for thin film microextraction can result in a synergistic combination that takes advantage of the appealing properties of both materials. The advantages of the cellulose membrane (high chemical stability and porosity) and the enhanced sorption ability inherent in nanostructured sorbents drive the fast sorption of target analytes. The coated stir bars can be agitated to reduce the diffusion layer, and sorbent coatings have also been applied to planar geometries in TFME to increase sorbent surface area and analyte sorption significantly. TFME has been used to analyze EOPs in a suite of environmental matrices and is regarded as a versatile extraction platform for small molecules in water, oil, and biological samples (Du et al., 2022). The extraction efficiency of TFME, like that of SPME, is determined by the efficiency of liquid desorption, the nature of the extraction phase (sorptive vs headspace), and methods of analysis (LC/GC system) (Wan et al., 2021).

#### 5.1.4. Microextraction by packed sorbent (MEPS)

Microextraction by packed sorbent (MEPS) has been used as a sample preparation (fast and simple) method that has proven useful for qualitative and quantitative detection of ECs in various environmental samples (Wang et al., 2021). MEPS employs the same sorbents as traditional SPE columns. Unlike traditional SPE columns, the MEPS sorbent bed is combined into a liquid-handling syringe, allowing manual or robotic manipulation of low-void-volume samples. MEPS can be used with most existing SPE methods by reducing the reagent and sample volumes. The principle differences between the two methods (MEPS and SPE) can be stated that in SPE, the solution flow is one way (up to down), whereas, in MEPS, it is usually in two ways (up and down), so the optimization of the washing and elution steps is critical (Yang et al., 2021; Wu et al., 2022). When compared to SPE, MEPS has numerous advantages, such as the requirement of a small amount of sorbent (1–2 mg), solvent (in μL), and sorbent packing materials that can be regenerated up to 100 cycles (Pei et al., 2022).

#### 5.1.5. Bar adsorptive microextraction (BAμE)

This microextraction process has a significant advantage over other approaches, such as traditional SBSE, when using polydimethylsiloxane (PDMS), which allows the selection of the most appropriate sorbent phase (e.g., activated carbons (ACs), polymers (Ps), etc.) for each type of application. By doubling the enrichment factor and lowering the

analytical limits, the novel improvements of reduced solvent volume (μL) demonstrated excellent performance, ease of manipulation, and a greener analytical approach that can be used successfully for a wide range of polar and non-polar trace analytes (Du et al., 2022). Shi et al. (2022) have applied the BAμE method for ECs such as tricyclic antidepressant pharmaceuticals, insecticide repellents, nicotine, bisphenol A, and paracetamol in tap, river, and groundwater samples.

### 5.2. Liquid phase-based microextraction (LPME)

As the target compounds have different solubilities in two immiscible liquids, this method can separate compounds from the liquid sample using appropriate solvents (Li et al., 2021). There are two types of LPME approaches, i.e., two-phase and three-phase extraction. The extracting phase in two-phase LPME remains in direct contact with the sample solution, which may ease the sample cleanup process and limit solvent extraction to water-immiscible organic liquids. In three-phase LPME, however, the sample solution and final solvent (acceptor) phase usually remain separated by a third solvent that is immiscible with both phases. This configuration significantly improves method selectivity and allows using the aqueous acceptor phase. Wan et al. (2021) used different types of LPME for the analytical quantification of pharmaceuticals in surface water samples collected from lakes and rivers. An exhaustive classification of different types of LPME has been provided below.

#### 5.2.1. Single drop microextraction (SDME)

Conventional liquid-liquid extraction involves using large amounts of potentially toxic organic solvents, which can be time-consuming and labor-intensive. Various solvent-minimized extraction or liquid-phase microextraction (LPME) implementations, such as single-drop microextraction (SDME) and dispersive liquid-liquid-phase microextraction (DLLME) in their various modes, have been developed over the years to address these disadvantages (Ohoro et al., 2022; Sadutto et al., 2020). The goals of designing an SDME approach include several benefits, such as (i) achieving high enrichment factors and (ii) mitigating sample matrix interferences. Because the fundamental basis of SDME is liquid-based extraction, two extraction modes are commonly available, i.e., two and three extraction phases. Sample extraction from an aqueous sample to an organic solvent is typically included in two-phase SDME. SDME is a micro version of LLE that, in its most basic form, requires only a common laboratory syringe, a few μL of pure extracting solvent, and, due to excellent enrichment factors (EFs), a small amount of both polar and non-polar samples, as well as the headspace (HS) for these samples for HS-SDME technique (Nitti et al., 2022; Mojiri et al., 2022).

