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REVIEW ARTICLE

Tracking drugged waters from various sources to drinking water—its persistence, environmental risk assessment, and removal techniques

Dixita Phukan[1] · Vipin Kumar[1]

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Abstract

Pharmaceuticalshave become a major concern due to their nature of persistence and accumulation in the environment. Very few studies have been performed relating to its toxicity and ill effects on the aquatic/terrestrial flora and fauna. The typical wastewater and water treatment processes are not efficient enough to get these persistent pollutants treated, and there are hardly any guidelines followed. Most of them do not get fully metabolized and end up in rivers through human excreta and household discharge. Various methods have been adopted with the advancement in technology, sustainable methods are more in demand as they are usually cost-effective, and hardly any toxic by-products are produced. This paper aims to illustrate the concerns related to pharmaceutical contaminants in water, commonly found drugs in the various rivers and their existing guidelines, ill effects of highly detected pharmaceuticals on aquatic flora and fauna, and its removal and remediation techniques putting more emphasis on sustainable processes.

Keywords Pharmaceuticals · Emerging pollutants · Risk assessment · Drinking water · Adsorption · Bio-electrochemical cell

Introduction

The use of pharmaceuticals in our day-to-day life has been increasing with the rapid development of medical facilities. But since most of the pharmaceutical products that we consume are not being metabolized completely, hence, they get into the water through human or animal excreta thus polluting the water bodies. So they are broadly termed "emerging contaminants" and the conventional wastewater system is inefficient in the removal of these emerging contaminants. Not only pharmaceuticals used for human consumption but also drugs used for veterinary treatment and rapid production of livestock at a lower cost lead to water as well as soil pollution. In comparison to the monitoring of heavy metals, fertilizers, and pesticides, almost no attention has been paid to these emerging pollutants until few scientists have found their ill effects on the environment and aquatic flora and fauna (Daughton 2002; Dębska et al. 2004; Heberer 2002; Hernando et al. 2006; Zuccato et al. 2006; Nikolaou et al. 2007; Kümmerer 2009). Some of them have even carried out a risk assessment on various organisms and also reported the potential effects of these pharmaceuticals such as delay in the growth and development of fish and frogs and hindrance in the metamorphosis of frogs. Moreover, alteration in behavior and reproduction has been observed along with an increase in the feminization of fish (Hernando et al. 2006). Since these pharmaceutical compounds can affect non-target organisms to a great extent, so regular monitoring of these chemicals in water has become a necessity. According to research carried out in 2018, India has been ranked 3rd in the production of pharmaceutical products and ranked 13th in consumption respectively (Mutiyar et al. 2018). Recently, an experimentation was carried out on the bioaccumulation and risk assessment of 43 PPCPs in 3 Asian countries on the locally available fish species, and high concentration of diclofenac (6.8–8.7 ng/mL) and gemfibrozil (3.4–9.7 ng/mL) was detected in the plasma of catfish (*Clarias* spp.) of India and around 0.47–1.8 ng/mL in tilapia (*Oreochromis* spp.) and1.3–7.7 ng/mL in carps (*Cyprinidae*) from Yen So Lake (Site R) in Vietnam (Nozaki et al. 2023).

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✉ Vipin Kumar
vipinmicro1@iitism.ac.in

[1] Department of Environmental Science and Engineering, Indian Institute of Technology (Indian School of Mines), Dhanbad, Jharkhand, India 826004

Thus, this paper aims at investigating the occurrence and persistence of various pharmaceuticals in different water bodies of India, along with the various guidelines introduced in different countries for its constant monitoring and its remediation techniques used so far.

Various sources of pharmaceutical wastes in various rivers worldwide

Occurrence of pharmaceuticals in major rivers of India

Ganges River

In India, Ganges being the largest river meets the drinking requirement of most people, and also, most of them are dependent on it to carry out their daily activities, irrigation, and industrial purposes. As most of the effluents from various point and non-point sources get discharged into the river, the river gets highly polluted, and the major concern gaining attention these days is the pharmaceutical wastes which fall under the category of emerging contaminants, and as they do not get easily degraded, they escape the conventional wastewater treatment.

Very limited research work has been carried out on these emerging contaminants, and among many, some of the pharmaceutical compounds which are highly detected in most of the sampling areas of the river are atenolol, acetaminophen, carbamazepine, ciprofloxacin, caffeine, diclofenac, clofibric acid, hydrochlorothiazide, sulfamethoxazole, ibuprofen, naproxen, and ketoprofen, few personal care products (triclosan, triclocarban, diethyltoluamide (DEET)), and also artificial sweeteners (acesulfame K, aspartame, cyclamate, sucralose, saccharine). Caffeine was detected in a higher amount (743 ng/L), followed by ketoprofen (107 ng/L) in most of the sampling sites of the river at the Himalayan reach. Moreover, in the cities like Patna, Varanasi, and Kanpur which lie in the downstream part of the river, a huge amount of pharmaceutical compounds and personal care products has been detected as there are around 764 industries around the banks of the river that discharge their effluents directly into the river and effluent load per day is around 501 million l per day. Along with the surface water, groundwater in and around the vicinity of the river also gets affected by these pollutants, and the reasons behind this are the leakage of septic tanks, leaching from landfills where most of the medical wastes are illegally dumped along with expired medicines (Sharma et al. 2019).

Caffeine, being found in elevated concentrations in most of the sites of the river which covers areas of Uttarakhand, Uttar Pradesh, along with cities like Allahabad and Varanasi which are places of religious importance, has been considered a useful indicator of anthropogenic inputs into the river (Chakraborty et al. 2021).

Yamuna River

The Yamuna River passing through metro cities like Delhi has become highly polluted as a huge amount of waste is being dumped in the river. Also, wastewater from various water treatment plants and STPs gets discharged into the river, and thus, it gets highly accumulated with these emerging contaminants. Although the flow rate of the river changes drastically with every passing season, the pollution load during the winter season is considered very high in comparison to the summer or monsoon season as photo-degradation and dilution potential play a vital role during these seasons. In most of the sites of the river, the concentration of drugs that were highly detected is aspirin, caffeine, codeine, carbamazepine, diazepam, diclofenac, ibuprofen, paracetamol, and ranitidine (Mutiyar et al. 2018). Also, research was being carried out on risk assessment of the aquatic flora and fauna found in the river and the risk corresponds to a coefficient which indicates the transfer of pharmaceuticals from the water body to the organisms, and the study concluded that these pharmaceutical wastes have high potentiality for persistence, bioaccumulation, and toxicity thus creating a threat to the aquatic life (Khan et al. 2021).

Brahmaputra River

Like Yamuna and Ganges, Brahmaputra too is loaded with pharmaceutical wastes which pose a threat to the aquatic life as well as give rise to potential pathogenic microbes. Kumar et al. (2019a, b) found that the compounds which are most commonly detected in all the seasons of the year are acetaminophen, caffeine, theophylline, carbamazepine, and crotamiton, and the risk assessment of these compounds was being carried out. It was being carried out in Bharalu, one of the tributaries of the Brahmaputra on organisms like daphnia, algae, and fish, and it was found that the risk quotient of acetaminophen and caffeine was high for all these organisms taken into an experiment for all the seasons of the year.

Another study revealed that samples collected from various sites of the Brahmaputra River and nearby the wetland Dipor Bil showed the presence and prevalence of PPCPs (pharmaceuticals and personal care products) in the following order: caffeine (35–22,733 ng/l) was detected in huge amounts, followed by acetaminophen (<LOD–5967 ng/l), theophylline (<LOD–2939 ng/l), carbamazepine (<LOD–75ng/l), and crotamiton (<LOD–8 ng/l). It was also concluded that these PPCPs were directly related to raw sewage and hence highly detected in the drains whereas their detection was low upstream of the river Brahmaputra

due to the natural processes which were being carried out in the river (Kumar et al. 2019a, b).

Also, the river in the Guwahati city is highly loaded with these emerging contaminants as being the largest city in the NE region; it is the industrial and commercial hub of the region, and most of the raw sewage from various industries is being dumped into the river.

Godavari River

According to Reinventing Telangana, Socio-Economic Outlook, 2017, in India, the contribution of Hyderabad to the production of pharmaceutical products is 30%, and Telangana itself makes millions of profit by exporting its pharmaceutical products.

Larsson et al. (2007) reported that a huge amount of active pharma ingredients was being discharged into the river from various pharmaceutical industries. He concluded this after testing samples from a common effluent treatment plant at Patancheru where effluents of around 90 bulk drug manufacturers are being treated. Larsson also concluded that this effluent treatment plant in Hyderabad received the highest amount of pharmaceutical compounds containing wastewater than any other place in the entire world. Hans India (2016) reported that the pharmaceutical companies which are placed on the banks of the river Godavari, especially in the districts of Adilabad, Khammam, Karimnagar, and Warangal, release their raw effluents directly into the river.

It was also found that the industries which are located in the vicinity of the villages near the bank of the Manjira tributary discharge their effluents in the tributary which ultimately flows into the river Godavari. In addition to it, groundwater samples collected from open wells in Southern India located near effluent-treated plants observed the prevalence of various pharmaceutical compounds like terbinafine, enoxacin, citalopram, cetirizine, and ciprofloxacin (Balakrishna et al. 2017).

According to Patneedi and Prasadu (2015), flora and fauna and as well as human lives living in the vicinity of these industrial zones are greatly affected as these pharmaceutical wastes dumped into the river not only contaminate the sources of drinking water of the people but also give rise to various health-related problems along with affecting the aquatic organisms and livestock as a reduction in milk output has been reported as an ill effect of these PPCPs containing water.

Along with pharmaceutical compounds, these industries release toxins which consist of heavy metals like arsenic, lead, vanadium, and cadmium directly into the river thus contaminating the sources of drinking water as these metals have been found in concentrations levels that are higher than the permissible limits prescribed by World Health Organization (WHO) and Bureau of Indian Standards (BIS) (Purushotham et al. 2017).

