Pharmaceuticals in the Aquatic Environment Impact on Aquatic Ecosystem and Humans: A Review

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ABSTRACT

Pharmaceuticals are long-lasting biological compounds, extensively used for aging people and treating chronic diseases; longevity has become an emerging pollutant for humans, aquatic ecosystems, and wildlife. Pharmaceuticals have been reported in marine, terrestrial, fresh, and surface waters as well as in aquatic fauna and flora. These compounds enter the water bodies via human and animal waste, wastewater, hospital effluent, and leaching from landfills. These pollutants in water not only impact the behavior, reproduction, neurotoxicity, and cytotoxicity of aquatic animals but also reduce the oxygen content of water and light. Due to the presence of pharmaceutical residues in water bodies in developing countries, the abundance and species richness of fish have decreased by 35-47%. Pharmaceutical-contaminated wastewater is used for the irrigation of agricultural fields which results in the accumulation of these pollutants in vegetables and fruits. When humans uptake these compounds via food and drinking water adversely affects human health. They may cause breast or prostate cancer, infertility, abnormal childhood development, diabetes, early puberty; immune and autoimmune system; causes heart disease, Alzheimer's disease, Parkinson's disease, and attention deficit hyperactivity disorder besides asthma. The presence of antibiotic residues in small amounts causes the development of multi-antibiotic-resistant bacteria. This review aims to report the amount of commonly used pharmaceuticals in wastewater, hospital effluent, surface water, and drinking water and their impact on aquatic flora and fauna and humans to realize the potential impact of these pollutants on the environment.

Key Words: *Pharmaceuticals, Antibiotics, Human, Environment, Vegetables, Fish*

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INTRODUCTION

Due to urbanization, industrialization, and economic development pharmaceuticals and personal care products (PPCPs) are becoming an integral part of human life. Out of the total pharmaceuticals used globally, 65% are used for human treatment, 29% in the veterinary sector, and 6% in agriculture and as food additives. The global market of pharmaceuticals in 2022 was more than 800 billion US dollars. Pharmaceuticals are those compounds that are used for diagnosing, curing, or treating diseases. About 4000 chemicals are used as pharmaceuticals for therapeutic purposes in humans/animals. Global consumption of pharmaceuticals is more than 250, 000 tonnes per year, European countries together consume approximately 25% of it. Studies have shown that globally people of the age group 15-64 consume at least one medicine once a year. Covid-19 has increased the frequency of uptake of it. Increased consumption of pharmaceuticals by humans is due to changes in lifestyle, an aging population, an increase in the number of chronic disease patients, and easy accessibility. As pharmaceuticals are complex molecules and are extensively used they are present in all the matrices of the environment of all the 5 UN regional groups, i.e. wastewater, surface water, groundwater, drinking water, marine water, hospital effluent, sewage sludge, which causes significant harm to aquatic microorganisms, fauna and flora and also impacts soil fertility, soil biodiversity. The residues of pharmaceuticals in the environment have

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been reported even in Northern Antarctica. UNESCO [1] has set its target to eliminate these pharmaceuticals from water by 2030.

Water an integral and essential part of living organisms on earth has diverse uses viz., domestic, industrial, and agricultural purposes. Contamination of the water bodies by pollutants including pharmaceuticals poses a serious threat to aquatic ecosystems, humans, and animals. It has been reported that globally 30,000 kg of natural steroid oestrogens is discharged per year by the human population. Additionally, 700 kilograms per year of synthetic oestrogens are added via birth control pill practices. Besides hormones antidepressants (the amount significantly increased during covid-19), anti-inflammatory drugs, beta-blockers, anticancer drugs, antibiotics, and anti-diabetics are added in aquatic environments. The concentration of the pharmaceuticals in water is reported from ng to mg/L.

The present review reports the concentrations of commonly used pharmaceuticals in wastewater, hospital effluent, surface water, and drinking water and their impact on aquatic flora and fauna, and humans.

Types of pharmaceuticals

Based on their therapeutic uses human and veterinary pharmaceuticals can be classified as:

Anti-diabetics (Anti-glycaemic drugs):

These are those medicines that are used to stabilize and control blood glucose levels in citizens suffering from diabetes i.e. are commonly used to manage diabetes. As per global studies globally 537 million people were suffering from diabetic Mellitus disease in 2021 and it is estimated that the number will increase to 643 million by 2030 [2]. Insulin, metformin, amylin, Byetta, and Victoza are some drugs that are generally used as antidiabetics. Globally, the most prescribed, anti-diabetics drug is metformin.

Antidepressants

These are those pharmaceuticals that are used for the treatment of depression, anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), some addictions, and chronic pains. Benzodiazepine-pines, Diazepam, Doxepin, Fluoxetine, Citalopram, Imipramine, and Venlafaxine are some compounds that are generally used as antidepressants.

Antiepileptics

These are those pharmaceuticals that are used to control epileptic seizures, neuropathic pain, and mood stabilizers these compounds change the levels of chemicals in the brain by influencing the pattern of the neuroendocrine signal. Commonly used antiepileptics compounds are acetazolamide, Carbamazepine, Gabapentin, Lorazepam, Phenytoin, etc.

Antihistamines

The pharmaceuticals used to treat allergies viz., hay fever, hives, conjunctivitis and reactions to insect bites or stings, nausea, motion sickness, and as a short-term treatment of insomnia. Generally used antihistamine medicines are Diphenhydramine, Cetirizine, Chlorpheniramine, Cyclizine, Doxylamine, Hydroxyzine, Meclizine, and Ranitidine etc.

Antihypertensive

These are those medicines that lower blood pressure and are used to treat hypertension. Commonly used antihypertensive pharmaceuticals are Losartan, Ramipril, Labetalol, Almodioine, and Valsartan.

Beta-blockers

These pharmaceuticals retard the release of adrenaline and noradrenaline (Stress hormones). Doctors prescribe these medicines for angina, heart failure, abnormal heart rhythms, and to control blood pressure. Atenolol, Metoprolol, Solatol, Propanolol, and Nadolol are used as, beta-blockers.

Analgesics including opioids and non-opioids

Any compounds that can relieve pain without sleep or loss of consciousness are called analgesics. Acetylsalicylic acid, acetaminophen, ibuprofen, diclofenac, naproxen, COX-2 etc are used as analgesics.

Antipyretics

Antipyretics are the compounds that lower the elevated body temperature caused when the concentrations of prostaglandin E_2 (PGE_2) are increased in a certain part of the brain in the hypothalamus which alters the neuron's firing rate, by inhibiting the secretion of the enzyme cyclooxygenase and reducing the levels of PGE_2 within the hypothalamus. Globally, the most commonly used antipyretics are acetaminophen, acetylsalicylic acid, paracetamol, propoxyphene, ibuprofen, Naproxen, Ketoprofen, and methimazole.

Antibiotics

Antibiotics obtained from natural sources or synthetic are used to kill and inhibit the growth of bacteria and are used for fighting and preventing bacterial infections. Any chemical compound that can kill bacteria in the living body is technically called an antibiotic. Those antibiotics that kill bacteria by interfering with either the formation of the bacterial cell wall or its cell contents are called bactericidal. Those antibiotics that stop the multiplication of bacteria are called bacteriostatic. Antibiotics are not only used for humans but also for food-producing animals, farm animals, aquaculture, and agricultural purposes. Global consumption in 2020 only for food-producing animals was 99502 tonnes. Amoxicillin, Ampicillin, azithromycin, Cephalosporins, Carbapenems, erythromycin, Fluoroquinolones, vancomycin, linezolid and tedizolid, aztreonam, sulfonamides, Rifamycins, Gentamycin, Streptomycin, Norfloxacin, Levofloxacin, Tetracycline, sulfonamides, Rifamycins, Neomycin, etc are globally used antibiotics.

Immunosuppressive

Immunosuppressive are those compounds that prevent the activity of the immune system and are given to those patients who are suffering from autoimmune diseases. Prednisone, Tacrolimus, Mycophenolic acid, Azathioprine, and Alemtuzumab are used as immunosuppressive agents.

Hormones

These compounds send the signals into the bloodstream and tissues so are called as body's chemical messenger. These compounds regulate different physiological and behavioral activities in the body i.e. growth and development, metabolism, sexual function, reproduction, constant regulating blood pressure and blood sugar, fluid (water) and electrolyte balance, and body temperature and sleep-wake cycle. Compounds act as hormones 17-alpha-ethinyloestradiol, 17-beta-oestradiol, Oestrone, Oestriol, Progesterone and Testosterone.

