Chemosphere 364 (2024) 143055

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Wastewater reuse and pharmaceutical pollution in agriculture: Uptake, transport, accumulation and metabolism of pharmaceutical pollutants within plants

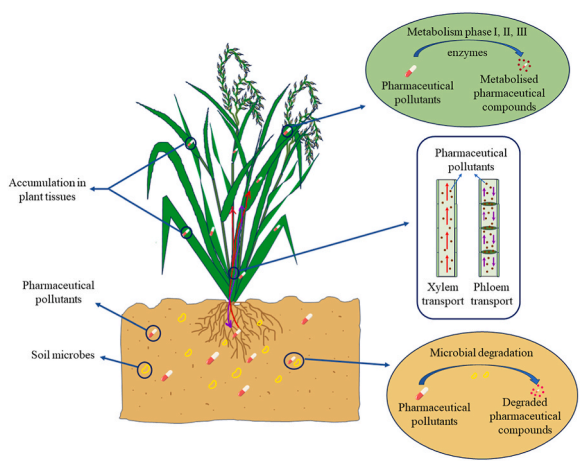
Md Khaled Mosharaf [a,b,*], Rachel L. Gomes [c], Sarah Cook [d], Mohammed S. Alam [a], Amanda Rasmusssen [a]

[a] Agriculture and Environmental Sciences Division, School of Biosciences, Sutton Bonington, University of Nottingham, LE12 5RD, United Kingdom
[b] Department of Environmental Science, Faculty of Agriculture, Bangabandhu Sheikh Mujibur Rahman Agricultural University, Gazipur, 1706, Bangladesh
[c] Food Water Waste Research Group, Faculty of Engineering, University of Nottingham, NG7 2RD, United Kingdom
[d] Water and Environmental Engineering, School of Engineering, University of Warwick, Coventry, CV4 7AL, United Kingdom

HIGHLIGHTS

- Use of reclaimed water or livestock waste in agriculture introduces pharmaceuticals to the land surface.
- Uptake of pharmaceuticals in plants primarily depends on the physicochemical properties.
- Aquaporin and anion channels participate in the uptake of pharmaceuticals.
- Plants utilize numerous phase I and phase II enzymes to metabolize pharmaceuticals.
- Exposure to pharmaceuticals interrupt major physiological processes in plants.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Contaminants of emerging concern
Pharmaceutical pollutants
Environmental impact
Plant uptake
Pharmaceutical metabolism in plant
Wastewater

ABSTRACT

The presence of pharmaceutical pollutants in water sources has become a growing concern due to its potential impacts on human health and other organisms. The physicochemical properties of pharmaceuticals based on their intended therapeutical application, which include antibiotics, hormones, analgesics, and antidepressants, is quite diverse. Their presence in wastewater, sewerage water, surface water, ground water and even in drinking water is reported by many researchers throughout the world. Human exposure to these pollutants through drinking water or consumption of aquatic and terrestrial organisms has raised concerns about potential adverse effects, such as endocrine disruption, antibiotic resistance, and developmental abnormalities. Once in the

* Corresponding author. Agriculture and Environmental Sciences Division, School of Biosciences, Sutton Bonington, University of Nottingham, LE12 5RD, United Kingdom.
E-mail address: md.mosharaf@nottingham.ac.uk (M.K. Mosharaf).

https://doi.org/10.1016/j.chemosphere.2024.143055
Received 8 May 2024; Received in revised form 2 August 2024; Accepted 6 August 2024
Available online 9 August 2024
0045-6535/Crown Copyright © 2024 Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

environment, they can persist, undergo transformation, or degrade, leading to a complex mixture of contaminants. Application of treated wastewater, compost, manures or biosolids in agricultural fields introduce pharmaceutical pollutants in the environment. As pharmaceuticals are diverse in nature, significant differences are observed during their uptake and accumulation in plants. While there have been extensive studies on aquatic ecosystems, the effect on agricultural land is more disparate. As of now, there are few reports available on the potential of plant uptake and transportation of pharmaceuticals within and between plant organs. This review summarizes the occurrence of pharmaceuticals in aquatic water bodies at a range of concentrations and their uptake, accumulation, and transport within plant tissues. Research gaps on pharmaceutical pollutants' specific effect on plant growth and future research scopes are highlighted. The factors affecting uptake of pharmaceuticals including hydrophobicity, ionization, physicochemical properties (pKa, $\log K_{ow}$, pH, Henry's law constant) are discussed. Finally, metabolism of pharmaceuticals within plant cells through metabolism phase enzymes and plant responses to pharmaceuticals are reviewed.

1. Introduction

Water scarcity is poised to emerge as one of the most significant challenges in the immediate future and according to estimates, 40% of the world's population would experience severe water scarcity by the year 2050 (UNESCO, 2020). Worldwide, a mere 3% of the total freshwater is available for drinking and irrigation according to the European Commission (European Commission, 2018). Water shortage is worsened as the population grows, food and energy demand rise, economic development, and as environmental degradation increases (Water, 2018). Industries such as food and beverage, textiles, dyeing, tannery, and pharmaceutical manufacturing are functioning globally to meet human needs, concurrently generating substantial volume of wastewater in the process (Liu and Racherla, 2019; Hubbard et al., 2022; Scott et al., 2018). Around two million tons of waste including organic pollutants, inorganic heavy metals and waste products of biological origins are discharged into the ocean on a daily basis throughout the world (Saravanan et al., 2022; Gomathy et al., 2021; Karimi-Maleh et al., 2021). Approximately 80% of wastewater from industries and municipalities across the world is discharged into the environment without any treatment, which has a severe negative impact on ecosystems and human health (Lin et al., 2022). Along with pollutants such as plastic, steel, fertilizer, tannery and heavy metal, pharmaceutical pollutants are also a major concern in terms of releasing toxic substances into the aquatic environment (González-González et al., 2022; Margot et al., 2015).

Pharmaceuticals, often ascribed as life savers for millions of people around the globe, have also emerged as a novel category of environmental contaminants in the last few decades (Sathishkumar et al., 2020; Patel et al., 2019; Van Boeckel et al., 2015; Kolpin et al., 2002). The residues of pharmaceutical products i.e., actual pharmaceutical pollutants or their metabolized forms have been discovered in almost every environmental sphere and matrices including surface water (Wilkinson et al., 2022; Minh et al., 2009; Watkinson et al., 2009), groundwater (Fick et al., 2009), wastewater treatment process effluent, influents, and sludge (Lapworth et al., 2012), geospheres (Riaz et al., 2018; Yang et al., 2011b), the polar regions (González-Alonso et al., 2017) as well as in the air (Osytek et al., 2008). Apart from the persistence of pharmaceutical pollutants, their continuous addition to the environment also poses a serious threat for flora and fauna (Nikolaou et al., 2007). They are categorized as emerging pollutants in aquatic environments due to their lack of regulation or ongoing efforts to establish regulatory measures (Kolpin et al., 2002). Some of these pharmaceuticals such as antibiotics and steroids have been extensively studied in the past 20 years with the help of advanced detection methods that can identify these molecules at their relatively low levels (Lozano et al., 2022; Noguera-Oviedo and Aga, 2016).

The demand for pharmaceuticals throughout the globe is continuously rising. Between 2015 and 2020, the number of doses of medication administered globally have increased by about 24% (Dunn et al., 2017). It is suggested that half of the world's population, particularly from China, India, Brazil, and Indonesia, consume more than one dose of medication per person per day (Dunn et al., 2017). In 2010, an estimated 2,00,000 tons of antibiotics were consumed worldwide, while 63,200 tons was used in the treatment of cattle and these numbers are predicted to double by 2030 (Kovalakova et al., 2020; Van Boeckel et al., 2015). Currently, there are around 4000 active pharmaceutical components available on the global market (Patel et al., 2019; Rehman et al., 2015). Around 30% of the pharmaceutical industry worldwide exclusively functions in Asia, focusing on the production of pharmaceuticals and personal care products (Kar et al., 2020). According to Majumder et al. (2019), up to 90% of ingested pharmaceutical substances remains unmetabolized in human body and is subsequently eliminated through urine or faeces, ultimately finding its way into the wastewater collection and treatment (USEPA, 2012). So, a large quantity of pharmaceutical residues is continuously being added to the wastewater system across the world.