Occurrence of pharmaceuticals in major Chinese basins

Dai et al. (2021) experimented on major river basins of China and they reported that most of the drugs have been detected in the Yangtze, Haihe, and Pearl River basins as these basins cover areas that are densely populated. The drugs which were detected in high amounts and exceeded 1μg/l are ofloxacin, chlortetracycline, oxytetracycline, tetracycline, sulfamethoxazole, trimethoprim, roxithromycin, sulfapyridine, diclofenac, and norfloxacin. Li et al. (2018) reported that the contamination of waters by antibiotics was found mostly in the Haihe River basin, and their concentrations exceeded more than 100ng/l. It was also found that since there are aquaculture industries present in the River Pearl basin, so high amount of sulfonamides and fluoroquinolones had been detected in this basin (Liu et al. 2017). It was also seen that the drug carbamazepine (CBZ) was highly detected in the Pearl River basin with higher concentrations and the reason behind this might be due to its consumption by a larger amount of people (Fekadu et al. 2019). Also in areas near Shanghai, a huge amount of CBZ had been observed, and this was linked to the high usage of this drug in areas of Shanghai. CBZ is a drug whose photodegraded metabolites are far more toxic than the parent drug, and so its removal and constant monitoring are of utmost importance. Dai et al. (2021) also observed in their study that the presence of sulfapyridine (SPD) was detected in all the major basins of China and the concentration ranged from 0 to 287 ng/l.

Occurrence of pharmaceuticals in African water bodies

NSAIDs (non-steroidal anti-inflammatory drugs) that are highly detected in the African rivers are ketoprofen, naproxen, ibuprofen, and diclofenac, and this is mainly due to the poor sanitary facilitation and partially treated wastewater. According to K'oreje et al. (2012), among all the NSAIDs, ibuprofen is highly detected in the surface waters of Africa which are estimated to be around 30 μg/l.

Among antibiotics, the ones which are detected in higher concentrations are sulfamethoxazole, sulfapyridine, sulfathiazole, sulfamethizole, sulfadimidine, azithromycin, trimethoprim, clarithromycin, tetracycline, roxithromycin, doxycycline, oxytetracycline, and chlortetracycline (Segura et al. 2015). It was observed in the sampling sites that the concentration of antibiotics in African rivers was lower than that of the NSAIDs, and the reason behind this might be the NSAIDs being non-prescribed drugs over the counter.

Anti-retroviral drugs have also been detected in the African waters, and according to K'oreje et al. (2016) and Ngumba et al. (2016), these drugs have been highly detected in the Kenyan rivers where their concentration ranged from 167μg/l (lamivudine), 17 μg/l (zidovudine), and 6 μg/l (nevirapine). Also, high concentrations of the drug nevirapine have been detected as it is highly used in the treatment of HIV (Schoeman et al. 2015). Again, among the steroid hormones which are highly detected in the African Rivers are estradiol, estrone, estriol, mestranol, and 17-α-ethinylestradiol. Their concentrations are mostly below ng/l, and they are generally found in the waters only because of insufficient treatment in the wastewater plants.

Occurrence of pharmaceuticals in the Portugal Rivers, Europe

Various studies have been carried out on the presence of different drugs in the Lis and Leca rivers of Portugal. NSAIDs and psychiatric drugs have been highly detected in these rivers, along with antibiotics such as ciprofloxacin, azithromycin, and sulfamethoxazole. It was found by Gonçalves et al. (2013) that the concentration of acetaminophen (398 ng/l) was higher in the Leca River in comparison to the Lis River whereas in the case of NSAIDs, it was found that its concentration was higher in the Lis River than the Leca River. An analgesic such as acetaminophen was highly detected in both the rivers as it is being continuously added to the water and its continuous entry into the water body overlaps its degradation process and so its presence is evitable in both the rivers. Rabiet et al. (2006) also detected the presence of salicylic acid which is a metabolite of acetylsalicylic acid in the Lis River, and the reason behind it was its consumption by a large sum of people in Portugal. Paíga et al. (2016) found that sertraline and fluoxetine in all the sampling points of the Lis River and antibiotics were found to be in lower concentrations than that of the NSAIDs. Thus, they concluded in his study that the drugs fluoxetine, acetaminophen, ibuprofen, carbamazepine, and salicylic acid were detected in all the samples of the Lis River.

Taking into account the surface waters of Europe, it was found that 33 countries have been polluted with pharmaceutical residues. Among all the countries, the pharmaceuticals whose concentrations were above the detection limits were highly found in Spain, i.e., 67% (153 out of 227). The compounds which were detected in more than 28 countries were ibuprofen and diclofenac under the category of NSAIDs, gemfibrozil and bezafibrate, which are 2 lipid-regulating drugs, caffeine, a stimulant, carbamazepine(anticonvulsant), and sulfamethoxazole, the most detected antibiotic (Zhou et al. 2019).

Occurrence of pharmaceuticals in the Oceanian waters

Among all the countries of the continent Oceania, Australia is the most populated country and Wilkinson et al. (2022) had already found Adelaide of Australia as the most contaminated sampling site in his study. Long et al. (2023) carried out their analysis primarily on carbamazepine, tramadol, and venlafaxine from the samples collected along the coastline of South Australia. The study was carried out on the surface waters, wastewater, and also on the accumulation of these compounds by aquatic organism. Carbamazepine was detected in the wastewater samples at a range of 807–893 ng/l, tramadol at a range of 359–525ng/l, and venlafaxine at a range of 490–598ng/l whereas the same compounds were detected in surface waters in the following range carbamazepine (< LOQ–0.50 ng/l), tramadol (0.90–2.05 ng/l), and venlafaxine (0.89–1.44 ng/l). These compounds were also detected in the benthic flora where tramadol ranged from 14.38 to 34.67 ng/l dry weight and venlafaxine ranged from 8.26 to 16.46ng/l dry weight but carbamazepine ranged from a non-detectable value to a value which was below the limit of quantification.

Occurrence of pharmaceuticals in the water bodies of North and South America

In the Quebec region of Canada, water samples were examined from municipal drinking water for detection of pharmaceuticals and pesticides in it, and out of 70 chemicals, 15 were compounds out of which 9 were pharmaceuticals and 6 were pesticides which have been detected in their study. Out of all the contaminants, the three highly detected contaminants were caffeine, atrazine, and naproxen which were about 29%, 24%, and 21% of the total samples collected for analysis. It was found that both the sources of drinking water in Quebec, i.e., ground as well as surface water, had concentrations of pharmaceuticals and pesticides ranging from 30 to 1846 ng/l and 21–856 ng/l (Husk et al. 2019).

Griffero et al. (2019) investigated the occurrence of emerging contaminants in the coastal lagoons of Uruguay, South America, and the pharmaceutical compounds like tamoxifen (0.06–2.40 μg/l), caffeine (0.05–1.17 μg/l), 17-β-estradiol (0.16–0.45 μg/l), terbutaline (0.16–0.45 μg/l), morphine (below limits of quantification), ibuprofen (0.30–0.30 μg/l), lomefloxacin (below limits of quantification), 17-α-ethynilestradiol (0.13–45 μg/l), diclofenac(below limits of quantification), atenolol (below limits of quantification), and ciprofloxacin (below limits of quantification) were detected along with few insecticides, herbicides, and fungicides.

A study was carried out in the waters of the beach area of Sao Paulo State of Brazil, South America, to find out the persistence of pharmaceuticals in it. Carbamazepine (0.1–8.0 ng/L), caffeine (33.5–6550.0 ng/L), cocaine (0.2–30.3 ng/L), benzoylecgonine (0.9–278.0 ng/L), citalopram (0.2–0.4 ng/L), acetaminophen (18.3–391.0 ng/L), diclofenac (0.9–79.8 ng/L), orphenadrine (0.2–1.5 ng/L), atenolol (0.1–140.0 ng/L), propranolol (limit of detection: LOD-0.9 ng/L), enalapril (2.2–3.8 ng/L), losartan (3.6–548.0 ng/L), valsartan (19.8–798.0 ng/L), rosuvastatin (2.5–38.5 ng/L), chlortalidone (0.1–0.4 ng/L), and clopidogrel (0.1–0.2 ng/L) were detected in the samples and the reason behind high concentrations of caffeine was assumed to be the high production of coffee in the state of Brazil (Roveri et al. 2020).

Pharmaceutical pollution in the waters of Antarctica

With the curiosity for research and tourism in Antarctica, the population has been increasing and so is the pharmaceutical pollution in its waters. In a study carried out in 2017, 25 pharmaceutical and 21 recreational drugs have been analyzed in the northern Antarctic Peninsula where it was found that analgesics and stimulants like caffeine had been detected in the highest concentrations. Among the analgesics, acetaminophen had the highest concentration of about 48.74 μg/l, followed by diclofenac at about 15.09 μg/, ibuprofen at 10.04 μg/l, and for the stimulant caffeine, it was found to be 71.33 μg/l.

It was also assessed that the hazard quotient (HQ) values for acetaminophen, diclofenac, and ibuprofen were exceeding 10 at various sampling points of the ocean waters. Due to the high toxic values obtained in the study, it was concluded that analgesics and anti-inflammatory drugs pose a higher risk of threat Antarctic aquatic ecosystem (González-Alonso et al. 2017).

Another study was conducted in the Admiralty Bay region of King George Island to test the presence of pharmaceutical compounds in the seawater. Due to untreated wastewater discharged into the seawater, the pharmaceutical compounds which were detected in high concentrations were naproxen (2653 ng/l), diclofenac (747 ng/l), ketoconazole (760 ng/l), ibuprofen (477 ng/l), acetaminophen (332ng/l), benzotriazole (6340 ng/l), and caffeine (3310 ng/l). It was also found that due to the high-risk quotients (RQ) of these analgesics, stimulants, and antifungals, the whole ecosystem was under a high toxic burden (Szopińska et al. 2022).