Antiviral drugs

These are the compounds that help the body fight harmful viruses; these medicines shorten the length of a viral infection by inhibiting virus development. Most of the antivirals are specific in action while broad-spectrum antiviral is effective against several viruses. Commonly used antiviral drugs are Baloxavir, marboxil, remdesivir, oseltamivir (Tamiflu), darunavir and zanamivir are antivirals which are generally used.

Routes of pharmaceuticals in the aquatic environment

Both in developed and developing countries due to advancements in the pharmacology branch, economic development, aging population, and increasing chronic diseases consumption and production have increased many folds. The pharmaceutical products enter the aquatic bodies via wastewater treatment plants (as there is a lack of technology to remove these compounds) [3], human and animal excretion (via municipal wastewater), hospital effluent, bathing, pouring of the expired/unused medicines in the drain and/or flushing in the toilet. Hospitals, medical institutions, and household wastes also contain pharmaceuticals and are not properly disposed of reaches water bodies [4]. The water bodies are also contaminated by the pharmaceuticals via waste disposal of the pharmaceutical industries. Several research studies have shown that 30-90% of pharmaceuticals consumed by humans or animals are excreted unaltered or as active metabolites via urine and feces as the gut cannot absorb all the consumed chemicals [5]. Another route of contamination of water bodies by pharmaceuticals is via leaching from soils (soils are contaminated via the application of fertilizers, sewage sludge, etc) and dumping grounds (after rainfall). The survey of literature denotes that 65% of pharmaceuticals in the wastewater bodies are from urine which contributes only 1% of total wastewater volume. The flow chart is given in **Figure 1**.

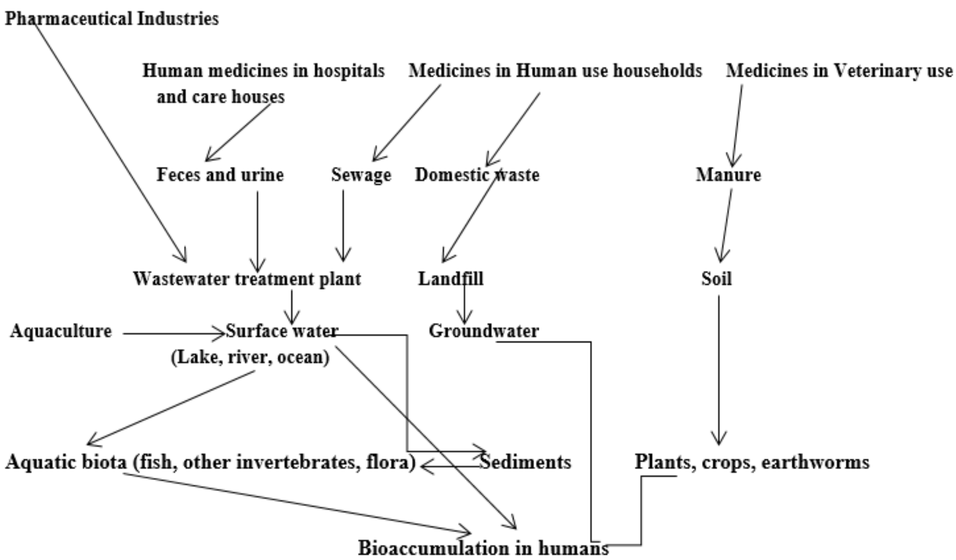

Figure 1. Different sources of pharmaceuticals in aquatic environments and Human

Pharmaceuticals in the aquatic environment

Due to urbanization, the urban population is expected to be 70% of the total population by 2050, causing serious major stress on water bodies. Due to low degradation, extensive use, continuous release, and lesser evaporation the pharmaceuticals are easily bio-accumulated in the aquatic ecosystem [5]. Pharmaceuticals are designed in such a way can achieve the target at very low doses by targeting specific cell, metabolic, or enzymatic signals [6]. As per data reported in the literature the concentration of pharmaceuticals in surface water, groundwater, and hospital effluent, and municipal effluent, marine water ranged from 0.01ng/L to 3500µg/L [7, 8]. The data of literature also denotes that the effluents of pharmaceutical industries in the countries India, China, USA, Korea, and Israel contain active pharmaceutical ingredients up to mg/L, and the surface water of the adjoining area contains higher pharmaceuticals concentration than in the blood of patients who are undergoing treatment.

The concentrations of different pharmaceuticals in water bodies are recorded in **Table 1**.

Table 1. Concentration of different pharmaceuticals in sewage wastewater, hospital effluent, groundwater, surface water, seawater, aquaculture water, river water, and drinking water

Compound	**Wastewater/ Sewage water**	**Hospital Effluent**	**Freshwater/ Surface water**	**River water**	**Aquaculture water**	**Coastal water/seawater**	**Groundwater /Drinking water**
Acetaminophen	4-1090000ng/L [8]; 11.3-1586 ng/L [9];	2660-580000ng/L[8];524-667.8ug/L[10];9.6-51.2ug/L[11];52 ng/L [12]	0-242ng/L[13];1-12430 ng/L [9]; 341.6 ng/L[14];4-485.5ng/L[15];	27ng/L[16]			0.5-188ng/L[9]; 16.4 ng /L [17];0.6-15580 ng/L [8];16-30ng/L (DW[8]
Acetyl salicylic acid	0.4-0.7 ug/L[18]; 1.4-60.4ug/L[19]; 0-190.06 ug/L[20]						0-62.27 ug/L[20]
Amoxicillin	0-91495ug/L[21];352-509ug/L(after covid)[22];41.09-2134.8 ug/L (after covid,sludge)[22];0-6940ng/L[23]; 147-1670 ng/L[24]; 350-1020 ng/L [25]	30-50ng/L[26];90-900 ng/L [23]; 13.3-18.47ug/L[25]	87-272150ng/L[9];0-20000 ng /L [23]; 1614 ng/L[9]		326.7 ng/L [27]		44-6490 ng/L[12];238 ng/L;358 ng/L(DW) [9]
Ampicillin	23.5-263.3ng/L[26]	1840-12960ng/L[26]		40-164ng/L[4];			
Antipyrine	206 ng /L[9]		32 ng/L[12]				

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Atenolol	138-424ng/L[28]; 129-1451ng/L [24];91.1-94.5 ng/L[29]	0-919ng/L[29];0.2-0.44ug/L [11]	0-93ng/L[13]		2.4ng/L[17]
Atrovasatin	2756.5 ng/L[30]; 22-180 ng/L [24]	0.15-6.79ug/L[10];14 620 ng/ L [31]	42-209 ug/L[31]	0.56-1990 ug/L[31]	
Azithromycin	45.2-597.5ng/L[32];728-1890ng/L [24];	1.21-11.63ug/L[10];0.29 7-0.382ug/L[33]	20.61 ug/L [31]		
Caffeine	95-670000ng/L[8];3600-55500 ng/L[34]	0.57-8.32ug/L[11]	2.7-591768ng/L[8] 1-10234 ng/L [13]; 4-1080ng/L[9];527.4 ng/L [14] ;33.9-2980ng/L[15]	19300ng/L[9];	4-166ng/L[9];15-14150 ng/L; 0.1-503.7 ng/L **(DW)** [8];683ng/L; 3390 ng/L **(DW)**[34]; 384-426 ng/L[35]
Carbamazepine	3.14-3.35ug/L[36];42.4-7100ng/L [9] ; 1.1ug/L[37]; 78760 ng/L [38]; 1.17ug/L[39];0-136 ng/L [28]; 73-151 ng/L;327-949 ng/L[24]; 10.66 ug/L [40]	0-7008ng/L[28];7.5-1900 ng/L [8]; 0.02-6.26 ug/L [10]; 3 ng/L[41]	1-342ng/L[9];0.6-4880ng/L [9] ;0-290ng/L[13];81.8-36576.2ng/L [42]		385 ng/L[38]; 1-50 ng/L [9] ; 105.9 ng/L[26] ; 0.2-1000 ng/L ;1.3-30 ng/L **(DW)**[7]
Cefuroxime	];590-7940ug/L[28]				
Cephalexin	0.0-308.0 ng/L[32]				
Chloroamphenicol	0.0-23 ng/L[24]	105.4-106.3ng/L[26]			