Wastewaters containing pharmaceuticals can come from industries, in particular pharmaceutical manufacturing and municipal (or community) sources. In pharmaceutical manufacturing, it is estimated that a hundred kilograms of waste is generated for only 1 kg of medicine produced (Askey et al., 2021). Moreover, the effluent wastewaters produced from this sector is different from municipal sewage effluents due to containing excessive organic pollutants and drug components including antibiotics, vitamins, antiepileptics, and cosmetic ingredients (Khasawneh and Palaniandy, 2021). These effluents also carry a considerable amount of total dissolved solids, biochemical oxygen demand, chemical oxygen demand, and suspended solids that can immediately reduce the dissolved oxygen and contaminate the water (Sher et al., 2020).

Studies reveal that hormonal pharmaceuticals can imitate endogenous steroid hormones and cause similar physiological reactions, even at low dosages (Kumar et al., 2019). Endocrine disrupting compounds like estrone (E1) and estradiol (E2) can mimic and hinder human endocrine systems, leading to issues like diabetes, obesity, abnormal reproductive growth, endometriosis, and cancer (Ismail et al., 2020). Additionally, aquatic organisms exposed to psychiatric drugs may experience impacts on photosynthesis, reproduction, and endocrine function (Subedi and Kannan, 2015). Meanwhile, antibiotics can contribute to the development of antibiotic-resistant bacteria and genes, reducing antibiotic effectiveness against pathogens in both humans and animals (Pei et al., 2019; Tran et al., 2018).

Wastewater treatment plant effluents, aside from being released back into waterways, can be reclaimed as a crucial water supply alternative that has substantial advantages for the environment, economy, and society (Delli Compagni et al., 2020). Consequently, in many areas of the world, this practice is being adopted as a central component of water resource management strategies (Singh, 2021). In recent years, there has been increasingly stringent standards for wastewater treatment due to the rising need for high-quality water for drinking, sanitation, agriculture, and industrial usage (Sunyer-Caldú et al., 2022). For instance, policymakers in India recently considered a new drugs bill on rules for importing, manufacturing and selling medicines, with the objective of highest possible regulatory standards and a transparent regulatory

regime (Meshram et al., 2023). In low-income countries, wastewater is reused for different purposes without adequate treatment but in high-income countries, reuse of the wastewater is done mainly after its treatment (Thebo et al., 2017). According to latest studies, countries particularly in China, India, Pakistan, Mexico and Iran, approximately 80% of wastewater is not treated properly and is utilized for irrigating around 11% of croplands (Jones et al., 2021; Kookana et al., 2020; Thebo et al., 2017). But water treatment processes only remove some of the pollutants or partially eliminate pharmaceutical pollutants, meaning a wide range of potentially harmful compounds can still be found in wastewater especially pharmaceutical pollutants and personal care products where they eventually enter environmental compartments (Antunes et al., 2021; Gago-Ferrero et al., 2017). Using reclaimed water or releasing water directly into the environment therefore can have serious negative impact on aquatic organisms, lands, and crop fields (Meyer et al., 2019; Cizmas et al., 2015). Humans can also be exposed to possible health risks by eating crops and fish grown on affected areas through bioaccumulation (Keerthanan et al., 2021). Recently it has been reported that use of treated wastewater in agriculture for irrigation could be a major pathway for introducing organic contaminants i.e., pharmaceutical pollutants, to food crops eventually posing a serious threat to all life forms and environment (Masoner et al., 2023; Christou et al., 2019; Picó et al., 2019), highlighting the importance of a thorough understanding of the fate of these molecules in the environment.

Currently, information on plant uptake of pharmaceuticals is limited to a few drugs and plant species, and the fundamental mechanisms related to plant uptake, transport, metabolism, and accumulation of pharmaceuticals remain largely unknown. In this review, we provide a comprehensive and up-to-date overview of reported pharmaceutical pollutants in wastewater, their physicochemical properties, concentration in water bodies and their mechanistic pathways through the environmental components. The mechanisms regulating the uptake and translocation of different pharmaceutical pollutant groups in plants, and the main factors influencing uptake and transfer processes are summarized with a focus on pollutants that have a high potential for plant uptake from irrigation. The accumulation patterns, the metabolism pathways of pharmaceuticals and their potential impacts on plants are also elucidated. Lastly, the currently available analytical methods for the detection of pharmaceutical pollutants in plant tissues are summarized. The novelty of this work focuses on the comprehensive review and gathering dispersed information on the occurrence of pharmaceutical pollutants and their uptake, accumulation, transport, and metabolism in plants with an in-depth exploration of the fundamental mechanisms of these processes.

2. Occurrence, physicochemical characteristics and pathways of pharmaceutical pollutants in the environment

The pharmaceutical pollutants examined in this review were selected based on several factors: (i) high consumption rates, (ii) frequent detection in wastewater, (iii) potential environmental risks, and (iv) the availability of analytical data (Tran et al., 2018). The collected data on the occurrence of pharmaceuticals were categorized into different therapeutic groups. Based on the data collected from the literature, the presence of the selected pharmaceutical pollutants in different water sources are defined and reported in Table 1. The physicochemical attributes of the wastewaters containing pharmaceutical pollutants are also presented in Table 2. Finally, the pathway of pharmaceutical pollutants from possible source to the disposing sites and their environmental fate are depicted in Fig. 1.

2.1. Occurrence

Since the initial identification of pharmaceutical pollutants in aquatic systems in the 1990s, a long list of pharmaceutically active substances has been found in water (Rathi et al., 2021). Pharmaceutically active pollutants are complex molecules with diverse physicochemical and biological properties and functionalities. They are generally polar compounds with molecular weights typically ranging from 200 to 500/1000 Da. As they are often found in the ng to μg per litre range in the water environment, they are considered "micro--pollutants" (Kümmerer, 2009c). Pharmaceuticals can be grouped based on factors such as their mechanism and mode of action, chemical structure, and the type of diseases they are used to treat. Their properties, chemical structure and hazard statements also differs based on these groups.

Pharmaceutical or medicinal pollutants detected in waterways falls under eight groups: (i) anti-inflammatories and analgesics, (ii) antibiotics, (iii) antiepileptics, (iv) antidepressants, (v) lipid lowering agents, (vi) antihistamines, (vii) β-blockers, and (viii) other substances (Rivera-Utrilla et al., 2013). The detection of these pollutants vary depending on the sampling location, pharmaceutical consumption pattern, manufacturing industries, animal and crop farming practices, and wastewater treatment facilities of that area (aus der Beek et al., 2016; Hughes et al., 2013). For instance, Metformin, an antidiabetic drug has been reported to be detected frequently and also in higher concentrations in a global stream study (Wilkinson et al., 2022). Recently, the global COVID-19 pandemic has resulted in a widespread utilization of massive amounts of pharmaceuticals by healthcare facilities (Sharma et al., 2021). The pandemic has also caused various psychological disorders i.e., anxiety, depression, insomnia, and post-traumatic stress, resulted in increased consumption of antidepressants. Consequently, the occurrence of antidepressants in wastewater treatment plant influent was recently reported in UK (Ng et al., 2020), Belgium (Boogaerts et al., 2019), Costa Rica (Ramírez-Morales et al., 2020), and Brazil (Cortez et al., 2019). Diaz-Camal et al. (2022) compared the occurrence of antidepressants in pre- and post-Covid- 19 pandemic period and found substantial increase of these pollutants after Covid-19 in the environment. Nevertheless, the pharmaceutical pollutants detected are specific to environmental sections of wastewater sources such as groundwater, surface water, drinking water, hospital effluents, industrial effluents, and effluents and influents of sewage treatment plants (Moreno-González et al., 2014; Baker and Kasprzyk-Hordern, 2013; Castiglioni et al., 2008).