#### 5.2.2. Dispersive liquid-liquid microextraction (DLLME)

Dispersive liquid-liquid microextraction (DLLME), a novel, rapid, economical, and robust method, is becoming more popular because of the wide range of applications for organic and inorganic analytes. The method employs a ternary solvent mixture system composed of an aqueous phase, an apolar extraction, and a polar water-miscible solvent known as a dispersive solvent. DLLME is usually performed by dispersing tiny droplets of an organic extracting solvent into the sample with a disperser that is fully miscible with both the aqueous and organic phases. The wide applications of DLLME have been found quite effective ($\geq$80 % relative recovery) for sea, swimming pool, and river water samples contaminated with UV-filters, phthalate esters, naftopidil, haloacetic acids, Irgarol, cotinine, surfactants, and engineered nanomaterials (Al-Baldawi et al., 2021; Li et al., 2021; Du et al., 2022).

### 5.3. Quick, easy, cheap, effective, rugged, and safe (QuEChERS)

QuEChERS was introduced as a fast and simple extraction technique that stands for “quick, easy, cheap, effective, rugged and safe”, where the method was used for tracing pesticides and other organic compounds in complex matrices (Ademoyegun et al., 2020; Adeleye et al., 2022). The entire QuEChERS process consists of four steps: (i) addition of an organic solvent to the sample followed by separation through centrifugation; (ii) addition of $MgSO_4$ to the extracted solvent, (iii) a dispersion sorbent to clean the extract further and (iv) advanced analytical instruments to analyze the supernatant.

Several new methods are popularized nowadays, including miniaturized analytical flow-based approaches, i.e., millifluidic platforms (bead injection-based techniques) that promote the applications of automatically renewable functionalized solid-phases or biochemical ligands for fresh portion of sorbents (Horn et al., 2022; Chaves et al., 2022). Although several automatic microfluidic manipulation methods have been developed for each sample to ease the sample preparation steps, the lab-on-valve (LOV) format has proven the most successful. LOV is made up of a micro-machined methacrylate, and recently, the concept of 3-D printing has been commonly used to customize LOV devices (Gomes et al., 2020; Huang et al., 2021a). Microfluidic detection technology is becoming more popular in South Korea, China, Brazil, Italy, and the USA due to high precision-based measurements for microscale fluids. Microfluidic paper-based analytical devices (μPADs) are one of the promising methods that are commonly used (with capillary action) in different transdisciplinary fields such as material science, physics, chemistry, biology, electronics, and particularly for the monitoring of ECs in small volumes of environmental samples with high sensitivity, simplicity and efficient extraction times. μPADs have been used to effectively monitor pharmaceuticals in the environment, such as sulphonamides, tetracycline, trimethoprim, and some antitumor drugs (Li et al., 2022; Ebele et al., 2020).

### 5.4. Analysis of contaminants

After SPE, the next step in the analytical pipeline is to extract analytes using either LCMS or GCMS. So far, all the papers reviewed here have used high-pressure liquid chromatography (HPLC) or Ultra-performance liquid chromatography (UPLC) coupled with a triple quadrupole mass spectrometer (HPLC or UPLC-MS/MS) in positive or negative electrospray ionisation (ESI) mode (Table S5). Water, acetonitrile, and methanol supplemented with formic acid or ammonium acetate were used as mobile phases to separate the pharmaceuticals in a gradient, mostly using C18 columns. The choice of column and mobile phase plays a critical role in such an analysis as pharmaceuticals are present at very low concentrations, and their exact quantification with better accuracy and precision is important from a regulatory point of view. The right combination of SPE technique, analytical column, and LC-MS/MS technique could result in achieving the lowest limit of detection (LOD) and limit of quantification (LOQ) of the order of 0.5 pg/L-0.1 ng/L and 1.00 pg/L-0.50 ng/L, respectively, as reported for 71 PPCPs by Liu et al. (2019) in tap water samples in China.