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Ciprofloxacin	4300ng/L[38];54.6-501575ng/L[9]; 330.3-639 ng/L[41];27ng/L[6];38.4-584.9 ng/L[32]; 199-2950 ng/L[24];	7410-7840ng/L[26];0.356-0.571 ug/L [33];1980-24000 ng/L [8]; 2.79-195.09 ug/L [10] ; 0.03-125ug/L [41]	0.5-1727ng/L[8];			0.5-298 ng/L;0.3-0.7ng/L **(DW)** [8]
Clarithromycin	;5.3-21700ng/L[8];60ng /L[41];0.0-313.2ng/L[32]; 3-501 ng/L[31];	88-26800 ng/L[8];0.85-2 ug/L [41]	1.3-500ng/L[8];4.8-3280.4 ng/L [42]			5ng/L;4ng/L **(DW)**[8]
Clofibric acid	0.04-0.26ng/L[28]	0.03-0.16ng/L[28]				
Cloxacillin	0-320ng/L[23]					
Codeine		0.2-50 ug/L[41]	2-1780ng/L[9]; 0.214 mg/L[23]			0.5-2440ng/L[9];0-37347 ng/L[27]
Diazepam			0.3-42 ng/L[13]			0.3-26 ng/L[9]; 16.2 ng/L[17]
Diclofenac	26-10340ng/L[8]; 40570.2 ng/L [43]; 4.75 ug/L [39];115.1ng/L[5]; 385-1709 ng/L[24]; 9680 ng/L [41]	0.11-22.41ug/L[10]; 112-3040 ng/L[7]; 0.527-0.588ug/L [33]; 7200 ng/L[44]; 0.24-15 ug/L [41]	0-1055ng/L[13];1-200 ng/L[13]; 0.1-19300 ng/L [8]; 5401.5ng/L [43]; 138ng/L[45]	41ng/L [46]	0-570 ng/L[47]	1-42 ng/L[9];114.3-2770ng/L[43]; 6-2770 ng/L; 0.08-7.6ng/L **(DW)** [8]; 79-3600ng/L [39]; 452.1ng/L[17]
Doxepin						4776-174821ng/L [36]
Doxycycline	100-10900 ng/L[23];	0.1-7 ug/L[41]		0.0-12.8 ng/L [24];		0-280ng/L[48]

Enrofloxacin	10-270 ng/L [23]	60-100ng/L[23]	60-100 ng/L[23]				
Erythromycin	27-1193 ng/L[8]; 12-4740ng/L[23]	1850-10613 ng/L[8];0.11-0.93 ug/L[10];7944-10613ng/L [23]; 27-83 ug/L[41]	0.3-4200ng/L[8];1-275 ng/L[19]; 11.2-11800 ng/L [42]; 1.41-15.9 ng/L [23]				1ng/L[9];838-63655 ng/L[27];5.2-57.60ng/L [8]
Fluoxetine	2.48-4.21ng/L[28]	2.51-2.57ng/L[28]	32.0 mg/L[23]	2.3-42.9 ng/L[49]			
Furosemide	491-2437 ng/L[24]	2600 ng/L [44]					
Gabapentin	12ng/L[38]	0.15-17.83ug/L[10]	1-67ng/L[9]				0.5-141ng/L[9]
Gatifloxacin	0-840 ng/L[23]			0-42ng/L[23]			
Gemfibrozil	0.9-13.5ng/L[28]; 42-1772 ng/L[24]	0.03-6.76ng/L[28]	4-552 ng/L[9]				4-730 ng/L[9]
Ibuprofen	46.1-81000ng/L[8]; 2770 ng/L[3]; 31250ng/L[43]; 5 ng/L[41]; 221ng/L [5]	0-3.3ug/L[11];88-141000 ng/L [8]; 0.116-0.124 ug/L [42]; 0.07-43 ug/L [41]	3.7-6297ng/L[8];4-2740 ng/L[9]; 3730.1 ng/L [44] ; 1-50 ng/L[13]; 62 ng/L[5] ;3040 ng/L[45]	780ng/L[16]	105 ng/L [46]	0-460 ng/L [47]	4-2250 ng/L[9];223-599 ng/L [43];6700ng/L[39] ;48.7-750 ng/L ;55-97ng/L **(DW)** [8];38 ng/L [38]

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Metroprolol	Metronidazole	Metaformin (Antidiabetic)	Lovastatin	Lincomycin	Levofloxacin	Ketoprofen
0-86.8ng/L[28]; 11-7433ng/L[8]; 0.0-196ng/L[24]	0.0-93.2 ng/L[32]; 13-392 ng/L[24]; 2310 ng/L[38]	5.61ug/L[39]		15.2-730ng/L[23]; 10800-33970 ug/L [21]	86700ng/[23]	50-5151ng/L[50];91100-159000 ng/L [44];1140-5330 ng/L [43];155-223 ng/L[51];33-2881 ng/L[52];0-10700 ng/L[30]; 490-1170ng/L[53]; 110-730 ng/L [54]; 1-15300 ng/L [55]; 6.2-77.3ng/L[56]; 353-822 ng/L [57]; 417 ng/L [58]; 1720-6007 ng/L[24]; 23000-159000 ng/L [42]
0.11-5.62u/L[10];370-2800 ng/L[9;0-1769ng/L[28]; 0.42-25 ug/L[41]	0.02-2.47ug/L[10]; 6610-6620 ng/L[26]; 0.1-90 ug/L[41]		2.4-3.2ug/L[9]	0.3-2 ug/L[54]		200-18100 ng/L [58]; 320-980 ng/L [11]
1-168ng/L[9];4.8-8420ng/L [7];0-772ng/L[13]		0.5-1760ng/L[9]		3.13-248.9ng/L[23];0-407ng/L [45]	414ng/L[23]	132.2ng/L[42];17-620ng/L[59]; 0.2-8ng/L[60]; 0.43-71.84 ng/L [61]
0-240 ng/L[9]						10.6 ng/L[62];1200-4300 ng/L [63];10-14215 ng/L [64]; 23800 ng/L[43]; 200ng/L [60]; 31-62 ng/L [65];5-99 ng/L [30]; 12.9-321.4 ng/L[66];30-198 ng/L[67];; 107 ng/L[25]; 0-245 ng/L [68] ;8070 ng/L[69]
						10-16.6ng/L [70];0-76 ng/L [59] 1.5-4451.6 ng/L [57]; 147-308ng/L[71]
1-54 ng/L[9]; 17-1089 ng/L[39];116.9 ng/L [17]; 57ng/L;3.9ng/L **(DW)[8]**		0.5-349 ng/L [9]	0-30989ng/L[29]	81.4ng/L[17]		166.9-731.8ng/L[43]; 262.4ng/L[26]5.5ng/L [56]; 0.16-153ng/L [61]

Propranolol	Penicillin	Paracetamol (Painkiller)	Ox etracycline	Ofloxacin	Norfloxacin	Neomycin	Nalidixic acid	Naproxen
0-7.43ng/L[28]	20-13800ng/L[23]	14.89-24.31ug/L[36]; 36.7 ug/L [37]; 0.1936ug/L[72]; 105780 ng/L [41]; 565ng/L[38];	0.2-47000ng/L[23]	0.14-420ng/L[23];0. 1-529ng/L [32]	76.6-77.6 ng/L[9];11.1-18200 ng/L [20]		0.0-50.3 ng/L[32]	7500ng/L[43];4.3-72000 ng/L[7]; 551960 ng/L[44];11-217ug/ L [18] ; 0.1223ug/L[72]; 109.3 ng/L[5]; 4161-10150 ng/L[24];7500ng/L[45]
0-118ng/L[28]		0.481-0.623ug/L[33];5-1368 ug/L [40];105910ng/L[41]; 211926 ng/L[31]	0.01-4 ug/L[41]	3400 ng/L [44]	0.03-3.85ug/L[8];90-1620 ng/L [27]; 0.03-44 ug/L [36]; 0.8- 4.4 ng/L [49]	9900-1000ng/L[23]	20ng/L[10]	1100-43360ng/L[7];5.9-10.6 ug/L[11];0.166-0.184 ug/L [33]; 9ng/L[12]
]; 0.80 mg/L [23]	1.8-5.9ng/L[23]		110-4200ng/L[23]	0-488ng/L[23];08 770ng/L[74]	30-25100ng/L[20]; 383.3ng/L[11]		0-116 ng/L[73]	4.6-4880ng/L[7]3-2120 ng/L [13]; 1091.9 ng/L[43]; 6.8 ng/L[5]
					0.87-6800ng/L[20]			2.98-221 ng/L[43]; 4334 ng/L [46]
7ng/L[39]				14.37-145.37ng/L[75]				3-17ng/L[9] 13-21 ng/L[37]; 200-98390ng/L;404ng/L **(DW)[8]**