Among all groups of pharmaceuticals, antibiotics are the most highly demanded prescription drug. During the past few decades, both their use and demand have climbed by 30% (Tiwari et al., 2017). Among the most widely used antibiotic classes include cephalosporins, quinolones, macrolides, tetracyclines, penicillins, lincomycins, and sulfonamides (Calderón and Sabundayo, 2007). It is reported that, 90% of the antibiotics consumed by humans are removed without undergoing any change or partially metabolized via urine or faeces (Tiwari et al., 2017). Commonly found antibiotics in wastewater effluents include amoxicillin, tetracycline, sulfamethoxazole, azithromycin, chloramphenicol because of their extensive use, highly hydrophobic property, and low volatility. They also show resistance to degradation during the wastewater treatment process by forming stable complexes with suspended matter (Mutuku et al., 2022; Anjali and Shanthakumar, 2019; Liu et al., 2018; Ahmed, 2017). One of the major problems created by antibiotics in the environment is the evolution and dissemination of genes linked to antibiotic resistance, which has been identified as a global public health crisis (WHO, 2014).

Analgesics and anti-inflammatories is another major contributor of pharmaceutical contaminants in wastewater. Diclofenac, ibuprofen, and paracetamol are the most popular, readily available and widely used anti-inflammatory and analgesic medications (Jiménez-Bambague et al., 2020; Albaiges et al., 1986). On the basis of mechanism of action, analgesics are classified into groups such as paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs, opioids, cannabis (medical marijuana) and alcohols (Batt et al., 2007). Feng et al. (2013) reported that the ingestion of non-steroidal anti-inflammatory drugs is more than 30 million doses per day worldwide. Commonly detected opioids in

Table 1
Occurrence of pharmaceutical pollutants with their reported concentration in various water sources (WWTP = Wastewater treatment plant; STP = Sewerage treatment plant; DWTP = Drinking water treatment plant; n.d. = Not detected; LOD = Limit of detection; LOQ = Limit of quantification; MDL = Minimum detection level).

Pharmaceutical compound	Relative molecular mass (g/mol)	Country	Sampling site	Source	Reported concentration (ng L^{-1}) [min – max (avg)]	Reference
Antibiotic						
Sulfamethoxazole ($C_{10}H_{11}N_3O_3S$)	253.3	Switzerland	Altenrhein	Municipal wastewater primary effluent	641 ± 4.0	Göbel et al. (2004)
		Sweden	Stockholm, Henriksdal	STP influent	674	Lindberg et al. (2005)
		USA	Hagerman	Municipal wastewater (influent or effluent not mentioned)	1000	Brown et al. (2006)
		USA	Las Vegas	Municipal wastewater (influent or effluent not mentioned)	2060	Vanderford and Snyder (2006)
		Canada	Edmonton	–	650	McClure and Wong (2007)
		UK	Colsech	WWTP influent	20–274 (115)	Kasprzyk-Hordern et al. (2009)
		Australia	Brisbane	WWTP influent	360	Watkinson et al. (2007)
		Croatia	Velicka Gorica	Raw wastewater	4664	Senta et al. (2008)
		China (HK)	Stanley	WWTP influent	220	Li and Zhang (2011)
		France	Limours	Municipal wastewater (influent or effluent not mentioned)	538	Dinh (2012)
		Spain	Girona	WWTP influent	528	Gros et al. (2013)
		Brazil	Porto Alegre	WWTP effluent	473	Jank et al. (2014)
		India	Coimbatore	STP influent	552	Subedi et al. (2015a)
		Pakistan	Lahore	Household and hospital effluent	4600	Khan et al. (2013)
		Germany	Dresden	STP influent	515	Rossmann et al. (2014)
		Greece	Athens	WWTP influent	218	Dasenaki and Thomaidis (2015)
		Kenya	Nairobi	Untreated wastewater (influent or effluent not mentioned)	89	Mathenge et al. (2017)
		Turkey	Istanbul	DWTP influent	240	Vergili et al. (2019)
		Bangladesh	Cox's Bazar	Brackish water Shellfish Aquaculture	0.31–16.77	Hossain et al. (2017)
		Bangladesh	Old Brahmaputra River	Surface water	LOD - 7.24	Hossain et al. (2018)
Analgesic and antipyretic						
Acetaminophen ($C_8H_9NO_2$)	151.16	Poland	Swarzewo	WWTP influent	6.5	Kołecka et al. (2020)
		Scotland	Wick	WWTP influent	67483	Niemi et al. (2020)
		UK	Cilfynydd	WWTP influent	211380	Kasprzyk-Hordern et al. (2009)
		UK	River Tyne	River water	6000–65000	Roberts and Thomas (2006)
		UK	Southeast of England	STP effluent	<50	Hilton and Thomas (2003)
		Pakistan	Lahore	WWTP effluent	64	Ashfaq et al. (2018)
		Canada	Ontario	Drinking water	17–298	Kleywegt et al. (2011)
		France	Hérault watershed	Drinking water	210	Togola and Budzinski (2008)
		Spain	Northeastern. Spain	Drinking water	10–260	Boleda et al. (2011)
		USA	New Jersey	Drinking water	0.3–120	Stackelberg et al. (2007)
		Japan	11 WWTP in Japan	WWTP influent	1700	Okuda et al. (2008)
		Australia	Gerringong Gerroa Sewerage Scheme	WWTP influent	23300	Al-Rifai et al. (2007)
		Switzerland	Cantonal hospital of Baden	WWTP influent	107000	Kovalova et al. (2012)
		Malaysia	STP in Kajang town	STP effluent	70	Al-Odaini et al. (2010)
		Mexico	Tula river	River water	20,960.9	Garduño-Jiménez et al. (2023)
Opioids						
Tramadol ($C_{16}H_{25}NO_2$)	263.37	Germany	Dresden	WWTP influent	662.8	Gurke et al. (2015)
		Sweden	Dal river	River water	3.01	Lindim et al. (2016)
		China	30 major cities across China	WWTP influent	6.7–40.3	Du et al. (2021)
		Slovakia	Bratislava	WWTP influent	860 ± 120	Mackuľak et al. (2015)
		EU-wide sampling campaign	WWTPs in EU countries	WWTP effluent	256	Loos et al. (2013)
		Czech Republic	Prague	WWTP effluent	870	Diaz-Sosa et al. (2020)
		Germany	IWAR facility	WWTP influent	1100 ± 200	Knopp et al. (2016)
		Germany	12 German STPs	Ground water	87	Hummel et al. (2006)

(continued on next page)

Table 1 (*continued*)