The analysis discussed above falls under targeted analysis. Recently, non-targeted analysis (NTA) has gained significant attention, as it involves scanning the entire mass spectrum of samples using high-resolution mass spectrometry (HRMS) (Mohapatra et al., 2022). In NTA, the HRMS1 (MS) full-scan mode captures a comprehensive range of distinct molecular ions. Subsequently, HRMS2 (MS/MS) spectra are captured to improve identification accuracy, with the sequential windowed acquisition of all theoretical fragment ion mass spectra (SWATH-MS) being a popular approach (Xia et al., 2025). Potential structures are identified by comparing unique molecular features against public databases such as PubChem and ChemSpider. Several of these databases integrate extensive HRMS2 spectra and computational tools tailored to manage large-scale data for prioritization (Ciccarelli et al., 2025). To enhance the reliability of NTA results, high-throughput structure prediction employs both statistical analyses and cheminformatics tools rooted in physical chemistry principles. Further research in this area has coupled Effect-directed analysis with NTA to prioritize contaminants, as has been reported for androgenic compounds (Alvarez-Mora, 2025). This integrated approach strengthens the

accuracy and confidence in the screening outcomes.

## 6. Modelling the transport and fate of pharmaceuticals in surface water, groundwater and drinking water treatment

### 6.1. Numerical modeling in surface water

To govern the safety of surface water resources, the foremost step is to track the pollution sources, the pathway of pollutant transport, and their final destination (Ebele et al., 2017). Numerical modelling, as a powerful toolbox can simulate and predict the transport and fate of pharmaceuticals in surface waters (Ji, 2017). Several modeling suites can be applied to surface water, typically classified into process-based (PB) and data-driven (DD) models (Tong et al., 2022b). PB modelling describes step-by-step processes (e.g., physical-biochemical processes) using a set of mathematical equations (Vaze and Chiew, 2003). For pharmaceuticals, as typical organic micropollutants, the key processes in the aquatic environments include (1) physical transport (advection-diffusion) in a horizontal, longitudinal, and vertical direction driven by hydrodynamics; and (2) physical-biochemical processes like sorption/desorption, degradation, and transformation (Wilkinson et al., 2017).

Several studies have investigated the transport and fate of pharmaceuticals in surface water based on PB modelling. Tong et al. (2021) developed a comprehensive hydrodynamic-water quality (HWQ) modeling approach integrating the processes of eutrophication and pharmaceuticals to predict the dynamics of pharmaceuticals in four multi-compartments: the dissolved phase, suspended solid phase in the water column, pore water phase, and particle phase in sediments within a tropical reservoir in Singapore. Similarly, Hosseini et al. (2012) developed a PhATE (Pharmaceutical Assessment and Transport Evaluation) model incorporating chemical loss parameters to simulate the variations of pharmaceuticals in a river watershed in Canada. These studies demonstrate the potential of PB models in characterizing pharmaceutical fate across different environmental compartments, but their applicability depends on the availability of extensive datasets for parameterization.

Despite their mechanistic foundation, PB models face challenges related to parameterization, computational cost, and uncertainty in describing complex pharmaceutical transformations under varying environmental conditions. To address these limitations, data-driven modeling (DDM) offers an alternative approach by statistically capturing input-output relationships based on past data (Berberich et al., 2020). DD models excel at solving complex non-linear relationships, emulating processes for pharmaceuticals in aquatic environments (Cózar et al., 2014). However, only a few studies have used DD modelling to predict the concentration of pharmaceuticals in surface water, due to the requirement for extensive historical environmental datasets (Tong et al., 2022a). To overcome these limitations, Tong et al. (2022b) introduced a novel modeling framework in a separet study that combines PB and DD models to enable the rapid and accurate prediction of pharmaceuticals in a tropical reservoir. Their findings suggest that hybrid modeling approaches may provide the most effective solutions.

### 6.2. Numerical modeling of groundwater-surface water interactions

The interactions between groundwater and surface water can also be simulated via numerical modelling. Introduced in the mid-1960s, numerical modelling has been instrumental in studying these interactions (Winter, 1995). Pharmaceuticals can migrate between groundwater and surface water through these interactions, making multimedia models a valuable tool for studying pharmaceutical transfer between environmental media. One such model is the Quantitative structure-activity relationship (QSAR), which has been commonly used to assess pharmaceuticals in the natural environments (Gaston et al., 2019). Moreover, the Groundwater Watch List (GWWL) proposed a scoring system to indicate the likelihood of pharmaceuticals reaching groundwater (WGGW). Ki and Ray (2015) developed a GIS-assisted regional screening tool to address intrinsic groundwater vulnerability to pesticide contamination, which can also be applied to pharmaceuticals scored under the GWWL.