Wilkinson et al. (2022) studied the occurrence of pharmaceutical pollution in the rivers around the globe. and it was found by his team that among the African countries, the most contaminated site was Ethiopia followed by Tunisia and the Democratic Republic of Congo (Fig. 1). Also among the Asian countries, the most contaminated samples were detected in Pakistan, followed by India and Armenia (Table 1). In the case of North America, the most contaminated samples were found in Costa Rica which had a mean range of around 25.8 μg/L. Madrid, Spain from Europe, and Adelaide, Australia, from samples of Oceania were found to be the most contaminated ones in Europe and Oceania which had a mean range value of 17.1 μg/L and 0.577 μg/L, and the maximum was found to be 59.5 μg/L and 0.75 μg/L.

Brief description of commonly prescribed drugs found in water bodies

Drugs have been categorized into various categories, and depending on the target problems or disease to be cured, they can be classified into the following—antipyretics, antidepressants, analgesics, NSAIDs, antihistamines, anticoagulants, and antacids. Most of these drugs do not get completely metabolized and hence come into the environment through human excreta. Along with these drugs, artificial sweeteners are another category that pollutes the water bodies thus affecting the aquatic life. Drugs like caffeine, triclosan, acetaminophen and ibuprofen, triclocarban, sulfamethoxazole, carbamazepine, and atenolol are highly prescribed, and therefore, they are mostly detected in the wastewater treatment plants of India.

Caffeine (1, 3, 7-trimethylpurine-2, 6-dione) is a widely used stimulant. It is commonly found in tea, coffee, chocolate, energy drinks, colas, etc. and helps to boost energy by stimulating the central nervous system. It is also found in many medications such as migraine and headaches and also in various dietary supplements. According to Hillebrand et al. (2012), caffeine possesses the potential to act as a chemical marker of domestic wastewater.

Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol) is an antibacterial and antifungal agent and is generally used in soaps, toothpaste and detergents, surgical cleaning treatments, etc. According to Nag et al. (2018), it is extremely toxic to aquatic organisms like algae, zooplankton, and fish. It has the potential to bioaccumulate and disrupts the endocrine system. Triclocarban (N-(4-chlorophenyl)-N′-(3,4-dichlorophenyl)urea) is used as an antimicrobial agent and antiseptic drug in many personal care products. Likewise, triclosan, it too can disrupt the endocrine system and is harmful to aquatic organisms like fishes, zooplanktons, etc.

Acetaminophen (N-acetyl-p-aminophenol), being an analgesic, is widely used in India and China for treating mild to moderate pain. It is also used to treat cold, flu, fever, toothaches, etc. Erhunmwunse et al. (2021) found that its higher concentration in the water ranging from 5 to 100μg/l seems to have an ill effect on organisms like catfish. Again, ibuprofen (2-(4-(2-methyl propyl)phenyl) propanoic acid) which is a non-steroidal anti-inflammatory drug (NSAID) used to treat fever, pain, and inflammatory-related problems caused due to toothache, back pain, arthritis, etc. has been found to have morphological and behavioral changes

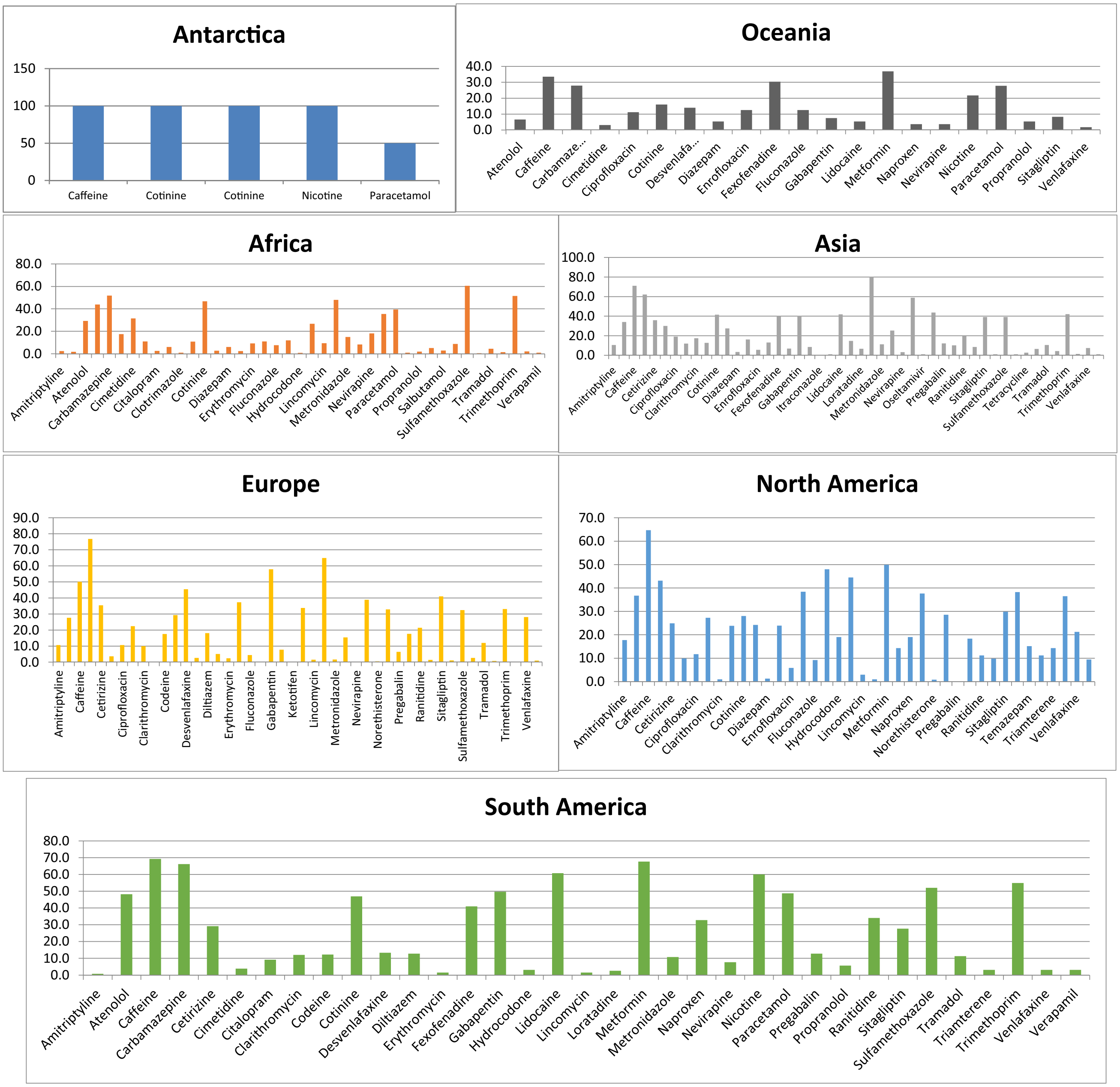

Fig. 1 Data has been adopted from Wilkinson et al. (2022) and modified to graphs showing detection frequency of pharmaceutical compounds in water bodies of all the continents

in fishes and various other model organisms (Chopra and Kumar 2020; Das et al. 2019; Zanuri et al. 2017; Di Nica et al. 2017; Geiger et al. 2016; Du et al. 2016; Jeffries et al. 2015; Sung et al. 2014, etc).

Sulfamethoxazole (4-amino-N-(5-methyl-1, 2-oxazol-3-yl)benzene sulfonamide) is an antibiotic used to treat infections in the urinary, respiratory, and gastrointestinal tract. Liu et al. (2020) reported that its environmentally detectable concentrations in the aquatic system, i.e., concentrations ranging from 0.1 to 100 μg/l, delay the hatchment and growth and development in zebrafish larvae along with changes in the immune system. Carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide) which is an anti-convulsant and anti-epileptic drug used in the prevention and control of seizures has also been found. According to Qiang et al. (2016), concentrations of carbamazepine in aquatic bodies disturb the development of the embryo of fish and also cause behavioral changes in the larvae of zebrafish. Atenolol(-2-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetamide) which is a synthetic beta-blocker is used to treat angina and hypertension has various ill effects on aquatic organisms. For example, Lin et al. (2022) found out that the bioaccumulation of atenolol in zebrafish causes morphological changes in it.

Persistence of pharmaceuticals in the environment and its associated risks

Owing to anthropogenic activities, a huge amount of pharmaceutical compounds and toxic ingredients from personal care products get flushed and disposed of into the Rivers (Fig. 2). Most of these pharmaceutical compounds get loaded into the environment through human urine or feces since they do not get completely broken down in the human body. These wastes are being received by the wastewater treatment plants where they escape the conventional treatment techniques and thus get flushed and mixed in the river water. Also, due to their capacity to linger in the environment and get transformed into various metabolites other than the parent compound, they do not get easily removed by the traditional sewage system, and thus, their persistence poses a threat to the aquatic organism in the longer run.

Daughton (2001) stated that a few among many pharmaceutical compounds such as caffeine, aspirin, and nicotine has been known to enter the environment and persist in it for a long time by now. He also concluded that the addition of these pharmaceutical and personal care products is a continual process and so natural processes like photodegradation, hydrolysis, and dilution fail to degrade these substances, and thus, they keep on lingering in the environment for a longer period. As these wastes keep on accumulating in the water bodies, they possess the capacity to create toxic effects even at very low concentration levels as ng/l (Pereira et al. 2015). Depending on their D_{ow}, these substances have a great potential to accumulate in the water and get biomagnified in the food chains.

Concern has been raised about antibiotic residues in water as these compounds can pose a threat to the aquatic habitat even at very low concentrations. These compounds also give rise to resistant and virulent pathogens which not only disturb the ecosystem but also prove to be harmful to human health.

Also, Cabello (2006) have reported that it takes less time to gain resistance in the water bodies than in the terrestrial environment. Therefore, contamination of water sources by these antibiotic residues can be very toxic to human health. Kolpin et al. (2002) in one of their works carried out in 139 water bodies detected 90 organic contaminants. Contamination level by some substances such as cholesterol, triclosan, coprostanol, and caffeine has been found more than 50%. He also found out that almost 30 drugs had concentrations larger than 0.1 ug/l, and those were codeine, ibuprofen, erythromycin, sulfamethoxazole, 1, 7-dimethylxanthine, stigmastanol, caffeine, acetaminophen, cholesterol, and coprostanol.