Pharmaceutical compound	Relative molecular mass (g/mol)	Country	Sampling site	Source	Reported concentration (ng L^{-1}) [min – max (avg)]	Reference
		Great Britain	Taff river	Surface water	5970	Kasprzyk-Hordern et al. (2009)
		Sweden	River Fyris, Uppsala	Surface water	1840	Fick et al. (2011)
		Hungary	Balaton lake	Surface water	0.2 ± 0.0	Maasz et al. (2021)
		Germany	Lahn, Hesse	Surface water	31–370	Rúa-Gómez and Püttmann (2012)
		Hungary	Danube	River water samples	1.44–262.4	Kondor et al. (2020)
		Wales, UK	Pontypridd point, River Taff	River water samples	244–5970	Kasprzyk-Hordern et al. (2008)
		Wales, UK	Peterson-super-Ely point, River Ely	River water samples	731–7731	Kasprzyk-Hordern et al. (2008)
		Germany	Conventional WWTP	WWTP influent	470	Wick et al. (2009)
Oxycodone ($C_{18}H_{21}NO_4$)	315.36	USA	Minnesota	Upstream, wastewater and downstream water	38.2–169.8	Campos-Mañas et al. (2019)
		USA	Clarks river	Upstream	2.90 ± 2.1	Skees et al. (2018)
		UK	7 WWTP in UK	WWTP effluent	25.3	Baker and Kasprzyk-Hordern (2011)
		USA	WWTPs in New Mexico	WWTP effluent	120	Batt et al. (2008)
		USA	WWTPs across the US	WWTP effluent	<310	Batt et al. (2016)
		Italy	Milan	WWTP influent	8.7	Castiglioni et al. (2018)
		South Africa	Leeuwkuil WWTP	WWTP influent	1560	Kamika et al. (2021)
		South Africa	Meyerton WWTP	WWTP influent	74.9	Kamika et al. (2021)
		South Africa	Rietgat WWTP	WWTP influent	177	Kamika et al. (2021)
		South Africa	Sandspruit WWTP	WWTP influent	187	Kamika et al. (2021)
		USA	Denver, Colarado	WWTP influent	126	Bai et al. (2018)
		USA	Across the country	WWTP influent	10–100	Phillips et al. (2010)
		Italy	Milan	Ground water (Surface layer)	7.2–286	Castiglioni et al. (2018)
		Canada	Grand river watershed in southern Ontario	DWTP effluent	5.1 ± 0.7	Davoli et al. (2019)
Anticonvulsant						
Carbamazepine ($C_{15}H_{12}N_2O$)	236.3	China	Beijing	Drinking water	0.37–1.15	Cai et al. (2015)
		Serbia	Novi Sad, Zrenjanin, Bečej, Vrbas and Obrenovac	Drinking water	<LOQ - 8.7	Petrović et al. (2014)
		Italy	Milan	Drinking water wells	1.05	Riva et al. (2018)
		Bangladesh	Old Brahamaputra river	River water	<LOD - 8.80	Hossain et al. (2018)
		China	Shanghai	River water	25.3	Wu et al. (2015a)
		Portugal	Lis river	River water	24.9–214	Paiga et al. (2016)
		Serbia	Novi Sad, Zrenjanin, Bečej, Vrbas and Obrenovac	Surface water	0–35.5	Petrović et al. (2014)
		Singapore		Mangrove water	0.06–4.63	Bayen et al. (2016)
		Sweden	Dal river	River water	0.38–0.51	Lindim et al. (2016)
		United States of America	Skaneateles Lake, New York	Lake water	0–0.17	Subedi and Kannan (2015)
		Vietnam	Hanoi	Surface water	<0.144–0.53	Tran et al. (2014)
		France	Orléans	WWTP influent	51–937	Thiebault et al. (2017)
		Germany	Dresden Kaditz	STP influent	246–815	Gurke et al. (2015)
		India	All over	WWTP influent	22–8200	Balakrishna et al. (2017)
		Canada	5 different STPs across Canada	STP influent	757	Lajeunesse et al. (2012)
Antidepressant						
Alprazolam ($C_{17}H_{13}ClN_4$)	308.8	Mexico	14 states of Mexico	WWTP effluent	56	Adhikari et al. (2023)
		Tehran	municipal wastewater treatment plant in South Tehran	WWTP effluent	2.21–6.46	Golbaz et al. (2023)
		Brazil	Cascavel River, Paraná	Surface water	5.9 ± 0.5	Nunes et al. (2015)
		China	Beijing	Hospital effluent	32 ± 0.2	Yuan et al. (2013)
		Sri Lanka	Kandy	Hospital effluent	<MDL - 11	Goswami et al. (2022)
		Spain	Castellon province	WWTP effluent	0.01	Gracia-Lor et al. (2012)
		USA	Albany area, New York	WWTP influent	3.09–12.6	Subedi et al. (2015b)
		China	Guangdong province	WWTP influent	n.d. - 0.98	Lei et al. (2020)
Steroids						
Estrone ($C_{18}H_{22}O_2$)	270.4	China	Hanjiang river	Surface water	n.d. – 2.3	Hu et al. (2019)
		Switzerland	River Jona and Dachseggbach	Surface water	0.21–0.91	Zhang and Fent (2018)
		France	Paris	Surface water	0.2–3.0	Cargouët et al. (2004)
		China	Guangxi Province	Wastewater influent	19.7–1330	Liu et al. (2012)

(*continued on next page*)

Table 1 (*continued*)

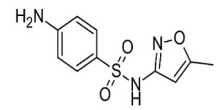
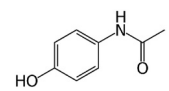
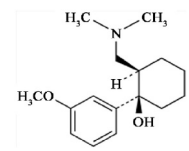
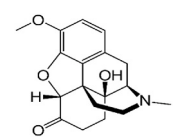
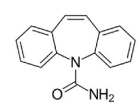
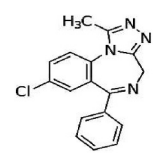
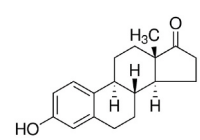
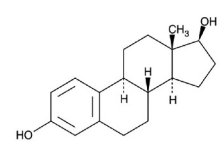
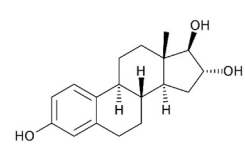
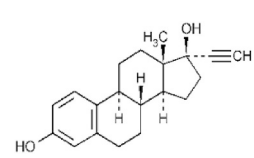
Pharmaceutical compound	Relative molecular mass (g/mol)	Country	Sampling site	Source	Reported concentration (ng L^{-1}) [min – max (avg)]	Reference
		India	Yamuna river	Surface water	1781.8 ± 0.7	Biswas and Vellanki (2021)
		Mexico	Xochimilco wetland	Surface water	13000000	Díaz-Torres et al. (2013)
		Mexico	Across the country	Surface water	179.6	De La Torre (2011)
		Mexico	Tula Valley	Irrigation water	2.5	Chávez-Mejía et al. (2019)
		Poland	Kraków	Ground water	5.4	Rusiniak et al. (2021)
		France	Across the country	Ground water	9.0	Lopez et al. (2015)
		Austria	Across the country	Ground water	1.6	Hohenblum et al. (2004)
		China	Beijing and Tianjin	WWTP effluents	74	Lei et al. (2020)
17−β−estradiol ($C_{18}H_{24}O_2$)	272.4	Austria	Across the country	Ground water	n.d. - 0.79	Hohenblum et al. (2004)
		Belgium	Different rivers	Surface water	n.d. - <0.13	Glineur et al. (2018)
		France	Rhône-Alpes	Ground water	n.d. - 1.3	Vulliet et al. (2008)
		Luxembourg	Pontpierre	Streams	n.d. - 3.0	Banzhaf et al. (2013)
		Poland	Kraków	Ground water	n.d. - <0.2	Rusiniak et al. (2021)
		Spain	WWTP Quart, Catalonia, Spain	Raw wastewater	6.05–8.72	Čelić et al. (2017)
		Iran	Ahvaz City	Slaughterhouse wastewater	98.3	Hassani et al. (2016)
		Italy	Ticino River	Surface water	34	Merlo et al. (2020)
		China	Huangpu River	Surface water	74.8	Zhang et al. (2014a)
		Tunisia	Southern East Tunisia	Sewage treatment plants effluents	10.8	Belhaj et al. (2015)
		Tanzania	Ngerengere and Morogoro River	River water	9.3	Msigala et al. (2017)
		South Africa	Fort Hare WWTP in Alice	Wastewater effluents	135.0	Farounbi and Ngqwala (2020)
		South Africa	Bloukrans river	Upstream water	16.3	Farounbi and Ngqwala (2020)
		England	River Arun	River water	0.6	Peck et al. (2004)
		England	River Ouse	River water	0.6	Peck et al. (2004)
		Taiwan	Dan-Shui River	River water	1.4–33.9	Zhang et al. (2014a)
		USA	Redwood River	River water	0.96	Writer et al. (2012)
		Netherlands	Dutch surface water	Surface water	0.3–7.2	Zhang et al. (2014a)
		South Africa	surface water catchment stations at Blue Downs	Surface water	15,700	Olatunji et al. (2017)
Estriol (E3) ($C_{18}H_{24}O_3$)	288.4	South Africa	surface water catchment stations at Phillipi	Surface water	45,550	Olatunji et al. (2017)
		China	Pearl river delta	Receiving river water	n.d. - 0.37	Xu et al. (2014)
		Japan	Tama river	River water	<0.2	Furuichi et al. (2004)
		France	Paris	Surface water	0.6–3.1	Cargouët et al. (2004)
		USA	Elkhorn River, Nebraska	Surface water	n.d. - 3.3	Kolok et al. (2007)
		Brazil	Campinas	Surface water	n.d. - 2.3	Sodré et al. (2010)
		Australia	Tanilba bay, New South Wales	Raw influent	109.94	Islam et al. (2021)
		Canada	Québec	Influent water	83	Goeury et al. (2022)
		China	Xiamen	Influent water	316–586	Ashfaq et al. (2017)
		Germany	STP in Wiesbaden	Conventional activated sludge	97	Andersen et al. (2003)
		Italy	STP located in Rome	Conventional activated sludge	96.6	Laganà et al. (2004)
		Great Britain	STP located in United Kingdom	Influent water	100	Kumar et al. (2011)
		Switzerland	Lausanne wastewater treatment plant	Wastewater effluent	>75 (±12)	Margot et al. (2013)
Ethinyl estradiol (EE2) ($C_{20}H_{24}O_2$)	296.4	China	South of China	Sewage treatment plant influent	155.7–501.1 (269.1)	Wang et al. (2010)
		Korea	Han River, the Nakdong River, and the Youngsan River	Surface water	n.d. - 1.3	Kim et al. (2007)
		Malaysia	Klang Valley	WWTP effluent	0.8	Fang et al. (2019)
		Turkey	in Istanbul	WWTP effluent	7	Can et al. (2014)
		Australia	Southeast Queensland	Effluent from WWTP	1.14	Ying et al. (2009)
		Australia	Southeast Queensland	WWTP effluent	1.5–2 (1.77)	King et al. (2016)
		France	14 WWTP across the country	French WWTP effluent	1.6–4.4 (2.7)	Gabet-Giraud et al. (2010)
		USA	Gwinnett County, GA	Wastewater reclamation treatment plant effluent	<10	Yang et al. (2011a)
		France, Germany, Italy, UK,	Various WWTPs	WWTPs effluents	<1–2.1 (0.9)	Janex-Habibi et al. (2009)