Beyond these screening tools, HYDRUS-2D/3D, a widely used numerical modeling suite, provides robust simulation capabilities for unsaturated and saturated flow conditions, solute transport, and reactive chemical fate in soil-water systems. HYDRUS-2D/3D has been extensively applied to study pharmaceutical leaching from agricultural fields, infiltration from wastewater treatment plant effluents, and transport in vadose and saturated zones. Its ability to incorporate heterogeneous subsurface properties and various reaction kinetics makes it particularly valuable for understanding pharmaceutical persistence and transport pathways in groundwater. While HYDRUS models offer detailed process-based simulations, their applicability is sometimes constrained by high computational demands and data-intensive parameterization requirements. To address this, integrating HYDRUS simulations with machine learning-based surrogate models has been proposed to enhance computational efficiency while maintaining predictive accuracy (Huang et al., 2021). This highlights the increasing need for interdisciplinary approaches that combine traditional hydrological models with advanced computational techniques.

### 6.3. Modeling pharmaceuticals at DWTPs

Kinetic models have been frequently used in simulating the reactions of pharmaceuticals at DWTPs (Yeom et al., 2021). Guo et al. (2017) evaluated the degradation reactions of targeted pharmaceuticals in an emerging advanced oxidation process (AOP): the UV/chlorine process based on the kinetic modelling. Similarly, Guo et al. (2018) used the kinetic model to simulate the degradation of pharmaceuticals during UV/$H_2O_2$ processes in drinking water plants. Apart from kinetic models, DD models have been applied in simulating the removal of pharmaceuticals in drinking water system (Huang et al., 2021b; Teo et al., 2022). Another study by Samanipour et al. (2019) trained a DD model based on a machine learning algorithm to monitor drinking water contamination.

Numerical modeling, encompassing PB and DD models, plays a critical role in understanding the occurrence, transport, and fate of pharmaceuticals in aquatic environments. While PB models provide mechanistic insights, their accuracy depends on well-defined process equations and extensive parameterization. In contrast, DD models offer flexible, data-driven approaches but require rich environmental datasets. Integrating PB models (e.g., HYDRUS-2D/3D) with DD models presents a promising avenue for improving pharmaceutical fate predictions. Future research should focus on developing hybrid frameworks combining physical-based process simulations with machine learning techniques, enhancing computational efficiency and predictive reliability for pharmaceutical fate assessments in surface water, groundwater, and drinking water systems.

## 7. Conclusions

The concentrations of pharmaceuticals in the aquatic environment, especially surface water, have been increasing in recent years. China, being a major producer and consumer of pharmaceuticals, has reported high concentrations of these pharmaceuticals in surface waters, particularly in regions with industrial hubs for pharmaceutical production. Commonly detected antibiotics in Chinese surface waters include antibiotics like sulfadiazine and sulfamethoxazole, as well as other pharmaceuticals such as acetaminophen, diclofenac, and caffeine. Similarly, monitoring studies in Missouri, USA, revealed higher surface water concentrations than groundwater. Studies also highlight the widespread presence of acetaminophen, caffeine, and azithromycin in drinking water, with varying concentrations depending on the location. Notably,

the median concentrations of antibiotics and other pharmaceuticals remained consistently high in surface water. Surprisingly, their median concentrations in drinking water often exceed those in groundwater, highlighting the urgent need for risk assessment.

The removal of these pharmaceuticals significantly improved after passing through DWTPs employed with adsorption and advanced oxidation processes. However, conventional treatment processes such as coagulation, flocculation, sedimentation, and filtration are often inefficient in removing more polar compounds; these compounds are found in the aqueous phase. In ADWTPs, a two-stage biofiltration is often used after coagulation to remove antibiotics and other pharmaceuticals successfully. GAC serves as a key adsorbent in this process. Nonetheless, both GAC and biofiltration, as well as AOPs, proved efficient for pharmaceutical removal when combined with prechlorination as pretreatment.