Effects of different medicines on aquatic flora and fauna

These substances other than treating the target diseases also affect the non-target organisms and bring morphological and behavioral changes in them when they are present in higher amounts and continuously being added to the water bodies as a result of the anthropogenic pollution (Fig. 3).

Recently, these substances have been able to draw the attention of researchers as “emerging contaminants,” and research and risk assessments have been carried out on the aquatic flora and fauna (Table 2). A few of the substances, their classes, and the impacts they claim to have on different organisms have been listed below:

Human health risk assessment

There are basically 2 major ways through which these pharmaceutical compounds can get back to humans in the form of transformed products or metabolites (Figs. 4, 5). These are the following: (i) through intake of water and (ii) through the consumption of fishes or other such aquatic organisms in which these compounds get accumulated or concentrated. Many researchers have carried out human health risk assessments depending on different factors and levels of exposure. Kumar et al. (2010) stated that quantification of pharmaceutical risk assessment generally consists of 4 major steps and they are the following: (i) identification of the hazard, (ii) assessment of the exposure levels, (iii) relationship between dose and response, (iv) characterization of the possible risk.

Risk quotients (RQs) were established for different life stages of humans to predict the risk of different compounds on humans. These RQs are determined based on the quantification of pharmaceutical compounds found in the drinking water samples and also on the quantification of the pharmaceuticals in the source water by dividing the highest concentration of these compounds found in the samples for each parent compound by a respective drinking water equivalent level (DWEL). It was also considered that if an RQ value is found to be greater than 1, then it would suggest a probable risk in relation to the exposure through drinking water. (de Jesus Gaffney et al. 2015), According to him, RQ can be calculated by the following formula

$$RQ = \frac{Cs}{\mathrm{DWEL}}$$

Also, $\mathrm{DWEL} = \frac{\mathrm{ADI\ x\ BW\ x\ HQ}}{\mathrm{DWI\ X\ AB\ X\ FOE}}$ where C_s represents the amount of the specific pharmaceutical found in the sample,

Table 1 Table depicting the area of detection, highly detected compounds, and their range

Sl no	Area of detection			Highly detected compounds and their range	References
1	Asia	India	Ganga River	Caffeine: 743 ng/l Ketoprofen: 107 ng/l	Sharma et al. (2019)
			Yamuna River	Aspirin, ibuprofen, caffeine, codeine, carbamazepine, diazepam, diclofenac, paracetamol, and ranitidine—all > 1 µg/l	Mutiyar et al. (2018)
			Brahmaputra River	Caffeine: 35–22,733 ng/l Acetaminophen: < LOD–5967 ng/l Theophylline: < LOD–2939 ng/l Carbamazepine: < LOD–75 ng/l Crotamiton: < LOD–8 ng/l	Kumar et al. (2019a, b)
		China	Yangtze, Haihe and Pearl river	Drugs whose concentration exceeded 1 µg/l: ofloxacin, chlortetracycline, sulfamethoxazole, trimethoprim, roxithromycin, sulfapyridine, diclofenac, norfloxacin	Dai et al. (2021)
			Haihe River	Antibiotics: > 100 ng/l	Liu et al. (2017)
2	Africa	Kenya	Surface waters of Africa	Concentrations of NSAIDs > antibiotics	Segura et al. (2015)
			Kenyan rivers	Lamivudine: 167 µg/l Zidovudine: 17 µg/l Nevirapine: 6 µg/l	K'oreje et al. (2016) Ngumba et al. (2016)
3	Europe	Portugal	Lis and Leca rivers	NSAIDs > antibiotics Acetaminophen: 398 ng/l	Gonçalves et al. (2013)
4	Oceania	Australia	Wastewaters	Carbamazepine: 807–893 ng/l Tramadol: 359–525 ng/l Venlafaxine: 490–598 ng/l	Long et al. (2023)
			Surface waters	Carbamazepine: < LOQ–0.50 ng/l Tramadol: 0.90–2.05 ng/l Venlafaxine: 0.89–1.44 ng/l	
			Benthic flora	Tramadol: 14.38–34.67 ng/l dry weight Venlafaxine: 8.26–16.46 ng/l dry weight Carbamazepine: < LOQ	
5	North America	Canada	Quebec region municipal drinking water	Among all the detected compounds: Caffeine: 29% Atrazine: 24% Naproxen: 21% All total concentrations of pharmaceutical compounds ranged from 30 to 1846 ng/l	Husk et al. (2019)
6	South America	Uruguay	Coastal lagoons	Tamoxifen: 0.06–2.40 µg/l Caffeine: 0.05–1.17 µg/l 17-ß-estradiol: 0.16–0.45 µg/l Terbutaline: 0.16–0.45 µg/l Morphine: < LOQ Ibuprofen: 0.30 µg/l Lomefloxacin: < LOQ 17-α-ethynilestradiol: 0.13–45 µg/l Diclofenac, atnolol, ciprofloxacin: < LOQ	Griffero et al. (2019)

Table 1 (continued)

Sl no	Area of detection			Highly detected compounds and their range	References
		Brazil	Beach area of Sao Paulo state	Carbamazepine: 0.1–8.0 ng/l Caffeine: 33.5–6550.0 ng/l Cocaine: 0.2–30.3 ng/l Benzoylecgonine: 0.9–278.0 ng/l Citalopram: 0.2–0.4 ng/l Acetaminophen: 18.3–391.0 ng/l Diclofenac: 0.9–79.8 ng/l Orphenadrine: 0.2–1.5 ng/l Atenolol: 0.1–140.0 ng/l Propranolol: LOD–0.9 ng/l Enalapril: 2.2–3.8 ng/l Losartan: 3.6–548.0 ng/l Valsartan: 19.8–798.0 ng/l Rosuvastatin: 2.5–38.5 ng/l Chlortalidone: 0.1–0.4 ng/l Clopidogrel: 0.1–0.2 ng/l	Roveri et al. (2020)
7	Antartica	Antarctic Peninsula	Ocean waters	Acetaminophen: 48.74 µg/l Diclofenac: 15.09 µg/l Ibuprofen: 10.04 µg/l Caffeine: 71.33 µg/l	González-Alonso et al. (2017)
		King George Island	Seawaters of Admiralty bay region	Naproxen: 2653 ng/l Diclofenac: 747 ng/l Ketoconazole: 760 ng/l Ibuprofen: 477 ng/l Acetaminophen: 332 ng/l Benzotriazole: 6340 ng/l Caffeine: 3310 ng/l	Szopińska et al. (2022)

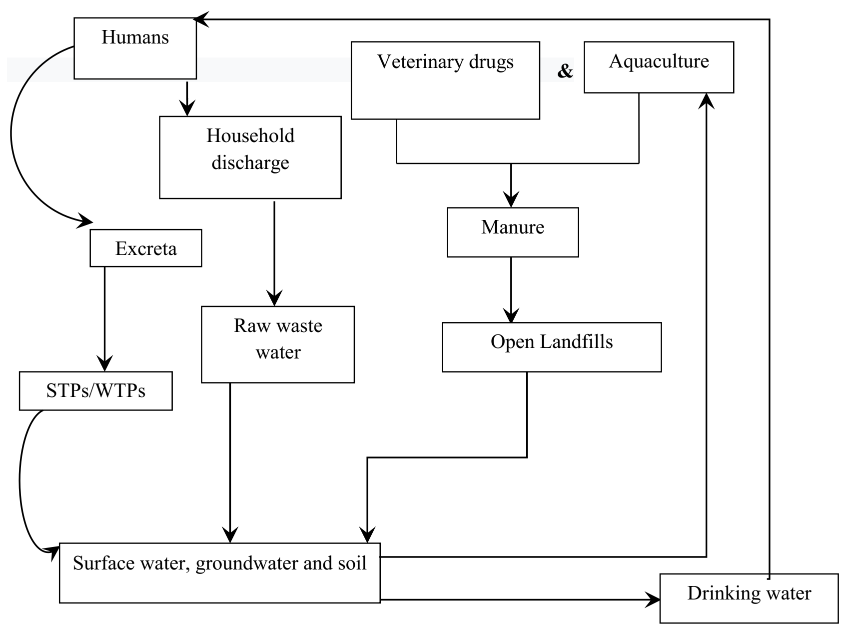

Fig. 2 Sources of pharmaceuticals in water bodies

ADI stands for the acceptable daily intake, and BW indicates the 50th percentile body weight for the different age groups in kg, HQ represents the hazard quotient and it is usually assumed to be 1, DWI represents the drinking water intake which is again determined based on different age groups and is based on the EPA "Exposure Factor Handbook" (EPA 2011), AB stands for the rate of gastrointestinal absorption and it is too assumed to be 1, and FOE stands for frequency of exposure.

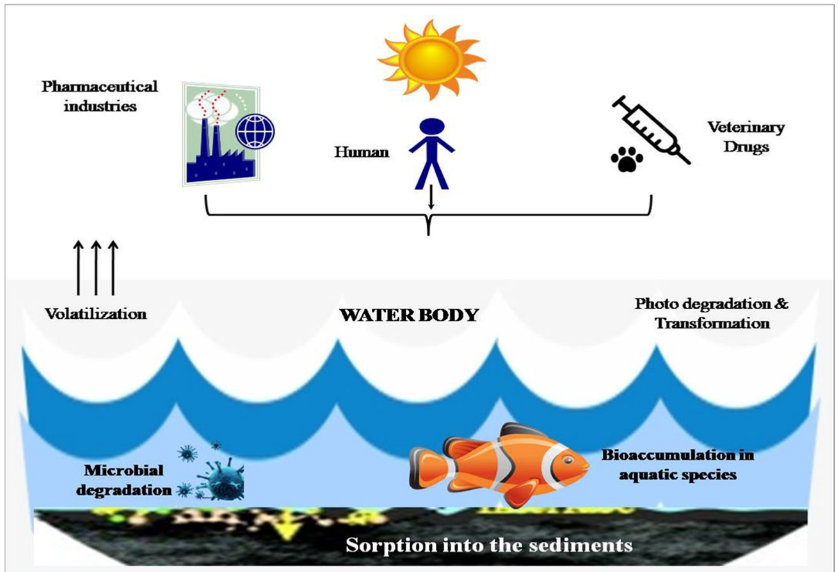

Fig. 3 Fate of pharmaceutical products in the water bodies

Recently, Dai et al. (2021) introduced a formula for the calculation of risk quotient for estimating the probable risk to humans through the intake of daily water and ingestion of fish.

$$RQ = \frac{\text{Iwater\&fish}}{\text{ADI}} + \frac{\text{Iwater} + \text{Ifish}}{\text{ADI}}$$

where I_{water} is the daily water intake which consists of pharmaceuticals in it, and I_{fish} is the estimation of pharmaceuticals ingested through the consumption of fish.