(*continued on next page*)

Table 1 (*continued*)

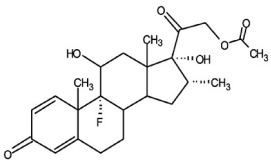
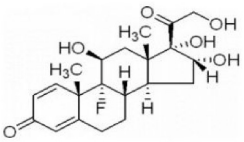
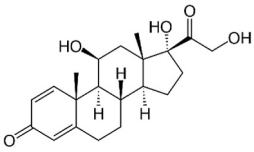
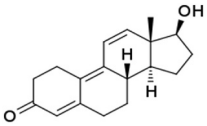
Pharmaceutical compound	Relative molecular mass (g/mol)	Country	Sampling site	Source	Reported concentration (ng L^{-1}) [min – max (avg)]	Reference
		Spain, USA				
Dexamethasone ($C_{22}H_{29}FO_5$)	392.5	Hungary	Danube River	Surface water	0.07	Tölgyesi et al. (2010)
		Malaysia	Rivers in Selangor district	Surface water	0.29	Praveena et al. (2018)
		China	Beijing	Surface water	0.11	Chang et al. (2007)
		China	Pearl River Delta	Surface water	0.33	Gong et al. (2019)
		USA	Los Angeles and San Gabriel Rivers	Surface water	n.d.	Sengupta et al. (2014)
		China	Beijing	Treated water from WWTP	0.02–0.09	Chang et al. (2007)
		China	River Wenyu, Beijing	Treated water from WWTP	390	Chang et al. (2009)
		USA	LA river	Surface water	55.6	Desgens-Martin and Keller (2021)
		Switzerland	Baden	Rivers surface water	8–13	Ammann et al. (2014)
		Switzerland	Baden	Hospital wastewater influent	1720	Ammann et al. (2014)
		Netherlands	Various sites	Industrial effluent	90 ± 9	Schriks et al. (2010)
		Germany	Various	Treated wastewater, rivers and streams	0–0.4	Weizel et al. (2018)
		Singapore	WWTP	Wastewater influent	0.236	Goh et al. (2018)
		South Africa	Daspoort WWTW	Wastewater effluent	0.92	Mhuka et al. (2020)
		France	STP, downstream from Lyon	Wastewater influents	15	Piram et al. (2008)
		Italy	Pavia municipal waterworks, Northern Italy surface waters	Treated wastewater, rivers and streams.	2–3	Merlo et al. (2020)
		Spain	Sewer of Girona University Hospital, Girona	Hospital effluents	360	Cruz-Morató et al. (2014)
		Spain	Katalan rivers (Ebre, Ter and Llobregat) and STPs located in Tarragona area	River waters, influent and effluent sewage	<20	Herrero et al. (2012)
Triamcinolone ($C_{21}H_{27}FO_6$)	394.43	China	Pearl River system	River water	<0.54–0.79	Gong et al. (2019)
		Hungary	Hungary Danube River	River water	<0.2 - <0.5	Tölgyesi et al. (2010)
		USA	Tucson	WWTP effluents	5.75–14.0	Jia et al. (2016)
		Germany	Groβ-Gerau, Bingen, Schwelm, Koblenz and Wandlitz	WWTP effluents	<28	Weizel et al. (2018)
		Germany	Rivers across the country	Surface water	<12	Weizel et al. (2018)
		Netherland	Various	WWTP effluents	<14	Schriks et al. (2010)
		Switzerland	Baden	WWTP effluents	1	Ammann et al. (2014)
		France	Various	WWTP effluents	3	Schriks et al. (2010)
		China	Seven important surface watersheds	Surface water	1.75–7.53	Xu et al. (2019)
Prednisolone ($C_{21}H_{28}O_5$)	360.4	Netherland	Across the country	Industrial wastewater effluents	247 ± 28	Van der Linden et al. (2008)
		Netherland	Across the country	Hospital wastewater effluents	315 ± 30	Van der Linden et al. (2008)
		Netherland	Various	Hospital wastewater influent	315–1918	Schriks et al. (2010)
		China	Pearl river system	Surface water	<0.39–1.8	Gong et al. (2019)
		China	Beijing rivers	Surface water	0.03–1.8	Chang et al. (2007, 2009)
		Germany	German rivers	Surface water	<0.2–0.4	Weizel et al. (2018)
		Switzerland	Swiss rivers	Surface water	10–13	Macikova et al. (2014)
		Czech	Czechic rivers	Surface water	3–5	Macikova et al. (2014)
		Hungary	Danube River	River water	<0.04–0.58	Tölgyesi et al. (2010)
		USA	Tucson, Arizona	WWTP effluent	0.16 ± 0.03	Wu et al. (2019)
		Sweden	Dal river	River water	0.033	Lindim et al. (2016)
Trenbolone ($C_{18}H_{22}O_2$)	270.4	USA	Southwest and central Ohio	Beef cattle feedlots discharge	10–120	Durhan et al. (2006)
		Germany	Freising-Weihenstephan	Liquid manure	5–75	Schiffer et al. (2001)
		USA	Stanislaus, Marin, and Sonoma counties in central California	Surface water	<25	Kolodziej and Sedlak (2007)
		USA	north central Indiana	Beef and dairy effluent	<8.9	Gall et al. (2011)
		USA	University of Nebraska Haskell Agricultural Laboratory near Concord	Feedlot runoff from treated cattle shed	<115	Bartelt-Hunt et al. (2012)
		USA	Purdue Animal Science Research and Education Center	Untreated lagoon water	22–1720	Khan and Lee (2012)

Table 2
Commonly reported pharmaceuticals in wastewater, their structure, and physicochemical properties.