Sulfamethoxazole	Sulfathiazole	Sulphonamide	Sulfapyridine	Sulfamethazine	Sulfadimethoxine	Sulfadiazine	Sparfloxacin	Roxithromycin
87.2-88.1ng/L[29];1.37ug/L[39];8.6-112000ng/L8];27.8ug/L[9];559.3 ng/L[5];0.4-2260ng/L[23];0-1195 ug/L [28]; 3000ng/L [38]			4.7-112ng/L [32]	1.1-1500ng/L[23];3.2-586 ng/L [24]	0.2-350ng/L[23]		0-63200ng/L [23]	870-1500ng/L[23]
3060-4890ng/L[26];00-300 ng/L[23];0.07-198.53ug/L [15]; 0.307-0.452ug/L[33]; 0.6-3.3ug /L[12];1-5800ng/L [9]; 0.04-83 ug/L[41]						0.01-0.27ug/L[10]		
0.2-6840ng/L[8];6.6-6969 ng/L [42];0-2000ng/L[23];390 ng/L [68]; 1-3180 ng/L[9]		0-4100ng/L[13]		20-120ng/L[23];0-654ng/L [24]	35-60ng/L[23]			
3.1-13700ng/L[23];30-56600 ng/L[76];1-5600 ng/L[16]							0-2090ng/L[30]	
1-64ng/L[9];4.2-27410 ng/L;0.1-55.5ng/L **(DW)[8]**	46.2ng/L[17]		43.8ng/L[17]	96.9ng/L[17]		46.6ng/L[17]		

Trimethoprim	20-20000ng/L[8];1.93-4010ng/L [23];];0.0504ug/L[72];15.2-190.6 ng/L[32]; 42-635ng/L[24];0-2815 ug/L[21]	0.095ug/L[33];20-20000 ng/L [7];0.04-21.86 ug/L [10]; 0.01-15ug/L [41]	0.6-6600ng/L[8];2-388ng/L [9] ; 3-710ng/L[23]	17-4000ng/L[23]	1-21ng/L[9];0.1-6950 ng/L;3.9ng/L(**DW)[8]**
Temazepam	257 ng/L[30]				
Tetracycline	0-48000ng/L[23];45.4ng/L[5];0-231.2ng/L[33];58-1960 ng/L[77]	0-80ng/L[23]; 0.01-4 ug/L[41]; 13-1598 ng/L [77]	110-4200ng/L[23]	31-25500ng/L[23]	
Thiabendazole			104ng/L[78]		
Tramadol		1.16-16.63ug/L[10]	2-852 ng/L[9]		2-883 ng/L[9]; 19.2ng/L [17]
Valsartan	92532.7 ng/L[30]	0.04-0.79ug/L[10]	1-3330 ng/L[9]		1-84ng/L[9];27 62.7 ng/L [17]
Vancomycin	45-140ng/L[79];900-43700ng/L [78]; 3200 ng/L [38]	4700-13000ng/L[79]	24ng/L[79]		
Anticancer Drugs			1-305ng/L[7]		

Studies have shown those pharmaceuticals are bioaccumulated in commercially farmed bivalves' (mussels, clams) and marine microalgae (*Saccharina latissima*, *Laminaria Digitata*, *Enteromorpha* sp., *Turbinaria conoides*, and *Ulva lactuca*) [80].

The residues of pharmaceuticals (human and veterinary) in water bodies significantly impact aquatic organisms by reducing the oxygen content of water and reducing light. Benitez *et al*. [81] have reported that in developing countries fish abundance and species richness have decreased by 35-47% due to the presence of pharmaceutical residues and their metabolites in rivers and lake water. Ecotoxicological studies have shown that on exposure to sulphonamides marine algae are most affected followed by crustaceans and fish. When fish are exposed to pharmaceuticals contaminated water for a longer period they start to change their natural behaviour, causing problems for their survival [82].

Developmental retardation and pathological abnormalities in the brain, heart, and kidney with morphological disorders were reported in common carp (*Cyprinus carpio*) embryos and larvae change in the swimming behavior of zebrafish (*Danio rerio*) larvae by Oliveira *et al*. [83**]** in the presence of antidepressant nortriptyline, while Gallego-Ríos *et al*. [84] found an alteration in antioxidant enzyme activity and enhanced lipid peroxidation activity. Residues of centrally acting analgesic tramadol in water not only disrupt the hatching time development of the fish but also alter the activity of the antioxidant enzyme and fish behavior [85]. The presence of analgesics in water causes organ damage reduced hatching probability in fish and genotoxicity, neurotoxicity, and oxidative stress in mollusks [85]. Enrofloxacin in grass carp (*Ctenopharyngodon idella*) affects hepatic cell lines due to apoptosis and production of reactive oxygen species showing cytotoxic effects. The growth, reproduction, and survival of water fleas (*Daphnia magna*) in the presence of enrofloxacin retarded was the observation of Bawa-Allah *et al*. [86**]**. Studies [73] have shown that antibiotics in aquatic systems not only significantly contribute to the development of antibiotic-resistant bacteria and antibiotic-resistance genes but also affect ecosystem functioning and nutrient cycle by disturbing the microbial community equilibrium in aquatic bodies. The residue of several pharmaceuticals including antidiabetics' drugs in water affects the endocrine system of aquatic organisms resulting in developmental and reproductive abnormalities with changes in sex ratio and retardation in growth and development**.** Residues of the estrogenic hormones in aquatic bodies' in fish cause feminization and induce the development of intersex traits and abnormal reproductive processes resulting in a decrease in the fish population. The residue of the analgesics and nonsteroidal anti-inflammatory pharmaceuticals in water bodies causes disruption of essential ecological processes and the balance of microbial population by retarding the development and activities of beneficial bacteria. Studies have shown that residues of psychotropic drugs in water, in fish, aquatic invertebrates, and other aquatic organisms, results in the alteration of behavior (feeding, boldness, activity, and sociality), reproductive patterns, and physiological functions disruption of hormones, brain function, and food uptake [87].

The concentration of beta-blockers in surface water ranges from 3 to 6,167 ng/L causing neurotoxic and reproductive disorders in aquatic living organisms [88]. Immobilization in *Daphnia similis* and mortality in fish and green algae in bisoprolol-contaminated water bodies have been reported by Krawczyky *et al*. [89]. Propranolol causes development and improvement issues in green growth such as *Synechococcus leopolensis* and *Cyclotella meneghiniana*]. Medkova *et al*. [90] found that propranolol residues in water negatively impact the embryonic development of *Danio rerio*. β-blockers in fish not only induce abnormal behavior but also disrupt testosterone levels, reduce fertility and reproduction rates, and cause neurotoxic effects in living organisms [88], reproduction toxicity is observed in other invertebrates in the presence of β-blockers. Pharmaceutical residues of Chemotherapy and anticancer medicines in aqueous bodies interfere with the normal cell division and DNA replication of aquatic organisms resulting in altered growth, development, and reproduction processes of fish and, other aquatic organisms [90]. These compounds also cause microbial population imbalance and disturb ecological processes. The presence of anticonvulsant pharmaceuticals (diazepam, carbamazepine, etc) in water affects fish behavior the fish *Lepomis gibbosus* spend more time in motion [87]. DNA damage cellular apoptosis and the formation of micronuclei in cells were observed in Zebra mussels when exposed to cocaine-contaminated water.

Histological damages viz, vacuolization, hypertrophy, pyknotic nucleus, hyperplasia, cellular degeneration, hemorrhage in gills and liver, edema, epithelial thickening, congestion of blood vessels necrosis in the gill tissues were observed by several researchers [32] in fish when exposed in pharmaceutical contaminated water. On exposure to pharmaceutical waters fish *Neogobios melanostomus* show reduced aggressive behavior and misplacing their nesting site.

Wildlife

The extensive decline in the Gyps vulture population is due to kidney malfunction due to the uptake of diclofenac an NSAID. When wildlife animals drink illegal drug-contaminated water like humans they also show behavioral changes [91].

Algae

Bisoprolol, Propranolol the beta blockers not only cause growth and development problems in algae *Synechococcus leopolensis* and *Cyclotella meneghiniana* but also cause mortality in green algae [89]. Pharmaceuticals in aquatic bodies alter community composition and disrupt photosynthetic capacity, respiration and the concentration of chlorophyll A was the finding of Robson *et al*. [92].