Kumar et al. (2010) when carrying out a risk assessment of meprobamate, carbamazepine, and phenytoin on human health found that the hazard quotients due to accidental ingestion of steam water and consumption of fish were smaller compared to that of injection through finished drinking water.

Risk assessment of antibiotics on marine species (fishes, crustaceans, and molluscs) and humans have been carried out in Qinzhou Bay, South China, and it was found that molluscs were very high potential accumulators of these antibiotics which ranged from 5.2 to 18 ng/g dw. Moreover, these marine species were found to be under the threat of these antibiotics especially azithromycin and norfloxacin. It was also assessed that children under the age group of 2–5 years are more viable to these antibiotics through the consumption of seafood. (Wang et al. 2023)

Although risk assessment of these pharmaceuticals has been carried out, it has been carried out on individual pharmaceutical compounds and not on the mixture of these compounds. Strict monitoring is required to find out the risk assessment on the mixture of these compounds or their metabolite to discover the long-term ill effects on both humans and aquatic organisms (Figs. 6, 7).

Guidelines for emerging contaminants in different countries

The frequency of usage of certain drugs varies with different locations; as such, the usage of antibiotics around the globe is highest in Asia, and the usage of painkillers has been found highest in Europe (Hughes et al. 2013). According to Kookana et al. (2014), the ecological footprint of a pharmaceutical is determined by the following factors: (a) demography, i.e., the size and age distribution of a human population, (b) access to health facilities, (c) the presence and size of manufacturing sectors in a particular area, (d) STPs and their connectivity to the drainage systems, (e) the effluents receiving environment, (f) how effective are the guidelines implemented in a particular area.

Considering these non-evitable facts, strict guidelines and assessment are required for those pharmaceuticals which are used in huge amount, and these are the ones that are usually being found in the water in greater quantity.

Australia was the very first country to introduce guidelines for pharmaceuticals in drinking water. According to the guidelines, the pharmaceuticals were categorized into 2 classes: one for humans and the other used solely for agriculture and veterinary reasons. The Australian guidelines utilized the lowest recommended therapeutic doses (LRTD) to establish acceptable levels of pharmaceutical drugs in water bodies, and then tolerable daily intakes have been calculated by using these LRTD values which are divided by safety factors (NHMRC 2008). The Environmental Protection Authority and the National Health and Medical Research Council implemented guidelines for the proper management of the pharmaceutical waste that is being produced in hospitals, dispensaries, and other health care centers. According to The

Table 2 Table showing common pharmaceutical drugs found in water bodies and their ill effects on various flora and fauna

Sl no	Therapeutic class	Pharmaceutical drug	Effects on aquatic flora and fauna	Reference
1	Analgesics	Acetaminophen (Paracetamol)	Effects on broods per female of *Daphnia magna*	Du et al. (2016)
			Inhibit the activity of acetylcholinesterase in *Brachionus koreanus*	Rhee et al. (2013)
			Cardiovascular and developmental and morphological deformities found in African catfish	Erhunmwunse et al. (2021)
82	Antibiotics	Ciprofloxacin	Growth inhibition in cyanobacteria, green algae, duckweed	Ebert et al. (2011)
		Clarithromycin	Suppressed the growth of algae	Yang et al. (2008)
		Sulfamethoxazole	Inhibit germination in rice and oat plants	Liu et al. (2009)
			Suppress the growth and productivity of phytoplanktons	Shan et al. (2021)
3	Anticonvulsants	Carbamazepine	Oxidative stress in rainbow trout	Li et al. (2010)
4	Antidepressants	Citalopram	Increased aggression in rainbow trout(*O. mykiss*)	Holmberg et al. (2011)
			Behavioral changes in Big Ramshorn snail	Ziegler et al. (2021)
		Sertraline	Changes in reproductive and behavioral traits in *P. promelas*	Schultz et al. (2011)
			Boldness in *P. promelas*	Valenti et al. (2012)
5	Anti-parasitic drugs	Ivermectin	A decline in eggs and larva of dung flies and beetles	Brinke et al. (2010)
6	Beta Blockers	Simvastin	Effects on the primary hepatocytes of *Oncorhynchus mykiss*	Ellesat et al. (2010)
		Atorvastatin	Adversely affect reproductive and population growth of amphipod *Gammarus locusta*	Neuparth et al. (2014)
7	Estrogen	Ethinylestradiol	Inhibit reproduction in fathead minnow	Lange et al. (2001)
			Gonadal alterations in zebrafish	Nash et al. (2004)
			Adverse impacts seen on marine bivalves at biochemical and molecular levels	Almeida et al. (2020)
8	Nsaids	Diclofenac	Renal lesions and alternations in the gills of rainbow trout	Swan et al. (2006)
			Damage caused to the internal organs of rainbow trout	Triebskorn et al. (2007)
9	Psychiatric drugs	Diazepam	Locomotor changes in female zebrafish, *Danio rerio*	Chen et al. (2021)
			Alteration in behavioral traits of polychaete, *Hediste diversicolor*	Nogueira and Nunes (2021)
		Oxazepam	Behavioral changes in sea bass	Brodin et al. (2013)
			Inhibit feeding rate and induce changes at the molecular level in *Radixbalthica*, a freshwater gastropod	Lebreton et al. (2021)
10	Stimulant	Caffeine	Delayed regeneration capacity in *Diopatra neapolitana*	Pires et al. (2016)
			Inhibit growth rate and induce mortality in macroalgae species *Codium fragile* subsp. *fragile*	Gray et al. (2021)

National Health and Medical Research Council, pharmaceuticals should be properly collected and undergo incineration instead of directly dumping those wastes in landfills. Moreover, steps are being taken by the Commonwealth Department of Health and Ageing Services in Australia in providing funds and help in developing systems that regulate the collection and disposal of unused and unwanted pharmaceutical drugs, and this operation is being carried out under the Return Unwanted Medicines (RUM) PROJECT (RUM 2011).

The USA too has taken several strict measures to control and manage these pharmaceutical wastes. The USA has implemented strict guidelines for the most prescribed drugs, and they are being categorized as hazardous wastes under the Resource Conservation and Recovery Act. Also, if someone violates the regulations, a heavy penalty is being imposed according to the act. The USEPA has also taken steps to develop a waste management program that would prove to be proper guidance for the stakeholders by allowing them to properly manage the pharmaceutical wastes (Pines and Smith 2006). USEPA had also developed a draft to guide the health care facilities on the reduction of pharmaceutical wastes and proper management and disposal of the unused drugs. Steps