Pharmaceuticals (CAS number)	Class/ therapeutic application	Chemical formula	Molecular weight (g mol^{-1})	Acid dissociation constant (pKa)	Octanol−water partition coefficients ($logK_{ow}$)	Henry's law constant (atm-cu m/mol at 25 °C)	Structure	References
Sulfamethoxazole (723-46-6)	Antibiotic/sulfa drug/ antibacterial/ Human and veterinary use	$C_{10}H_{11}N_3O_3S$	253.276	1.6, 5.7	0.89	6.42×10^{-13}		Patel et al. (2019)
Acetaminophen (Paracetamol) (103-90-2)	Analgesic/ antipyretic/ Human and veterinary use	$C_8H_9NO_2$	151.16	9.38	0.46	8.93×10^{-10}		Patel et al. (2019)
Tramadol (27203-92-5)	Opioid pain medication	$C_{16}H_{25}NO_2$	263.381	9.32, 13.48	3.01	1.54×10^{-11}		Patel et al. (2019)
Oxycodone (76-42-6)	Pain reliever/ Opioid drug/ Human use	$C_{18}H_{21}NO_4$	315.36	8.28	0.66	2.33×10^{-16}		Patel et al. (2019)
Carbamazepine (298-46-4)	Anti-epileptic/ Neuropathic pain reliever/ Anti-psychotic	$C_{15}H_{12}N_2O$	236.274	13.9	2.45	1.08×10^{-7}		Patel et al. (2019)
Alprazolam (28981-97-7)	Benzodiazepine/ Anti-anxiety drug/Human use	$C_{17}H_{13}ClN_4$	308.769		2.12	9.77×10^{-12}		Patel et al. (2019)
Estrone (E1) (53-16-7)	Steroid/Human and veterinary drug	$C_{18}H_{22}O_2$	270.366	10.3	3.43	3.8×10^{-10}		Adeel et al. (2017)
17 β-estradiol (E2) (50-28-2)	Steroid/Human and veterinary drug	$C_{18}H_{24}O_2$	272.38	10.6	3.94	3.64×10^{-11}		Adeel et al. (2017)
Estriol (E3) (50-27-1)	Steroid/Human and veterinary drug	$C_{18}H_{24}O_3$	288.38	10.33	2.45	1.33×10^{-12}		Ilyas and van Hullebusch (2020); Adeel et al. (2017)
Ethinyl estradiol (EE2) (57-63-6)	Steroid/Human and veterinary drug	$C_{20}H_{24}O_2$	296.403	10.4	3.67	7.94×10^{-12}		Adeel et al. (2017)

(*continued on next page*)

Table 2 (*continued*)

Pharmaceuticals (CAS number)	Class/ therapeutic application	Chemical formula	Molecular weight (g mol^{-1})	Acid dissociation constant (pKa)	Octanol−water partition coefficients ($logK_{ow}$)	Henry's law constant (atm-cu m/mol at 25 °C)	Structure	References
Dexamethasone (50-02-2)	Glucocorticoid/ Anti-inflammatory drug	$C_{22}H_{29}FO_5$	392.464	1.83	1,89 y 6.4	7.15×10^{-8}		Chacca et al. (2022); Chávez-Mejía et al. (2019)
Triamcinolone (124-94-7)	Glucocorticoid/ Anti-inflammatory drug	$C_{21}H_{27}FO_6$	394.434		1.16	1.97×10^{-9}		Patel et al. (2019)
Prednisolone (50-24-8)	Glucocorticoid/ Anti-inflammatory and ophthalmology drug	$C_{21}H_{28}O_5$	360.444		1.62	2.23×10^{2}		Patel et al. (2019)
Trenbolone (10161-33-8)	Androgen and anabolic steroid/ Veterinary and human drug	$C_{18}H_{22}O_2$	270.37			2.71×10^{-8}		Patel et al. (2019)

wastewater effluent include tramadol, oxycodone, methadone, codeine, ketamine, and morphine (Campos-Mañas et al., 2018). Non-steroidal anti-inflammatory drugs have long-lasting eco-toxic impacts on the biotic elements of ecosystems (Tyumina et al., 2020).

Anticonvulsants are used in the treatment of various conditions such as depression, mental illnesses, drug and alcohol dependencies, and post-traumatic stress disorders (Mohapatra et al., 2014). One anticonvulsant that is frequently detected in water bodies is carbamazepine, which is typically prescribed for seizures, epilepsy, trigeminal neuralgia, bipolar disorder, drug and alcohol dependencies, and diabetic neuropathy (Zhang et al., 2008). However, wastewater treatment plants are not designed to effectively remove pharmaceutical drugs, resulting in partial removal and the release of residues into the environment through effluent or sludge (Lajeunesse et al., 2012).

Steroid hormones are a class of biologically active substances synthesized from cholesterol and share the cyclopentane-perhydro phenanthrene ring (Ying et al., 2002). These are micropollutants that pollute water sources all over the world and pose a serious risk to both human health and the environment even at low amounts. The typical sources of steroid hormones in the environment include pharmaceuticals, veterinary medications, agricultural runoff, and human and animal excretion (Almazrouei et al., 2023). Estrone (E1), 17β-estradiol (E2) and estriol (E3) are three natural and 17α-ethinylestradiol (EE2) is the synthetic steroid hormone most predominantly found in wastewaters (Racz and Goel, 2010). Steroid hormones are extensively studied as endocrine-disrupting chemicals due to their prevalent use in hormonal treatments for specific purposes, such as growth, development, sexual differentiation, and reproduction. As a result of the ineffective removal techniques in conventional wastewater treatment plants and design limitations, these hormones are not properly being removed during wastewater treatment and make their way to the environment (Chimchirian et al., 2007). Water bodies receiving high steroid hormones have a significant impact on aquatic species. Oestrogens, responsible for developing female sexual characteristics, can interfere with normal biological functions by mimicking normal hormones and signalling pathways i.e., feminizing males, altered oogenesis in females and impact on gonadal development in fathead minnows (*Pimephales promelas*) when exposed to low 17β-estradiol concentrations (5–6 ng L^{-1}) (Kidd et al., 2007). Aquatic plants can also take up these steroid hormones and they can end up in the human food chain if contaminated water is used in agriculture (Chen et al., 2022).

Pharmaceutical residues have spread across all continents, including the Arctic and Antarctica, due to human actions (Wilkinson et al., 2022; González-Alonso et al., 2017a). The Ministry for Environment in Germany commissioned an evaluation on pharmaceutical pollutants in the environment including surface, ground and drinking water, wastewater treatment plant influents and effluents, also veterinary drugs in manure, dung and soil, which found that out of 713 pollutants tested, 631 pharmaceuticals were detected above analytical limits (aus der Beek et al., 2016). A global evaluation identified a total of 203 pharmaceuticals in 41 different countries as areas of concern (Hughes et al., 2013). Studies conducted in the USA, Germany and Japan have assessed the presence of emerging organic pollutants, including pharmaceutically active pollutants (Hughes et al., 2013). In the initial nationwide study conducted in the USA during 1999–2000, 95 pharmaceuticals were discovered in 139 streams across 30 states (Kolpin et al., 2002). Furthermore, 35 distinct pharmaceuticals were found in groundwater by a reconnaissance survey that covered 18 states. Among the detected pharmaceuticals, sulfamethoxazole was the most common occurring at 23% of the sampling locations, while ibuprofen had the highest average concentration of approximately 3 μg/L (Barnes et al., 2008). A thorough investigation was conducted in Serbia, examining 81 pharmaceuticals in various water sources, such as industrial and municipal wastewater, surface water, underground water, and drinking water. Out of the 81 pharmaceuticals analysed, 47 were found in the water samples, with amounts varying from ng/L to more than 1 μg/L (Petrović et al., 2014).