Pharmaceuticals in the plants and vegetables

For a proper health plants, fruits and vegetables are essential for humans and animals. Due to anthropogenic activities soil, plants, fruits, and vegetables are contaminated by harmful pollutants including pharmaceuticals. Economic growths, ease of availability, changes in dietary habits and increasing global population have increased global demand for fruits and vegetables. As per the UNESCO report by 2050, 40% global population will face water scarcity. Due to the scarcity of water wastewater is used for irrigation, restoration industries, as a source of groundwater, and municipal usage (potable and non-potable). As per the report of UNESCO on behalf of UN-Water at the UN (2023) Water Conference in New York, 26% of the global population does not have safe drinking water.

In the developed countries the wastewater treated/untreated is used in agriculture, industry, and municipal applications, while in the developing countries, untreated wastewater is used for agricultural irrigation. The data literature denotes that globally in 50 low and middle-income countries about 20 million hectares of land are irrigated by wastewater or partially treated wastewater which contains pollutants including pharmaceutical residues, their metabolites, and antibiotic-resistant genes. The data also denote that approximately 10% global population consumes vegetables and fruits grown on pharmaceutical-contaminated irrigated water. These pollutants via soil are bioaccumulated in the plant tissues and translocate to edible parts of the vegetables/fruits. Li *et al.* [93] reported that pharmaceuticals are bioaccumulated in cabbage, cauliflower, carrot, and cucumber from 2.33 to 189 ug/kg, they also reported that wastewater irrigation does not affect vegetable yields. The concentration of ofloxacin in green leafy vegetables (*Spinach oleracea)* grown on wastewater-irrigated soil near Delhi ranges from 1.382 µg/mg to 5.586µg/mg [75]. Several soil Scientists [93] during their research studies have found that antibiotics ciprofloxacin, enrofloxacin, sulphonamides, tetracycline, chlortetracycline, sulfamethazine, naproxen are bioaccumulated in tomato, radish, celery, spinach cucumber, coriander, ginger, cabbage, beans, corn, soybean plant species on irrigation with reclaimed wastewater the concentration ranged from 0.1-288.3 ug/kg the concentration depends on the source of the wastewater and reclaimed process. The bioaccumulation was most in leaves followed by roots and fruits. Plant development is affected by antibiotic residues in water bodies as the antibiotics impact chloroplast replication, transcription, translation, and synthesis of fatty acids [93]. Several researchers [89] have reported that a large amount of caffeine, carbamazepine, sulfamethoxazole, and hormones is bioaccumulated in lettuce leaves while accumulation in tomatoes was only in roots. The pharmaceuticals are easily bioaccumulated in green leafy vegetables (lettuce, spinach, and cabbage) and bioaccumulation of pharmaceuticals depends on the translocation potential of pharmaceuticals. Ben Mordechay *et al*. [94] during their studies found that the concentration of carbamazepine in green leaves ranges from 0.1 ng to 2470 ng/g. The bioaccumulation of gabapentin in carrots ranges from 10-40ng/g. Dudley *et al*. [95] found that antidepressant diazepam bioaccumulated in carrots, oranges, and potatoes, and concentration was higher in roots and fruits than leaves suggesting that diazepam is easily transformed in leaves. Fluoxetine an antidepressant adversely impacts the growth of the roots of Lemna minor while metamorphic (antidiabetic) retards the growth and biomass production of the plant *Dacus carota***.**

Impact on humans

Human consumes pharmaceuticals via food and drinking water and these compounds in humans cause several adverse effects. Respiratory tract infections, skin infections, and viral infections in humans are due to the bioaccumulation of pharmaceuticals in humans. The hormone (estrogens) contaminated food and water increases the risk of breast cancer in females and prostate cancer in males]. Endocrine-disrupting pharmaceuticals disrupt reproductive and endocrine, causing breast or prostate cancer, infertility, abnormal childhood development, diabetes, early puberty; immune and autoimmune system; causes heart disease, Alzheimer's disease, Parkinson's disease, and attention deficit hyperactivity disorder besides asthma. Excess bioaccumulation of Primidone affects the central nervous system with depression with dysarthria, nystagmus, and ataxia [96]. The bioaccumulation of antibiotics in food and potable water causes antibiotic resistance development in humans causing a serious health risk to humans. Accumulation of these compounds in humans may also cause cancer and neurological disorders. Concurring to the results of different studies, pharmaceutical, and chemical squanders as damaging components have harmful impacts on the environment and human health. In all these studies, the mortality rate, the rate of respiratory maladies and cancer, the predominance of hepatitis C, harming, and the chance of inherent distortions in individuals who lived close to chemical squander transfer locales and pharmaceutical waste were essentially high.

CONCLUSION

For humans and animals pharmaceuticals (medicines) are essential as they have an important role in the prevention and cure of diseases. Due to advancement via research and development, economic growth, increasing world population, aging people, increasing chronic diseases, and easy accessibility, the production and consumption of pharmaceuticals in the medical, agricultural, and animal husbandry sectors have increased in the last two decades. Due to the widespread and continuous use of pharmaceuticals and improper disposal worldwide surface water, groundwater, landfills, soils, vegetables, fruits, and other crops are contaminated by pharmaceuticals. The pharmaceutical residues in aquatic bodies not only impact behavior and reproduction but also cause genotoxicity and neurotoxicity. When humans uptake these compounds via food and water there may be serious damage to people's health, as they may cause respiratory and lung diseases, hepatitis C, risk of congenital malformations, neurological disorders, and cancer.

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REFERENCES

[1] UNESCO (United Nations Educational, Scientific and Cultural Organization). Emerging pollutants in water and wastewater, 2020. Available from: www.en.unesco.org/emergingpollutantsinwaterand wastewater
[2] International Diabetes Federation. 2021. Brussels, Belgium. atlas@idf.org
[3] Selwe KP, Thorn JPR, Desrousseaux AOS, Dessent CEH, Sallach JB. Emerging contaminant exposure to aquatic systems in the Southern African development community. Environ Toxicol Chem. 2022;41(2):382-95. doi:10.1002/ etc.5284
[4] Ding T, Wang S, Yang B, Li J. Biological removal of pharmaceuticals by Navicula sp. and biotransformation of bezafibrate. Chemosphere. 2020;240:124949. doi:10.1016/j.chemosphere. 2019. 124949
[5] Ngqwala NP, Muschesa P. Occurrence of pharmaceuticals in aquatic environments: A review & potential impacts in South Africa. S Afr J Sci. 2020;116(7/8):5730. doi:10.17159/ sajs.2020/5730
[6] Świacka K, Maculewicz J, Kowalska D, Caban M, Smolarz K, Świeżak J. Presence of pharmaceuticals and their metabolites in wild-living aquatic organisms - Current state of knowledge. J Hazard Mater. 2022;424(Pt A):127350. doi:10.1016 / j.jhazmat.2021.127350
[7] Nassour C, Barton SJ, Nabhani-Gebara S, Saab Y, Barker J. Occurrence of anticancer drugs in the aquatic environment: A systematic review. Environ Sci Pollut Res Int. 2020;27(2):1339-47. doi:10.1007/s11356-019-07045-2
[8] Hernández-Tenorio R, González-Juárez E, Guzmán-Mar JL, Hinojosa-Reyes L, Hernández-Ramírez A. Review of occurrence of pharmaceuticals worldwide for estimating concentration ranges in aquatic environments at the end of the last decade. J Hazard Mater Adv. 2022;8:100172. doi:10.1016/j.hazadv.2022. 100172
[9] Ebele AJ, Oluseyi T, Drage DS, Harrad S, Abdallah MA. Occurrence, seasonal variation and human exposure to pharmaceuticals and personal care products in surface water, groundwater and drinking water in Lagos State, Nigeria. Emerg Contam. 2020;6:124-32.
[10] Serna-Galvis EA, Botero-Coy AM, Rosero-Moreano M, Lee J, Hernández F, Torres-Palma RA. An initial approach to the presence of pharmaceuticals in wastewater from hospitals in Colombia and their environmental risk. Water. 2022;14(6):950. doi:10.3390/ w14060950
[11] Hernández-Tenorio R, Guzmán-Mar JL, Hinojosa-Reyes L, Ramos-Delgado N, Hernández-Ramírez A. Determination of pharmaceuticals discharged in wastewater from a public hospital using LC-MS/MS technique. J Mex Chem Soci. 2021;65(1):94-108.
[12] Tenorio-Chávez P, Cerro-López M, Castro-Pastrana LI, Ramírez-Rodrigues MM, Orozco-Hernández JM, Gómez-Oliván LM. Effects of effluent from a hospital in Mexico on the embryonic development of zebrafish, Danio rerio. Sci Total Environ. 2020;727:138716. doi:10.1016/j.scitotenv. 2020. 138716
[13] Merhabi F, Gomez E, Castro NA, Amine H, Rosain D, Halwani J, et al. Occurrence and ecological risk assessment of pharmaceutical products in the Kadicha river in Lebanon. Emerg Contam. 2021;7:196-203. doi:10.1016/j.emcon. 2021. 09.001
[14] Yu X, Yu F, Li Z, Zhan J. Occurrence, distribution, and ecological risk assessment of pharmaceuticals and personal care products in the surface water of the middle and lower reaches of the yellow river (Henan section). J Hazard Mater. 2023;443(Pt B):130369.
[15] You Y, Li Y, Xiao Y, Zhang J. Propranolol vs. steroids in the treatment of infantile hemangiomas: A meta-analysis. Mol Clin Oncol. 2021;15(1):2163. doi:10.3892/mco.2020.2163