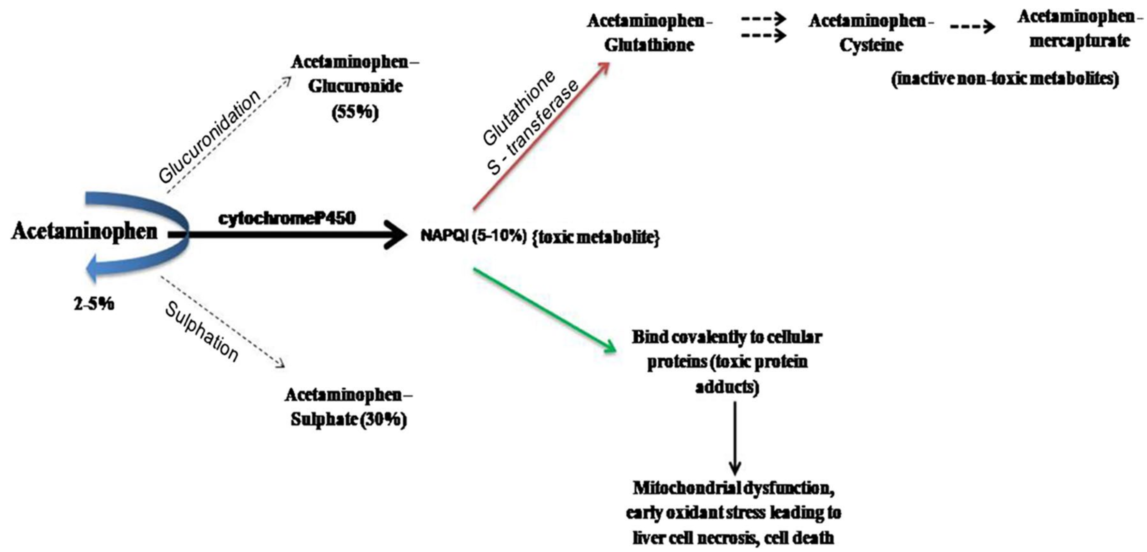

Fig. 4 Intermediates into which acetaminophen gets metabolized

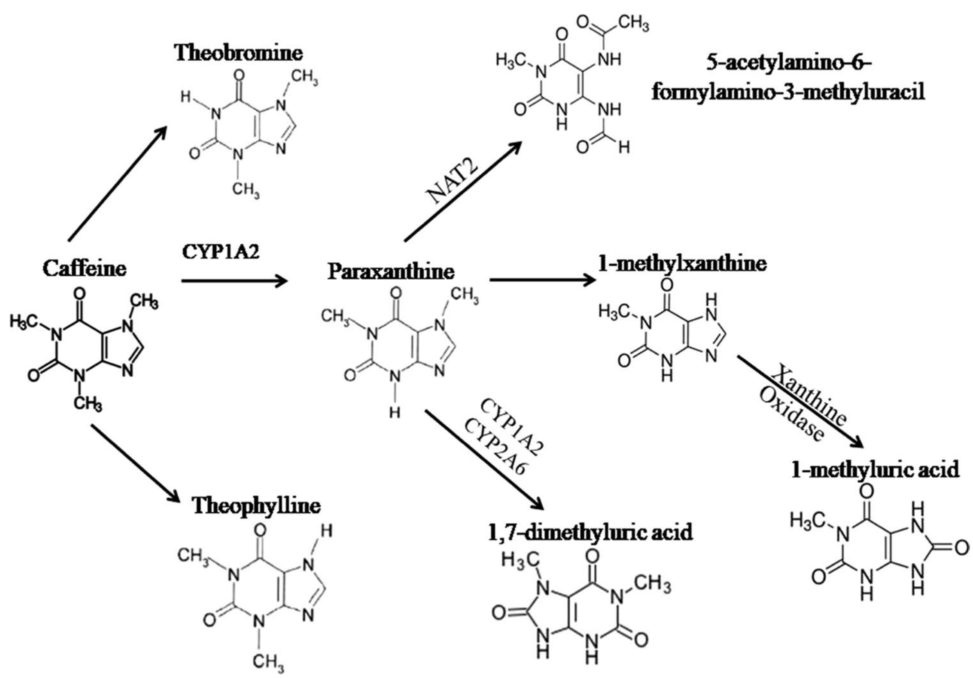

Fig. 5 Degradation pathway of caffeine. CYP1A2, CYP2A6 indicates cytochrome P450 1A2 and cytochrome P450 2A6 and NAT stands for N-acetyltransferase enzyme

were also being taken on receiving back unused medicines at pharmacies and sending them to authorities where proper disposal of these unused drugs is being carried out. Similar steps have also been implemented in Canada where stewardship programs are being followed which allows them to return unused drugs to the pharmacies for their safe disposal.

The United States Food and Drug Administration (USFDA) has guidelines for assessing human drugs which require the applicants of the US to undergo EIA (Environmental Impact Assessment) when it is expected that the concentration of a drug might exceed more than 1µg/l in the water bodies (USFDA 1998 and FDA-CDER 1998). Also, considering ill effects on soil organisms, the International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medical Products has set limits on the concentration of veterinary drugs in the soil to be around ≤ 100µg/kg (FDA 2001 and VICH 2000).

Europe too has such take-back programs where unused pharmaceutical drugs are being taken back or collected from household waste, and this operation is being carried out by pharmaceutical industries, retail pharmacies, or the public sector. Moreover, Environmental Risk Assessment needs to be

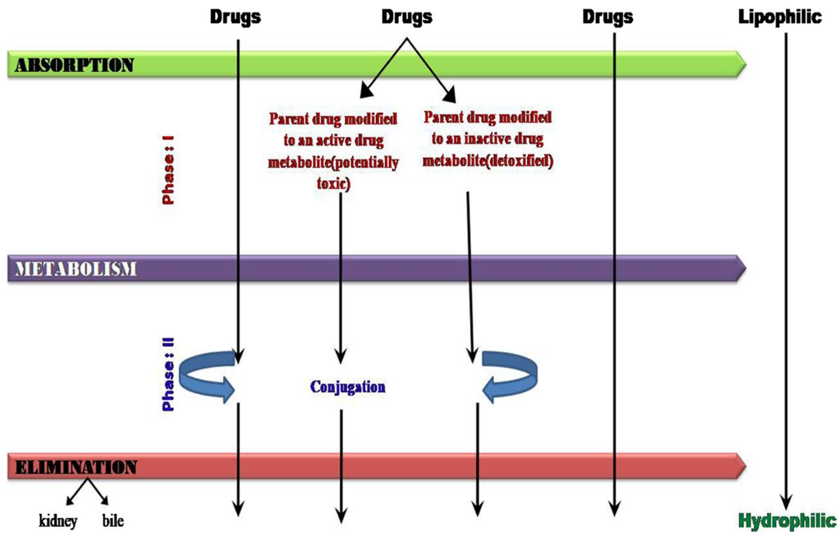

Fig. 6 Phase 1 and phase 2 reactions in drug metabolism

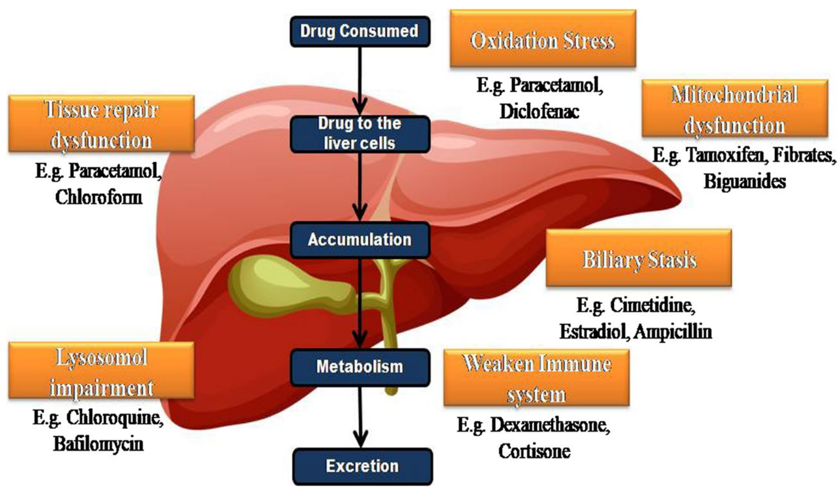

Fig. 7 Different drug manifestations which may lead to hepatotoxicity. Adopted and modified from Weaver et al. (2020)

carried out for the pharmaceutical compounds according to the guidelines issued by the European Medicines Agency (EMA) (Agerstrand et al. 2015 and EMA 2004). Based on the estimation of predicted environmental concentrations in the environment (PEC) or the measure of pharmaceutical concentrations in the environment (MEC), the European Union has set a value of 0.01ug/l to avoid contamination and toxicity of water bodies by these pharmaceutical substances (EMEA 2005).

WHO also directed that study on pharmaceutical wastes and their effects is of utmost importance as these substances might have adverse effects on the microbes thus giving rise to deadly pathogens.

In India, Bio-Medical Waste (Management and Handling) Rules, 1998, was published where rules and regulations have been drafted regarding the handling of the biomedical waste, its segregation, and discharge procedures. Although it has been mentioned in Guidelines for Management of Healthcare Waste Management Rules, 2016, that once there is 100% discharge of biomedical effluents into the water bodies, at least 96% survival of fish after 96 h is necessary, but there are hardly any guidelines regarding the permissible limits of drugs in these water bodies. Also, the lack of regular monitoring for assessing the possible short and long-term effects of these drugs on the aquatic species as well as on humans via drinking water has been a matter of concern now.

Different methods/strategies for the removal of pharmaceuticals

Microbial application of bioaccumulation and biosorption via bacteria, fungi, and algae

By bacterial strains

Although these pharmaceutical compounds are usually toxic to the bacterial strains, there are still few which have the potential to remove these pharmaceutical compounds (Fig. 8). These strains use the substances as their source of feedstock and thus degrade and remove the substances. Dawas-Massalha et al. (2014) carried out a study on the degradation of 5 pharmaceutical compounds such as iopromide, dexamethasone, ketoprofen, ibuprofen, and carbamazepine using nitrifying bacterial culture and found that ibuprofen was completely degraded followed by ketoprofen, carbamazepine, and iopromide. Zhang and Geißen (2012) reported that the bacterial species *Pseudomonas* can remove paracetamol to a great extent even when the concentration is around 2500 mg/l in less than 3-day time. Also, 100% degradation of salicylic acid was achieved by the use of the bacterial strain *Pseudomonas putida* as reported by Combarros et al. (2014).

By fungal strains

Fungus too has a high potential for the removal of pharmaceutical drugs, and few studies have been carried out as well. Sulfur antibiotics are being completely removed at a very fast rate by the use of strains such as *Trametes versicolor* (Rodríguez-Rodríguez et al. 2012). *Trametes versicolor* was also used for the degradation of ofloxacin which is a fluoroquinolone antibiotic (Gros et al. 2014). The white-rot fungus too has the potential to degrade a broad spectrum of pharmaceutical drugs as it produces oxidative enzymes (cytochrome P450, laccases, peroxidises, and ligninolytic enzymes) which degrade these contaminants. Studies were carried out in the stirred tank and fixed bed reactors where *Phanerochaete chrysosporium* degraded the