The extent of pharmaceutical pollution in low-income countries has received less attention compared to high-income nations

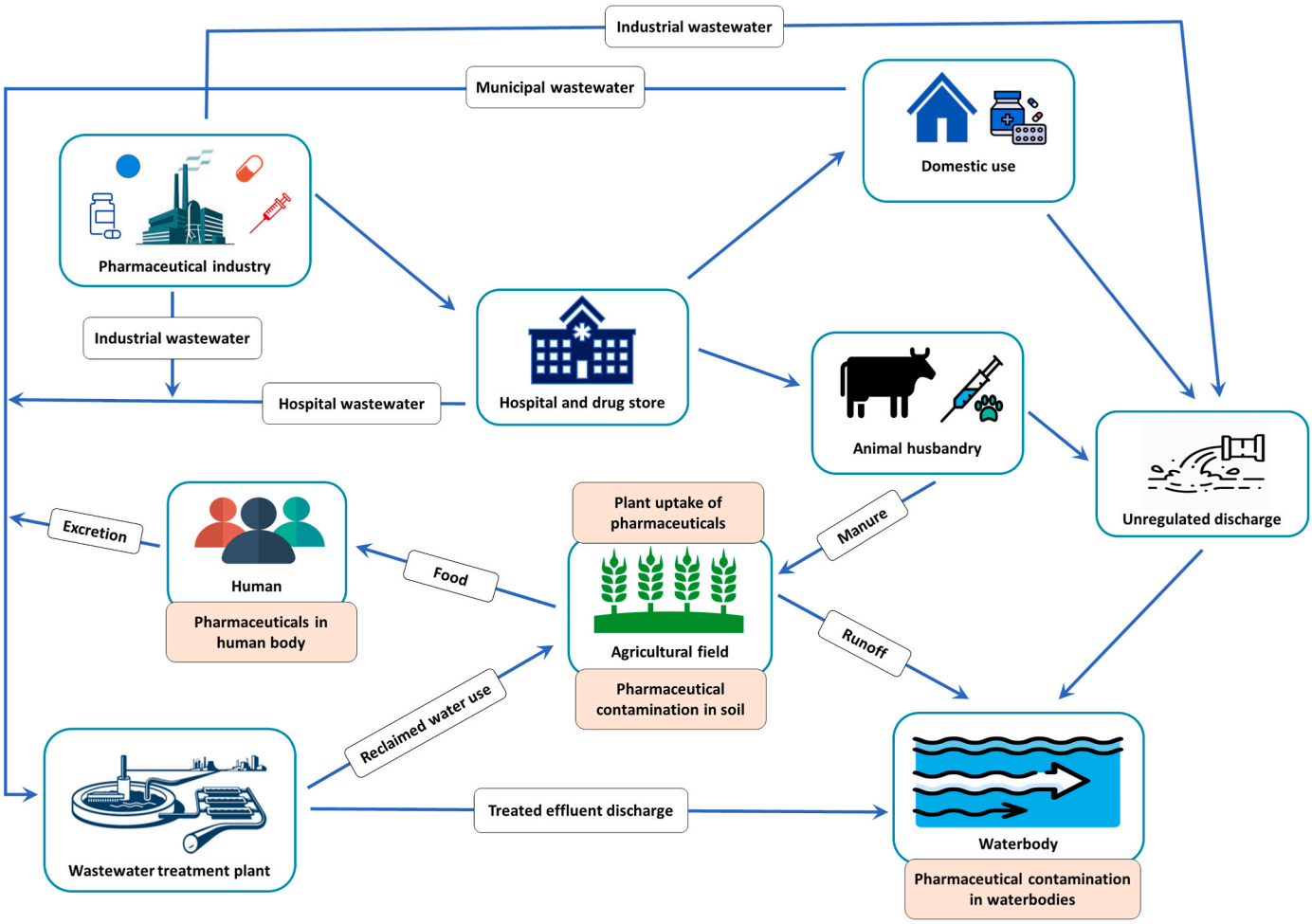


Fig. 1. The sources and pathways for the occurrence of pharmaceutical pollutants and their residues in the environment. Pharmaceutical industries serve as the main source of drugs for humans and animals and eventually end up in different environmental component as pollutants. Ultimately through the use of wastewater reuse in agriculture, pharmaceutical pollutants can be introduced into human food chain.

(Garduño-Jiménez et al., 2023). The limited presence and less advanced wastewater treatment plants in low-income countries increase the environmental risks and human vulnerability to pharmaceutical contamination (Segura et al., 2015). The occurrence of different pharmaceuticals varies in frequency depending on the location. Globally, painkillers are the most commonly detected pharmaceutical class. However, in Asia, antibiotics are the most frequently found and at the highest concentrations (Patel et al., 2019). Table 1 presents selected pharmaceuticals and their concentrations reported in the literature for water sources of different regions across the world.

According to literature, pharmaceutical's concentration in different water matrices also follows a general order from highest to lowest concentrations: industrial effluents > untreated municipal wastewater > hospital effluents > wastewater treatment plant effluents > surface water > groundwater > drinking water (Kallenborn et al., 2018). This is a generalisation based on losses at each step/transition/through the environmental system, but some exceptions apply, for example accumulation can occur in one or multiple of those compartments (Ebele et al., 2017). To minimise the introduction of these pharmaceuticals into the environment, improving efficiency of removal processes at each step is required.

2.2. Physicochemical characteristics

An extensive range of pharmaceutical pollutants exists in the environment, displaying diverse chemical compositions and exhibiting differences in their physicochemical properties, leading to considerable variations in their behaviour (Saravanan et al., 2022). Table 2 provides details on the characteristics and structures of the specified pharmaceuticals. Understanding the fate of pharmaceutical pollutants in aquatic environments involves consideration of properties such as hydrophobicity, water solubility, volatility, dissociation constants (pKa), octanol–water partition coefficients ($\log K_{ow}$), organic-carbon based sorption coefficients ($\log K_{oc}$) etc. These properties play a crucial role in influencing processes, including sorption, partition, hydrolysis, photodegradation, and biodegradation. Together, they contribute to the diverse pathways and outcomes of pharmaceutical pollutants in aquatic ecosystems (Pal et al., 2010; Yamamoto et al., 2009). Acid dissociation constant (pKa) values of pharmaceuticals impact physicochemical properties such as activity and reacting rates, biological uptake and receptor binding of substances at molecular level. Additionally, the charge state of pollutants, determined by pKa under different pH conditions, significantly affects absorption, distribution, metabolism, excretion, and toxicity (Manallack et al., 2013).

Pharmaceutical pollutants are categorized into three groups based on their hydrophilicity: hydrophilic ($\log K_{ow} < 1$), moderately lipophilic or hydrophobic ($1 < \log K_{ow} < 3$), and hydrophobic ($\log K_{ow} > 3$) (Verliefde et al., 2008). High molecular weight compounds with $\log K_{ow}$ values greater than 5.0 are unlikely to be found in surface water because they readily sorb to sediments and are mainly eliminated by coagulation (Vieno et al., 2007). Conversely, compounds with a $\log K_{ow}$ values less than 2.5 have low sorption and are more likely to be available in surface

water (Mompelat et al., 2009). Pharmaceuticals often contain acidic and/or basic functional groups, resulting in the existence of cationic, anionic, neutral, or zwitterionic forms under different pH conditions. The particular forms are determined by the molecules' $logK_{ow}$ and pKa values, which can differ greatly. The sorption coefficients of pharmaceuticals containing amines are often greater than those of carboxylic acids and neutral pharmaceutical environments (Yamamoto et al., 2009). Henry's coefficient is a vital metric for organic pollutants in the environment and research suggest that the removal of pharmaceuticals via volatilization can be ignored owing to low Henry coefficient values (Radjenovic et al., 2007). These factors play significant role with the pharmaceuticals' hydrolysis, sorption, photodegradation, and biodegradation in environment.