Detecting pharmaceuticals in pg/L-ng/L is now possible due to the efficient preconcentration of these contaminants in HLB cartridges, which offers high retention capability and excellent recoveries, particularly with large sample volumes. Besides SPE, other extraction techniques such as SPME, SBSE, TFME, BAμE, LPME, SDME, and DLLME may also be employed to analyze these pharmaceuticals. Advances in sample preparation techniques and analytical measurements using LC-MS/MS have provided researchers with a wide range of options to efficiently and effectively determine pharmaceuticals in water samples. These techniques enable LOD and LOQ limits ranging from 0.5 pg/L to 0.1 ng/L and 1.00 pg/L to 0.50 ng/L, respectively.

**Future research and recommendation**

- While extensive research has been conducted in Asia, Europe, and North America on the presence of pharmaceuticals in the aquatic environments, there remains a significant knowledge gap in Africa. At a global scale, more monitoring efforts should focus on antibiotics in DWTPs and drinking water, given that the current median concentrations in drinking water exceed those in groundwater. Given the increasing emphasis on wastewater reuse, monitoring pharmaceutical contamination is particularly crucial in water reclamation plants.
- Beyond the pharmaceuticals highlighted in this study, NTA should be employed to detect and quantify novel pharmaceuticals, including the fluorinated ones in wastewater effluent, surface water, and DWTPs. Non-targeted and effect-based analyses are essential for assessing drinking water safety. Water utilities should integrate these analyses into routine water quality monitoring at DWTPs. The "Network of Reference Laboratories, Research Centres, and Related Organisations for Monitoring of Emerging Environmental Substances" (NORMAN) database can serve as a valuable resource for screening new contaminants.
- More field-scale experiments on adsorption and AOPs, including those in operational DWTPs, are needed to determine their real-world efficacy. Most importantly, such measures should be implemented at WWTPs before wastewater is discharged. This remains a challenge, as regulatory discharge standards for pharmaceuticals currently exist only in a few countries in Europe. Where expensive quaternary treatment processes for WWTPs and DWTPs are not feasible, nature-based solutions should be encouraged.
- While antimicrobial resistance (AMR) is well-documented, stronger regulatory measures are needed to control antibiotics and other pharmaceutical consumption, especially in certain Asian and African countries, to mitigate the risk of AMR development. Governments and international organizations must collaborate on this effort. However, with United States Agency for International Development (USAID) funding cuts and the U.S. withdrawal from the World Health Organization (WHO), individual countries must take greater responsibility for safeguarding public health. Additionally, the development of eco-friendly pharmaceuticals through green chemistry should be explored, as such compounds offer benefits including minimal bioaccumulation, reduced persistence, lower toxicity, and decreased environmental impact.
- In resource-limited countries, the modeling approaches discussed in this review can provide a cost-effective option for regulating pharmaceutical pollution. Specific pharmaceuticals can be selected as chemical markers, and models can be developed to link water quality parameters with pharmaceutical contamination. A comprehensive HWQ modelling approach can be used to forecast the fate of pharmaceuticals across multiple aquatic compartments. However, extensive field studies remain necessary to understand the occurrence, fate, and transport of pharmaceutical mixtures in contaminated aquatic environments under varying climatic and temporal conditions.

The increasing presence of pharmaceuticals in daily life has not been countered by sufficient measures necessitating aforementioned research and development in this field to enhance the capabilities of these techniques, ultimately contributing to a better understanding of the occurrence, fate, and potential risks associated with pharmaceuticals in the environment.

## CRediT authorship contribution statement

**Sanjeeb Mohapatra:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Xuneng Tong:** Writing – review & editing, Writing – original draft, Visualization. **Santanu Mukherjee:** Writing – review & editing, Writing – original draft. **Monika Dubey:** Writing – review & editing, Writing – original draft, Visualization. **Sachin Subhash:** Writing – review & editing, Writing – original draft, Data curation. **You Luhua:** Writing – review & editing. **Jan Peter van der Hoek:** Writing – review & editing, Supervision, Funding acquisition. **Karina Yew-Hoong Gin:** Writing – review & editing, Supervision, Funding acquisition.

## Declaration of competing 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.

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## Supplementary materials

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## Data availability

The data can be found in the SI

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