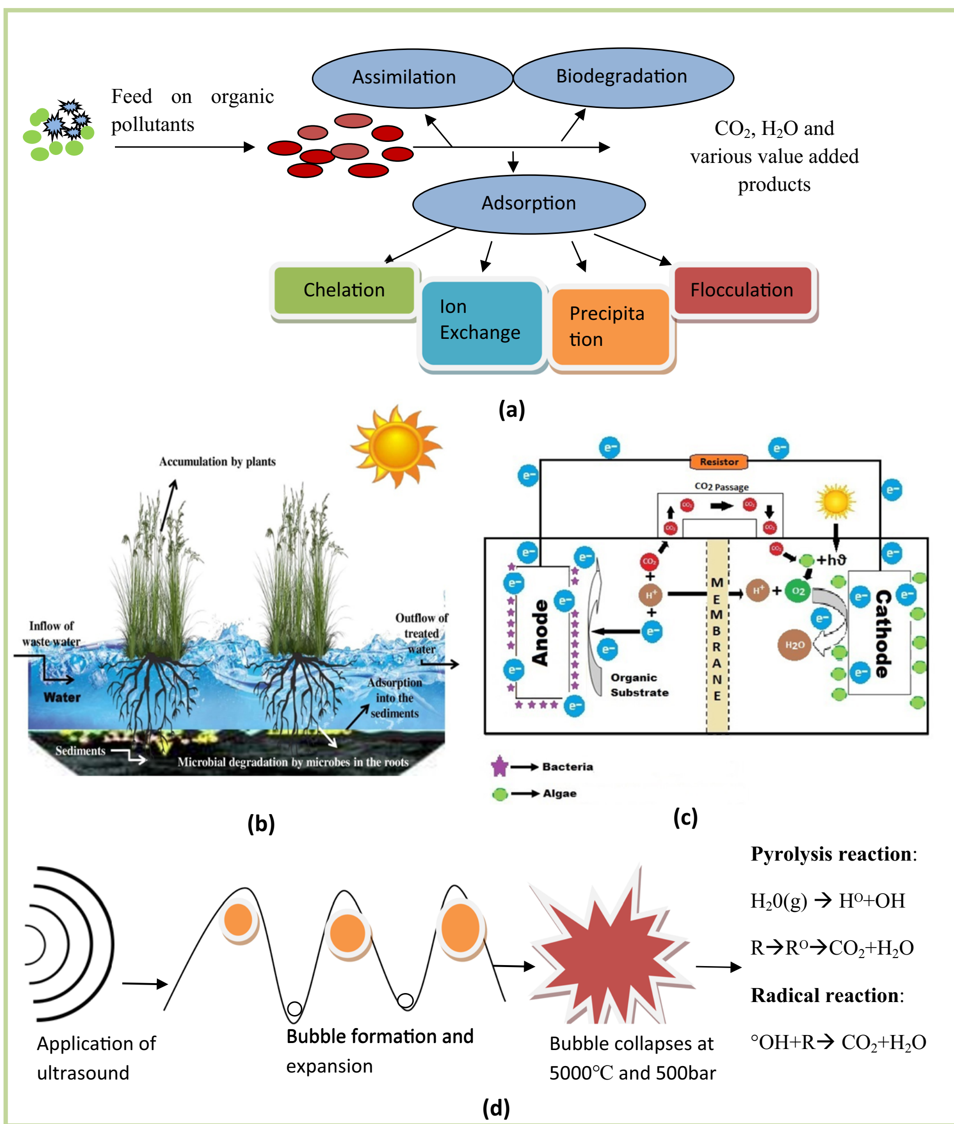

Fig. 8 **a** Removal of pollutants by microbes through their biological processes. **b** Various ways in which constructed wetlands treat pollutants in wastewater. **c** Components of an MFC integrated with algal biomass and its working principle Adapted and modified from Reddy et al. (2019). **d** Mechanism of sonolysis showing cavitation and implosive collapse of bubbles. Adapted and modified from Abdurahman et al. (2021)

few NSAIDs and psychiatric drugs (Rodarte-Morales et al. 2012). Marco-Urrea et al. (2009) studied the removal potential of 4white-rot fungi such as *Irpex lacteus*, *Phanerochaete chrysosporium*, *Ganoderma lucidium*, and *Trametes versicolor* on the drugs, ibuprofen, clofibric acid, carbamazepine, and found that ibuprofen was degraded within 7 days, and the removal efficiency of clofibric acid and carbamazepine by *Trametes versicolor* was 91% and 58%. White rot fungi such as *Ganoderma lucidium* and *Trametes versicolor* not only have the ability to degrade pharmaceutical drugs but also generate biodiesel from sludge (Vasiliadou et al. 2016).

By algal strains

There are studies that have been carried out to find the capacity of degradation of pharmaceuticals by algal strains. Freshwater algal species such as *Scenedesmus obliquus* and *Chlamydomonas mexicana* have been able to degrade carbamazepine by 28% and 35% when the concentration was 1mg/l, but the growth of algae was inhibited with the increased concentration (Xiong et al. 2016). Studies have been carried out on the degradation of paracetamol and salicylic acid by *Chlorella sorokiniana* and found that the rate of removal of salicylic acid was much more than paracetamol (Escapa et al. 2015). This algal species has also successfully degraded other pharmaceutical drugs such as diclofenac and metoprolol apart from paracetamol and ibuprofen (Escapa et al. 2017).

Membrane bioreactors (MBR)

Membrane reactors have started to gain importance only after the beginning of the twenty-first century, and with the passing of time, many industries have started to use MBRs for advanced wastewater treatment and removal of recalcitrant pollutants. In this process, a semi-permeable membrane, ultrafilter or microfilter, is being used in integration with a suspended growth bioreactor. According to Ngo et al. (2012), this MBR technology has the following advantages: (i) controllable SRTs and HRTs, (ii) generation of biomass, (iii) low production of sludge, (iv) improved effluent quality, (v) requirement of less space in comparison to the conventional water treatment plants, (vi) ability to separate microbial biofilm.

When Trinh et al. (2012) studied the removal of pharmaceuticals using a full-scale MBR, they observed that it had the ability to remove most of the drugs, although drugs like diclofenac, diazepam, gemfibrozil, omeprazole, trimethoprim, amitriptyline, fluoxetine, and carbamazepine had a removal percentage of 24–68%. Schröder et al. (2012) studied the removal of acetaminophen using this technology and found it very effective. Schröder et al. (2012) also studied the removal efficiency of other NSAIDs such as naproxen and ketoprofen and antibiotics such as sulfamethoxazole, roxithromycin, and trimethoprim and found that MBR technology is more effective for the abatement of NSAIDs than antibiotics.

Studies have been carried out by many researchers to find out how effective is the MBR technology compared to the typical wastewater treatment and observed that the use of MBR technology was more effective in the abatement of recalcitrant pharmaceutical compounds (such as paroxetine, ibuprofen, naproxen, acetaminophen, and hydrochlorothiazide) and micro-pollutants in comparison to the typical activated sludge processes (Radjenovic et al. 2007 and Chen et al. 2008). It has also been found that the removal of antibiotics by MBR technology was on the higher side compared to the traditional activated sludge processes (Sahar et al. 2011). A submerged photocatalytic membrane reactor integrated with ultrafiltration was set up to carry out the removal of ketoprofen in synthetic surface water, and it was concluded that the aeration process had influenced the degradation of ketoprofen by 75% in just 5 h using this unique submerged photocatalytic membrane reactor (Szymanski et al. 2023).

Constructed wetlands

This is a man-made biological process where wastewater treatment is being carried out with the usage of wetland vegetation, soils, and microbes and has the potential to purify water by eliminating the contaminants. Various studies have been carried out on the application of constructed wetlands for the treatment of wastewater containing pharmaceutical residues. (Zhang et al. 2014; Li et al. 2014 and Camacho-Muñoz et al. 2012). For the better efficiency of constructed wetlands, optimization of the parameters is of utmost importance. Also, the plant species and the composition of the support matrix play a vital role, and so careful selection of the plant species and materials should be done as it is very much important for the removal of the non-biodegradable compounds such as pharmaceuticals, pesticides, and phenols (Reddy and DeLaune 2008; Imfeld et al. 2009; Ahmad et al. 2010; Passeport et al. 2011). Özengin et al. (2016) carried out an experiment to find the efficiency of leca substrate and plant species *P. australis* on the removal of ibuprofen, carbamazepine, and sulfadiazine and found that leca substrate and *P. australis* have a high potential for removal of these pharmaceutical compounds with a removal rate of 89.23%, 95.94%, and 89.50% for carbamazepine, ibuprofen, and sulfadiazine. When removal studies on salicylic acid, paracetamol, caffeine, tetracycline, and sulfa drugs were carried out using constructed wetlands, it was found that 70% removal was achieved (Li et al. 2014). Li et al. (2014) also reported that constructed wetlands have the capacity to remove naproxen, acetaminophen, ibuprofen, diclofenac, and sulfamethoxazole in comparison to drugs like ketoprofen, salicylic acid, and carbamazepine.

Adsorbents

The use of adsorbents for the treatment of wastewater and especially emerging organic pollutants is very cost-effective and as well as efficient. Adsorbents can be particularly classified into two categories: (i) natural adsorbents such as clay, charcoal, and clay minerals and (ii) synthetic adsorbents are those which are being synthesized and prepared from agricultural waste, municipal and domestic waste, industrial waste, etc. The efficiency of the adsorbents depends entirely on the following parameters such as (a) the surface area of the adsorbent and (b) the availability of pores and high porosity. Clay, biochar, and activated charcoal are the frequently used adsorbents.

Clay

Styszko et al. (2015) in his study used natural clay such as montmorillonite, kaolinite, vermiculite, and bentonite, and also commercially available clay minerals such as montmorillonite K10 and K30 and carbonaceous–mineral nanocomposites such as MtG5%T and BAlG3%C for the removal of pharmaceutical drugs such as triclosan, bisphenol A, ketoprofen, ibuprofen, diclofenac, and carbamazepine. It was also observed in the study that vermiculite was the most efficient absorbent in removing all the drugs. According to Babel and Kurniawan (2003), as clays are chemically stable and they also possess the property of a high amount of ion exchange capacity, this makes them an efficient tool for the removal of pollutants. de Andrade et al. (2018) too found that since it possesses a good amount of negative charge, it allows them to be perfect adsorbents for ionic pollutants which are available in the environment in their cationic forms. They also reported that as clays possess these certain qualities, they can easily remove pharmaceutical waste and even has high removal capacity than activated carbon.

Biochar

Biochar, which is rich in carbon, is basically prepared by the process of pyrolysis. Organic matter such as agriculture or forest biomass undergoes pyrolysis at high temperatures with a negligible amount of oxygen. Being far more effective than activated carbon, biochar has been gaining importance as an efficient tool for the removal and bioremediation of several organic pollutants such as pesticides, dyes, and pharmaceutical wastes. According to Wang and Wang (2019), even biochar with a low surface area can be very effective as an adsorbent because of its swelling capacity in water which makes more space for adsorbates to get adsorbed. Ahmed et al. (2016) concluded that the sorption capacity of biochar can be increased by making certain chemical and physical modifications such as steam activation, treatment with heat, and impregnation.