[16] Nantaba F, Wasswa J, Kylin H, Palm WU, Bouwman H, Kümmerer K. Occurrence, distribution, and ecotoxicological risk assessment of selected pharmaceutical compounds in water from Lake Victoria, Uganda. Chemosphere. 2020;239:124642. doi:10.1016/j. chemosphere.2019.124642

[17] Jurado A, Labad F, Scheiber L, Criollo R, Nikolenko O, Pérez S, et al. Occurrence of pharmaceuticals and risk assessment in urban groundwater. Adv Geosci. 2022;59:1-7. doi:10.5194/age-59-1-2022, 2022

[18] Praveenkumarreddy Y, Vimalkumar K, Ramaswamy BR, Kumar V, Singhal RK, Basu H, et al. Assessment of non-steroidal anti-inflammatory drugs from selected wastewater treatment plants of Southwestern India. Emerg Contam. 2021;7:43-51. doi:10.1016/ j. emcon.2021.01.001

[19] Satayeva A, Kerim T, Kamal A, Issayev J, Inglezakis V, Kim J, et al. Determination of aspirin in municipal wastewaters of Nur-Sultan City, Kazakhstan. InIOP Conference Series: Earth and Environmental Science 2022 Dec 1 (Vol. 1123, No. 1, p. 012067). IOP Publishing. doi:10.1088/1755-1315/1123/1/ 012067

[20] Mirbahar WA, Talpur MM, Pirzada T, Musharraf SG. Determination of acetylsalicylic acid and naproxen in waste and tap water of the municipal area of the Sukkur city by SPE-LC-MS/MS. Pak J Anal Environ Chem. 2020;21(2):232-46. doi:10.21743/pjaec/2020.12.25

[21] Del Castillo De Loayza T, Maldonado I, Zirena Vilca F. Identification and quantification of antibiotic residues and evaluation of microbial resistance to antibiotics in huatanay river waters in Peru. Pollution. 2023;9(3):1236-50. doi:10.22059/poll.2023.352228.1718

[22] Samandari M, Movahedian Attar H, Ebrahimpour K, Mohammadi F. Monitoring of amoxicillin and cephalexin antibiotics in municipal WWTPs during covid-19 outbreak: A case study in Isfahan, Iran. Air, Soil Water Res. 2022;15:11786221221103879.

[23] Bhagat C, Kumar M, Tyagi VK, Mohapatra PK. Proclivities for prevalence and treatment of antibiotics in the ambient water: A review. Npj Clean Water. 2020;3(1):42. doi:10.1038/s41545-020-00087-x

[24] Voigt AM, Ciorba P, Döhla M, Exner M, Felder C, Lenz-Plet F, et al. The investigation of antibiotic residues, antibiotic resistance genes and antibiotic-resistant organisms in a drinking water reservoir system in Germany. Int J Hyg Environ Health. 2020;224:113449. doi:10.1016/j.ijheh.2020.113449

[25] Golchin M, Khani M, Sadani M, Sadeghi M, Jahangiri-rada M. Occurrence and fate of amoxicillin and penicillin G antibiotics in hospital wastewater treatment plants: A case study–Gonbad Kavous, Iran. S Afr J Chem. 2021;75:98-105. doi:10.17159/0379-4350/ 2021/ v75a11

[26] Deguenon E, Dougnon V, Houssou VM, Gbotche E, Ahoyo RA, Fabiyi K, et al. Hospital effluents as sources of antibiotics residues, resistant bacteria and heavy metals in Benin. SN Appl Sci. 2022;4(8):206. doi:10.1007/s42452-022-05095-9

[27] Su D, Wei Y, Ma Y, Chen Y, Liu Z, Ben W, et al. Distribution, ecological risks and priority of pharmaceuticals in the coastal water of Qinhuangdao, China. Sci Total Environ. 2024;907:167955. doi:10.1016/j.scitotenv.2023. 67955

[28] Ulvi A, Aydın S, Aydın ME. Fate of selected pharmaceuticals in hospital and municipal wastewater effluent: Occurrence, removal, and environmental risk assessment. Environ Sci Pollut Res Int. 2022;29(50):75609-25. doi:10.1007/ s11356-022-21131-y

[29] Mostafa A, Shaaban H, Alqarni A, Al-Ansari R, Alrashidi A, Al-Sultan F, et al. Multi-class determination of pharmaceuticals as emerging contaminants in wastewater from Eastern province, Saudi Arabia using eco-friendly SPE-UHPLC-MS/MS: Occurrence, removal and environmental risk assessment. Microchem J. 2023;187(25):108453. doi:10.1016/j.microc.2023. 108453

[30] Styszko K, Proctor K, Castrignanò E, Kasprzyk-Hordern B. Occurrence of pharmaceutical residues, personal care products, lifestyle chemicals, illicit drugs and metabolites in wastewater and receiving surface waters of Krakow agglomeration in South Poland. Sci Total Environ. 2021;768:144360. doi:10.1016/j.scitotenv. 2020. 144360

[31] Tete VS, Nyoni H, Mamba BB, Msagati TA. Occurrence and spatial distribution of statins, fibrates and their metabolites in aquatic environments. Arab J Chem. 2020;13(2):4358-73. doi:10.1016/ j. arabjc.2019. 08.003

[32] Rodriguez-Mozaz S, Vaz-Moreira I, Della Giustina SV, Llorca M, Barceló D, Schubert S, et al. Antibiotic residues in final effluents of European wastewater treatment plants and their impact on the aquatic environment. Environ Int. 2020;140:105733. doi:10.1016/j.envint. 2020.105733

[33] Mpatani FM, Kombo UM, Ally MS, Simai BO, Fakih MJ, Mbarak SA, et al. Prevalence and detection of pharmaceuticals in hospital wastewater:

A case of referral and district hospitals in zanzibar. Fine Chem Eng. 2023:175-92.
[34] Li S, Wen J, He B, Wang J, Hu X, Liu J. Occurrence of caffeine in the freshwater environment: Implications for ecopharmacovigilance. Environ Pollut.2020; 263:114371. doi:10.1016/j.envpol. 2020. 114371
[35] Khalik AW, Mohd W, Loh SH, Albani H, Alias S, Aisyah S, et al. Caffeine residue in terengganu river basins in Malaysia: Distribution and risk assessment. Nat Environ Pollut Technol. 2020;19(2):711-9. doi:10.46488/ NEPT.2020.v19i02.026
[36] Shigei M, Assayed A, Hazaymeh A, Dalahmeh SS. Pharmaceutical and antibiotic pollutant levels in wastewater and the waters of the Zarqa River, Jordan. Appl Sci. 2021;11(18):8638. doi:10.3390 /app 11188638
[37] Al-Mashaqbeh O, Alsafadi D, Dalahmeh S, Bartelt-Hunt S, Snow D. Removal of selected pharmaceuticals and personal care products in wastewater treatment plant in Jordan. Water, 2020:12:1122.
[38] Üstün-Odabaşı S, Maryam B, Özdemir N, Büyükgüngör H. Occurrence and seasonal variations of pharmaceuticals and personal care products in drinking water and wastewater treatment plants in Samsun, Turkey. Environ Earth Sci. 2020;79(12):311.
[39] Kayiwa R, Kasedde H, Lubwama M, Kirabira JB, Kayondo T. Occurrence and toxicological assessment of selected active pharmaceutical ingredients in effluents of pharmaceutical manufacturing plants and wastewater treatment plants in Kampala, Uganda. Water Pract Technol. 2022;17(4):852-69. doi:10.2166/ wpt. 2022.024
[40] Delgado N, Bermeo L, Hoyos DA, Peñuela GA, Capparelli A, Marino D, et al. Occurrence and removal of pharmaceutical and personal care products using subsurface horizontal flow constructed wetlands. Water Res. 2020;187:116448.
[41] Niemi L, Taggart M, Boyd K, Zhang Z, Gaffney PP, Pfleger S, et al. Assessing hospital impact on pharmaceutical levels in a rural 'source-to-sink'water system. Sci Total Environ. 2020;737:139618. doi:10.1016/j.scitotenv. 2020. 139618
[42] Vumazonke S, Khamanga SM, Ngqwala NP. Detection of pharmaceutical residues in surface waters of the Eastern Cape Province. Int J Environ Res Public Health. 2020;17(11):4067. doi:10.3390/ijerph17114067
[43] Ślósarczyk K, Jakóbczyk-Karpierz S, Różkowski J, Witkowski AJ. Occurrence of pharmaceuticals and personal care products in the water environment of Poland: A review. Water. 2021;13(16):2283.
[44] Dhingra A. Occurrence of high priority Pharmaceutical residues in hospital effluent and its treatment by Sequencing Batch Reactors. InInternational Conference on Environmental Toxicology and Pharmacology 2019 Feb 21 (pp. 21-22). doi:10.4066/2630-4570-C1-005
[45] Son DJ, Kim CS, Lee JH, Yoon JK, Lee SH, Jeong DH. Occurrence assessment of pharmaceuticals in various sewage treatment plants and effluent-receiving streams in Korea. Water. 2023;15(22):3897. doi:10.3390/w15223897
[46] Gopal CM, Bhat K, Ramaswamy BR, Kumar V, Singhal RK, Basu H, et al. Seasonal occurrence and risk assessment of pharmaceutical and personal care products in Bengaluru rivers and lakes, India. J Environ Chem Eng. 2021;9(4):105610. doi:10.1016/j.jece.2021.105610
[47] Pemberthy D, Padilla Y, Echeverri A, Peñuela GA. Monitoring pharmaceuticals and personal care products in water and fish from the Gulf of Urabá, Colombia. Heliyon. 2020;6(6):e04215. doi:10.016/j.heliyon.020.e04215
[48] Gros M, Catalán N, Mas-Pla J, Čelić M, Petrović M, Farré MJ. Groundwater antibiotic pollution and its relationship with dissolved organic matter: Identification and environmental implications. Environ Pollut. 2021;289:117927. doi:10.1016/ j.envpol. 2021.117927
[49] Wu R, Ruan Y, Lin H, Yuen CN, Feng H, Lam PK. Occurrence and fate of psychiatric pharmaceuticals in wastewater treatment plants in Hong Kong: Enantiomeric profiling and preliminary risk assessment. Acs ES T Water. 2020;1(3):542-52. doi:10.1021/acsestwater.0c00081
[50] Di Marcantonio C, Chiavola A, Gioia V, Leoni S, Cecchini G, Frugis A, et al. A step forward on site-specific environmental risk assessment and insight into the main influencing factors of CECs removal from wastewater. J Environ Manag. 2023;325:116541. doi:10.1016/j.jenvman.2022.116541
[51] Baresel C, Ekengren Ö, Filipsson S, Karlsson J, Friesen LW. The municipal wastewater treatment plant of the future–A water reuse facility. Evaluation of a full-scale tertiary treatment system for removal of pharmaceuticals and recovery of water at the WWTP Stengården in Simrishamn, Sweden. Stockholm, 2020. Available from: www.ivl.se
[52] Ávila C, García-Galán MJ, Uggetti E, Montemurro N, García-Vara M, Pérez S, et al. Boosting pharmaceutical removal through aeration in constructed wetlands. J Hazard Mater.

2021;412:125231. doi:10.1016/j.jhazmat.2021.125231

[53] Hara-Yamamura H, Nakashima K, Fukushima T, Okabe S. Transcriptomic response of HepG2 cells exposed to three common anti-inflammatory drugs: Ketoprofen, mefenamic acid, and diclofenac in domestic wastewater effluents. Chemosphere. 2022;286:131715. doi:10.1016/j.chemosphere. 2021. 131715

[54] Leiviskä T, Risteelä S. Analysis of pharmaceuticals, hormones and bacterial communities in a municipal wastewater treatment plant–Comparison of parallel full-scale membrane bioreactor and activated sludge systems. Environ Pollut. 2022;292:118433. doi:10.1016/j.envpol.2021.118433

[55] Petrie B, Camacho-Muñoz D. Analysis, fate and toxicity of chiral non-steroidal anti-inflammatory drugs in wastewaters and the environment: A review. Environ Chem Lett. 2021;19(1):43-75. doi:10.1007/ S10311-020-01065-Y

[56] Schwartz H, Marushka L, Chan HM, Batal M, Sadik T, Ing A, et al. Pharmaceuticals in source waters of 95 first nations in Canada. Can J Public Health. 2021;112(Suppl 1):133-53. doi:10.17269/S41997-021-00499-3

[57] Koumaki E, Noutsopoulos C, Mamais D, Fragkiskatos G, Andreadakis A. Fate of emerging contaminants in high-rate activated sludge systems. Int J Environ Res Public Health. 2021;18(2):400. doi:10.3390/ijerph18020400

[58] Mahjoub O, Mauffret A, Michel C, Chmingui W. Use of groundwater and reclaimed water for agricultural irrigation: Farmers' practices and attitudes and related environmental and health risks. Chemosphere. 2022;295:133945. doi:10.1016/j. chemosphere.2022.133945

[59] Chaves MD, Barbosa SC, Primel EG. Emerging contaminants in Brazilian aquatic environment: Identifying targets of potential concern based on occurrence and ecological risk. Environ Sci Pollut Res. 2021;28(47):67528-43. doi:10.1007/ S11356-021-15245-Y

[60] Ramírez-Morales D, Masís-Mora M, Beita-Sandí W, Montiel-Mora JR, Fernández-Fernández E, Méndez-Rivera M, et al. Pharmaceuticals in farms and surrounding surface water bodies: Hazard and ecotoxicity in a swine production area in Costa Rica. Chemosphere. 2021;272:129574. doi:10. 1016/j.chemosphere.2021.129574

[61] Papagiannaki D, Morgillo S, Bocina G, Calza P, Binetti R. Occurrence and human health risk assessment of pharmaceuticals and hormones in drinking water sources in the metropolitan area of Turin in Italy. Toxics. 2021;9(4):88. doi:10.3390/ toxics 9040088

[62] Hanafiah ZM, Mohtar WH, Abd Manan TS, Bachi NA, Tahrim NA, Abd Hamid HH, et al. Determination and risk assessment of pharmaceutical residues in the urban water cycle in Selangor Darul Ehsan, Malaysia. PeerJ. 2023;11:e14719. doi:10.7717/peers.14719

[63] Alkimin GD, Soares AM, Barata C, Nunes B. Evaluation of ketoprofen toxicity in two freshwater species: Effects on biochemical, physiological and population endpoints. Environ Pollut. 2020;265:114993. doi:10.1016/j. envpol. 2020.114993

[64] Benítez-Rico A, Pérez-Martínez A, Muñóz-López BI, Martino-Roaro L, Alegría-Baños JA, Vergara-Castañeda A, et al. Medical household waste as a potential environmental hazard: An ecological and epidemiological approach. Int J Environ Res Public Health. 2023;20(7):5366. doi:10.3390/ijerph20075366

[65] Kaur R, Talan A, Tiwari B, Pilli S, Sellamuthu B, Tyagi RD. Constructed wetlands for the removal of organic micro-pollutants. InCurrent developments in biotechnology and bioengineering 2020 Jan 1 (pp. 87-140). Elsevier.