As biochar prepared by the application of different techniques and different materials varies in their sorption capacities, Jia et al. (2018) reported that biochar prepared from wheat straw (WBC 600) showed a higher Langmuir capacity for the drug sulfamethazine, and biochar prepared from maize straw showed a Langmuir capacity of 4.32mg/g for the same drug sulfamethazine. Ahmed et al. (2016) also reported that biochars that are chemically and physically modified can have high removal efficiency than the parent biochar and thus have the capacity to replace other adsorbents namely activated carbon, carbon nanotubes, and graphene. Lian et al. (2015) carried out their experiments on biochar prepared from rice, corn, and cotton straws and chemically treated with humic acid and found that these biochars have the ability to absorb more sulfamethoxazole but less sulfanilamide when compared with the parent biochars. Thus, biochars prove to be good adsorbents that can be used for removing and remediating various pollutants without the production of any toxic byproducts.

Activated carbon

Activated carbon (AC) is the raw form of graphite, and unlike graphite, it is highly porous and its pore sizes vary from the molecular level to visible cracks and crevices. Activated carbon possesses a large surface area, and so it has the ability to absorb various pollutants. Zwiener (2007) stated that the adsorption efficiency of activated carbon depends upon the polar functional groups of the pharmaceutical substances such as oxygen-carrying functional groups, N-heterocyclics, and those amide and sulfur-containing functional groups. Activated carbon is an efficient way for the removal of harmful organics and inorganics from water as apart from having a high removal capacity, it does not produce any toxic products. Liu et al. (2013) in their work studied the sorption efficiency of activated carbon prepared from animal hair and cattail fiber on the removal of acetaminophen and norfloxacin and found that the acetaminophen adsorbed faster than norfloxacin achieving 95% of removal within 30 min at a temperature of 25℃ and having an initial concentration of 0.1mmol/l thus exhibiting second-order kinetics during the adsorption process. Baccar et al. (2012) too studied the removal of pharmaceutical drugs such as diclofenac, naproxen, ketoprofen, and ibuprofen using olive waste cake and found it very effective. But Ahmed et al. (2015) reported that the preparation and development of newly activated carbon adsorbents for specific pollutants (adsorbates) are not cost-effective at all, and so efforts should be made on the development of low-cost adsorbents which can be developed from locally and easily available resources. Studies have been conducted on the activated carbon developed from coconut and bituminous coal to remove ibuprofen from the toilet bowl, and a comparison was carried out between this coconut AC and normally used methylene blue and chlorine, and they found that AC had the capacity to adsorb and remove 50% of the ibuprofen drug there itself in the toilet bowl before entering drains or any sewage water system (Finn et al. 2021).

It was also observed that granular activated carbon such as Filtrasorb 400 and WG12 was highly effective in the removal of certain pharmaceutical compounds—caffeine, paracetamol, metronidazole, and carbamazepine—as it was able to remove 90% of the concentration (Ilavský et al. 2021).

Nano-adsorbents

Nano-adsorbents having a high surface area make a good tool for the removal of organics from the aquatic bodies. As carbon nanotubes have shown better results in adsorbance, so Zhang et al. (2011) investigated the efficiency of carbon nanotubes on the removal of the drug tetracycline and found that it had a high absorbance capacity (269.54 mg/g) when the pH and temperature were maintained at 5 and 25℃. In 2016, S.F. Soares et al. (2016) developed a magnetite nanoadsorbent characterized by k-carrageenan hybrid silicious shells and monitored it for removal of metoprolol tartrate from water, and the FTIR results concluded that the adsorption of the drug was possible due to the electrostatic interaction between the functional groups of the adsorbent and the drug. Raeiatbin and Açıkel (2017) too developed a magnetic chitosan nanoadsorbent to study the removal of tetracycline from medical wastewater, and it was able to show maximum adsorption capacity when the pH was 5 and temperature 25℃.

Bio-electrochemical cell

The use of bio-electrochemical cells for the removal of harmful pharmaceutical drugs has recently come into the scenario where resistant microbes degrade the harmful substances thus generating sustainable electricity. Certain modifications can be made in the anode or cathode which allows the microbes to have a better attachment to the electrodes and thereby the easy flow of electrons. For example, the use of metal or metal oxide catalysts at the anode causes changes in electrochemical properties which as a result influence the growth of the specific bacterial community. Also, an anode modified or coated with metal or metal oxides increases the degree of roughness on the surface of the anodes thus enhancing bacterial attachment and electron transfer at the electrode. In one such work, diclofenac (DCF), ibuprofen (IBF), and carbamazepine (CBZ) removal efficiency was studied in MFCs with anodes modified with MnO_2, Pd, and Fe_3O_4. It was also found that modified anode MFCs had a higher capacity for generation of power and drug removal efficiency than carbon black control anode. Also, they are claimed to have high electrocatalytic activity and low internal resistance. Anode modified with MnO_2 and Fe_3O_4 showed an abundance of *Geobacter* because of its capability to directly use MnO_2 and Fe_3O_4 as electron acceptors. Other than *Geobacter*, another species *Sphaerochaeta* was found to be quite dominating on electrodes modified with Pd, which was reported to produce hydrogen in BESs and had the capacity for dehalogenating DCF in the presence of hydrogen (Xu et al. 2018).

The bioelectrochemical cells can be integrated with the conventional waste systems for the removal of these recalcitrant organic wastes, and many researchers have carried out experiments by integrating BESs with traditional systems (Table 3).

Yeruva et al. (2016) carried out an experiment where pollutant degradation was carried out in bioelectrochemical cells in combination with aerobic and anaerobic sequence batch reactors and the aerobic SBR showed better degradation and generation of power due to the usage of simpler substrates. Zhang et al. (2015) too carried out an experiment on the most available pharmaceutical drug, i.e., paracetamol using the Fenton process coupled with MFC where the reaction was carried out between Fe^{2+} and H_2O_2 in the presence of hydroxyl radicals, and it was observed that the attack of hydroxyl on the benzene ring of paracetamol resulted in the conversion of p-aminophenol to p-nitrophenol and its further break down into fatty acids. Also, Zhang et al. (2017) carried out the degradation of SMX by coupling the mechanism of stacked constructed wetlands bio-electrochemical cells, and it resulted in better removal of the drug. Zhao et al. (2023) prepared bimetal anodes (Fe-Co@N/BC) with N doping for the removal of sulfamethoxazole, and it was found that the removal of his compound in this specialized microbial fuel cell was 2.1 times higher than that of any conventional anaerobic reactor.

Degradation by ultrasonic irradiation

This is an oxidation process by ultrasound where pharmaceutical products get degraded when on the application of sonolysis, and the hydroxyl radicals are generated by the process of pyrolytic cleavage of water molecules. According to Cintas and Luche (1999) and Margulis (1992), in the application of ultrasound, chemical effects are created due to an effect known as acoustic cavitation, and due to this phenomenon, there is the formation and growth of bubbles, and finally the implosive collapse of these bubbles. Moreover, as this phenomenon takes place, there is the generation of

Table 3 Types of BES systems used in the removal of pharmaceuticals from wastewater

Sl no	BES system	Function	Pharmaceuticals removed	Reference
1	Microbial electrolysis cell	A bioelectrical system by which organic pollutants in water are treated and energy is recovered in the form of hydrogen	Degradation of psychoactive drugs such as paroxetine, venlafaxine, and o-desmethylvenlafaxine	Akagunduz et al. (2021)
			Removal of mevastatin up to 90% along with the production of hydrogen	Catal et al. (2021)
2	Microbial fuel cell	It uses electrogenic bacteria to treat recalcitrant organic pollutants thereby generating electricity	Removal of pharmaceuticals such as paracetamol (generating highest electricity), caffeine, salicylic acid, trimethoprim, and sulfamethoxazole within 48–90 h	Bagchi and Behera (2022)
			Removal of tetracycline up to 90%	Wang et al. (2022)
3	Bio electro-Fenton process	It is an integration of MFCs and the Fenton process where Fe^{2+} and H_2O_2 aid in the degradation of pollutants thereby producing hydroxide radicals and CO_2	Removal of NSAIDs (particularly ketoprofen, Diclofenac, Ibuprofen and Naproxen)	Nadais et al. (2018)
			Degradation of sulfamethoxazole	Li et al. (2020)

hydrogen and hydroxyl radicals which combine with the target substances and gradually result in secondary oxidation, and a chain of reduction reactions takes place. Many studies have been carried out where sonolysis was being applied in combination with various other oxidation processes such as sono-ozonolysis, sono-electrochemical methods, sonocatalysis, and sonophotolysis. Naddeo et al. (2012) experimented with the degradation of recalcitrant compounds such as diclofenac using the effects of ultrasound, ozone solely, and also ultrasound in combination with ozone and found out that all the techniques are quite effective in removing such harmful substances from the wastewater though sonolysis showed better results than ozonation, and the combination of ozonation with ozonolysis was much more efficient, and this was due to degradation of O_3 by collapsing bubbles that produced additional free radicals which could easily attack the target substances, and thus, mineralization of diclofenac was possible which ultimately helped in removal of the product from wastewater. The removal of sulfacetamide and sulfapyridine was carried out using single and intermittent ultrasonic treatment where the removal of sulfacetamide and sulfapyridine was 1.7 and 1.95 times higher than the control. Moreover, it was found that the intermittent ultrasonic treatment showed better performance in the removal of both the drugs than that of the single ultrasonic treatment (Kurade et al. 2023).

Conclusions

In this review, certain techniques to remove these bio-accumulating pollutants have been discussed along with their risk assessment. It has been observed that the continuous flow of pharmaceutical compounds into the water system has proved to be detrimental to various aquatic organisms. It gets accumulated in the aquatic organisms and humans especially children below the age group of 5 can get easily exposed to these contaminants through the consumption of these aquatic organisms. Also in most parts of the world, the removal of these contaminants has been barely given any importance, so it is evident that due to a lack of advanced technologies, most of the industries in developing countries release these recalcitrant substances into the water which proves to be life-threatening to the aquatic life. Although these contaminants are released into the environment in a very minute amount, their continuous addition to the rivers makes them a cause for concern. Certain steps should be taken by the higher authorities to form regulations for these pharmaceutical products in water, and risk assessment of such substances should be carried out to know their toxicity level, and also, sustainable technologies should be adopted for better removal and remediation of these emerging substances.

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