[66] Palma P, Fialho S, Lima A, Novais MH, Costa MJ, Montemurro N, et al. Pharmaceuticals in a mediterranean basin: The influence of temporal and hydrological patterns in environmental risk assessment. Sci Total Environ. 2020;709:136205. doi:10.1016/j.scitotenv. 2019.136205

[67] Chafi S, Azzouz A, Ballesteros E. Occurrence and distribution of endocrine disrupting chemicals and pharmaceuticals in the river Bouregreg (Rabat, Morocco). Chemosphere. 2022;287:132202. doi:10.1016/j. chemosphere. 2021.132202

[68] Singh V, Suthar S. Occurrence, seasonal variations, and ecological risk of pharmaceuticals and personal care products in river ganges at two holy cities of India. Chemosphere. 2021;268:129331. doi:10.1016/ j.chemosphere.2020. 129331

[69] Mishra S, Kumar P, Mehrotra I, Kumar M. Prevalence of organic micropollutants in the Yamuna River, Delhi, India: Seasonal variations and governing factors. Sci Total Environ. 2023;858:159684. doi:10.1016/j.scitotenv.2022.159684

[70] Szopińska M, Potapowicz J, Jankowska K, Luczkiewicz A, Svahn O, Björklund E, et al. Pharmaceuticals and other contaminants of emerging concern in admiralty bay as a result of untreated wastewater discharge: Status and possible environmental consequences. Sci Total Environ.

2022;835:155400. doi:10.1016/j.scitotenv.2022. 155400

[71] Benedetti B, Baglietto M, MacKeown H, Scapuzzi C, Di Carro M, Magi E. An optimized processing method for polar organic chemical integrative samplers deployed in seawater: Toward a maximization of the analysis accuracy for trace emerging contaminants. J Chromatogr A. 2022;1677:463309. doi:10.1016/j.chroma.2022. 463309

[72] Mhuka V, Dube S, Nindi MM. Occurrence of pharmaceutical and personal care products (PPCPs) in wastewater and receiving waters in South Africa using LC-Orbitrap™ MS. Emerg Contam. 2020;6:250-8. doi:10.1016/j.emcon. 2020.07.002

[73] Liu N, Jin X, Feng C, Wang Z, Wu F, Johnson AC, et al. Ecological risk assessment of fifty pharmaceuticals and personal care products (PPCPs) in Chinese surface waters: A proposed multiple-level system. Environ Int. 2020;136:105454. doi:10.1016/j.envint.2019.105454

[74] Barbhuiya NH, Adak A. Determination of antimicrobial concentration and associated risk in water sources in West Bengal state of India. Environ Monit Assess. 2021;193(2):77. doi:10.1007/s10661-020-08801-5

[75] Akhter S, Bhat MA, Hashem A, Abd_Allah EF, Ahmed S, Siddiqi WA, et al. Profiling of antibiotic residues in soil and vegetables ırrigated using pharmaceutical-contaminated water in the Delhi stretch of the Yamuna river, India. Water. 2023;15(23):4197. doi:10.3390/w15234197

[76] K'oreje K, Okoth M, Van Langenhove H, Demeestere K. Occurrence and point-of-use treatment of contaminants of emerging concern in groundwater of the Nzoia River basin, Kenya. Environ Pollut. 2022;297:118725.

[77] Azanu D, Adu-Poku D, Saah SA, Appaw WO. Prevalence of pharmaceuticals in surface water samples in Ghana. J Chem. 2021;2021(1):7829477. doi:10.1155/2021/782947

[78] Giebułtowicz J, Nałęcz-Jawecki G, Harnisz M, Kucharski D, Korzeniewska E, Płaza G. Environmental risk and risk of resistance selection due to antimicrobials' occurrence in two Polish wastewater treatment plants and receiving surface water. Molecules. 2020;25(6):1470.

[79] Hricová K, Röderová M, Fryčák P, Pauk V, Kurka O, Mezerová K, et al. Prevalence of vancomycin-resistant enterococci and antimicrobial residues in wastewater and surface water. Life. 2021;11(12):1403. doi:10.3390/ life11121403

[80] Wu R, Sin YY, Cai L, Wang Y, Hu M, Liu X, et al. pharmaceutical residues in edible oysters along the coasts of the east and south china seas and associated health risks to humans and wildlife. Environ Sci Technol. 2024;58(12):5512-23. doi:10.1021/acs.est.3c10588

[81] Benitez JP, Dierckx A, Rimbaud G, Nzau Matondo B, Renardy S, Rollin X, et al. Assessment of fish abundance, biodiversity and movement periodicity changes in a large river over a 20-year period. Environments. 2022;9(2):22. doi:10.3390/ environments9020022

[82] Khan AH, Barros R. Pharmaceuticals in water: Risks to aquatic life and remediation strategies. Hydrobiology. 2023;2(2):395-409. doi:10.3390/hydrobiology2020026

[83] Oliveira AC, Fascineli ML, Andrade TS, Sousa-Moura D, Domingues I, Camargo NS, et al. Exposure to tricyclic antidepressant nortriptyline affects early-life stages of zebrafish (Danio rerio). Ecotoxicol Environ Saf. 2021;210:111868. doi:10.1016/j.ecoenv.2020.111868

[84] Gallego-Ríos SE, Peñuela GA, Martínez-López E. Updating the use of biochemical biomarkers in fish for the evaluation of alterations produced by pharmaceutical products. Environ Toxicol Pharmacol. 2021;88:103756. doi:10.1016/j.etap.2021.103756102

[85] Zhou W, Huang L, Zhang W, Shi W, Liu G. Toxicological impacts of pharmaceuticals for human and animal on marine bivalves. InMarine Bivalve Mollusks and Emerging Pollutants 2024 Jan 1 (pp. 103-127). Academic Press.

[86] Bawa-Allah KA, Ehimiyein AO. Ecotoxicological effects of human and veterinary antibiotics on water flea (Daphnia magna). Environ Toxicol Pharmacol. 2022;94:103932. doi:10.1016/j.etap.2022. 103932

[87] Zhu X, Luo T, Wang D, Zhao Y, Jin Y, Yang G. The occurrence of typical psychotropic drugs in the aquatic environments and their potential toxicity to aquatic organisms - A review. Sci Total Environ. 2023;900:165732. doi:10.1016/j.scitotenv.2023.165732

[88] Godlewska K, Jakubus A, Stepnowski P, Paszkiewicz M. Impact of environmental factors on the sampling rate of β-blockers and sulfonamides from water by a carbon nanotube-passive sampler. J Environ Sci. 2021;101:413-27. doi:10.1016/j.jes.2020.08.034

[89] Krawczyk B, Zięba N, Kaźmierczak A, Czarny-Krzymińska K, Szczukocki D. Growth inhibition, oxidative stress and characterisation of mortality in green algae under the influence of beta-blockers and non-steroidal anti-inflammatory drugs. Sci Total Environ. 2023;896:165019. doi:10.1016/ j.scitotenv. 2023.16501

[90] Medkova D, Lakdawala P, Hodkovicova N, Blahova J, Faldyna M, Mares J, et al. Effects of different pharmaceutical residues on embryos of fish species native to Central Europe. Chemosphere. 2022;291:132915. doi:10.1016/j.chemosphere.2021.13291
[91] Parker M, Ford A. Why fish are becoming addicted to illegal drugs: Trout enjoy the water that contains methamphetamine which leads to them being around sewage pipes. The Conversation, July 2021.
[92] Robson SV, Rosi EJ, Richmond EK, Grace MR. Environmental concentrations of pharmaceuticals alter metabolism, denitrification, and diatom assemblages in artificial streams. Freshw Sci. 2020;39(2):256-67.
[93] Li Y, Liu H, Xing W, Wang J, Fan H. Effects of irrigation water quality on the presence of pharmaceutical and personal care products in topsoil and vegetables in greenhouses. Environ Sci Pollut Res. 2023;30(5):13726-38. doi:10.1007/s11356-022-22753-y
[94] Mordechay EB, Tarchitzky J, Chen Y, Shenker M, Chefetz B. Composted biosolids and treated wastewater as sources of pharmaceuticals and personal care products for plant uptake: A case study with carbamazepine. Environ Pollut. 2018;232:164-72. doi:10.1016/j.envpol.2017.09.029
[95] Dudley S, Sun C, McGinnis M, Trumble J, Gan J. Formation of biologically active benzodiazepine metabolites in Arabidopsis thaliana cell cultures and vegetable plants under hydroponic conditions. Sci Total Environ. 2019;662:622-30. doi:10.1016/j.scitotenv.2019.01.259
[96] Manole F, Marian P, Mekeres GM, Csep AN. A review of the effects of pharmaceutical waste on the environment and human health. Pharmacophore. 2023;14(2):106-10. doi:10.51847/BI0oVRL99Q