2.3. Environmental pathway of pharmaceutical pollutants

The pathways and outcomes of pharmaceutical pollutants have been explored in the literature (Quesada et al., 2019; Rosman et al., 2018; Lee et al., 2017; aus der Beek et al., 2016; Bu et al., 2016). Understanding the transport pathways of pharmaceuticals through air, water, and soil is challenging due to limited information on the behaviour and fate of most of these pollutants in the environment. The characterization of these pathways depends on various physicochemical properties of the pharmaceuticals including their solubility in water, octanol–water partition coefficient ($logK_{ow}$) and persistence (Patel et al., 2019).

Additionally, the properties of surrounding matrices, such as soil or water, also play a crucial role in determining the transport behaviour of pharmaceutical pollutants (Fairbairn et al., 2016). Fig. 1 portrays the pathways for the occurrence of pharmaceutical pollutants in the environment. The major pathways by which pharmaceuticals as well as their residues can enter into the environment include-a) wastewater released from pharmaceutical manufacturing industries, b) municipal treated and untreated wastewaters, c) hospital effluents containing pharmaceutical pollutants discharged in the form of human urine and faeces, d) agricultural wastewaters mostly from livestock animals containing pharmaceuticals excreted in the urine and faeces of animals, e) disposing of unused or expired pharmaceutical products on land either through the septic system or at conventional waste disposal sites, f) stormwater runoff events discharging into rivers and reservoirs, g) leachate from landfill disposals (González-González et al., 2022; O'Flynn et al., 2021; Masoner et al., 2019; Patel et al., 2019; Tiwari et al., 2017; Veiga-Gómez et al., 2017; aus der Beek et al., 2016; Masoner et al., 2016). Exceptions to these pathways reported include the application of any pharmaceuticals directly in water for aquaculture (Patel et al., 2019; aus der Beek et al., 2016). Pharmaceuticals released into the environment through hospitals and households primarily occur through patient excretions (Bagheri et al., 2016). Subsequently, these excreted residues, including faeces and urine, can enter sewage treatment plants either in their original form or as metabolites (Helwig et al., 2016).

The effectiveness of treatment in wastewater treatment plants varies, resulting in only partial removal of pharmaceutical active pollutants and the introduction of remaining residues into the aquatic environment, such as surface and groundwater (Lee et al., 2017). Reports indicate that pharmaceuticals can persist in drinking water, even after undergoing conventional water treatment processes (Rosman et al., 2018).

The presence and movement of pharmaceuticals in soil are influenced by their properties, physicochemical characteristics, and fate (Gworek et al., 2021; Wu et al., 2021; Carter et al., 2014). The ionization of these substances directly affects their hydrophobicity and plays a crucial role in determining their environmental fate (Wang et al., 2021). Pharmaceuticals can accumulate in surface soil layers and subsequently migrate into deeper layers, eventually reaching groundwater aquifers. In these subsurface environments, pharmaceuticals interact with soil microbial communities, undergo biodegradation, and may be absorbed by plants and vegetables (Carter et al., 2014). Dalkmann et al. (2014) demonstrated the presence of pharmaceuticals in agricultural soils, with an average concentration of 0.2 μg kg^{-1}, which was attributed to irrigation with wastewater and the deposition of wastewater aerosols resulting from wind erosion and transportation.

Contamination of soils with pharmaceuticals can also occur when manure or sewage sludge is utilized as fertilizer. This risk extends beyond human pharmaceuticals, as veterinary pharmaceuticals also pose a substantial environmental threat. Residues of veterinary active pharmaceutical ingredients can be present in the manure and dung of treated animals in livestock farming. When manure is applied as a fertilizer, these pharmaceuticals can accumulate in the soil, potentially leading to their availability for plant uptake or migration into water bodies and groundwater (Klatte et al., 2017). Consumption of pharmaceutical contaminated edible plant parts can lead to the introduction of pharmaceutical pollutants into the food chain. Long term consumption of these contaminated foods could pose potential human health risk (Kumari and Kumar, 2021).

3. Water quality parameters of pharmaceutical manufacturing effluents

The characteristics of effluent wastewater generated during the manufacturing of pharmaceuticals mostly depend on the raw materials and formulation process (Gadipelly et al., 2014). Important physicochemical characteristics include temperature, turbidity, high concentration of organic and inorganic toxic substances including heavy metals and various mineral nutrients (Rana et al., 2017). Heavy metals present in pharmaceutical pollutants come from applied catalysts, raw materials, processing equipment or as impurities. Hence, treatment of these wastewaters exclusively depends on the physicochemical characteristics (Deegan et al., 2011). Most of the wastewater samples have higher biological oxygen demand, chemical oxygen demand and salt values. Specific to each industrial sector, regulations have been set for appropriate water treatment before any wastewater is released into the environment (Parida et al., 2021). Table 3 highlights water quality parameters of various pharmaceutical industry effluents across the world. Different countries use different parameters to regulate treated wastewater, but discharge limits are commonly set based on organic pollutants and nutrients (WHO, 2001; WFD, 2000). Other regulated parameters include chemical oxygen demand, total suspended solids, pH, and nutrients such as nitrogen and phosphorus. The specific parameters and limits vary depending on the country and regulatory agency. World Health Organization (WHO) published a report describing regulated wastewater parameters across different countries throughout the world in 2017 (Table 3) (Schellenberg et al., 2020).

Total suspended solids in untreated pharmaceutical wastewater were reported to be higher in several studies than standard values (Daouda et al., 2021; K'Oreje et al., 2016; Vanerkar et al., 2015). Elevated total suspended solid levels can promote the attachment of microbes, potentially resulting in increased microbial contamination (Babuponnusami et al., 2023). Pharmaceutical wastewater effluents also exhibit a diverse range of pH values depending on their origin. The pH range of the water affects the solubility and mobility of metals, availability of nutrient elements and infrastructures, and can create the habitat unsuitable for aquatic flora and fauna (Cohen and Kirchmann, 2004).

Some trace elements and heavy metals such as lead, cadmium, nickel, chromium, or zinc can make their way into the water bodies through the discharge of pharmaceutical wastewater as they were used in manufacturing process and not properly removed by treatment methods. Aquatic organisms can be affected by these pollutants and humans can also be exposed if these toxic metals get into the food chain (Rajendran et al., 2022). Usually, wastewaters contain high levels of salt which affects aquatic life (Fang et al., 2018) and pharmaceutical wastewater is no different (Bhatti et al., 2017).

Table 3
Review on water quality parameters of untreated pharmaceutical wastewater effluents from various locations (EC = Electrical conductivity; COD = Chemical oxygen demand; BOD = Biological oxygen demand; TSS = Total suspended solid; TS = Total solid; TOS = Total organic carbon; TDS = Total dissolved solid; a = United States Environmental Protection Agency (USEPA) (1999), National recommended water quality criteria–correction; b = World Health Organization (WHO) (2002), Guidelines for drinking-water quality).

Parameters	Locations											USEPA[a]	WHO[b]
	Sango industrial area of Ogun state, Nigeria	Medea, Algeria	Cotonou, Benin	Cuddalore, Tamilnadu, India	Nagpur, India	Rubí, Spain	Hyderabad, Pakistan	Guanajuato, Mexico	Pharmaceutical factory in Singapore	Anhui province, China	Eli Lilly & Company Ltd, Liverpool, UK		
Pharmaceutical type	–	Antibiotics	–	Penicillin-G	Herbal	Mixed	Mixed	Mixed	Penicillin	–	–		
Temperature (°C)	–	–	–	30–45	–	–	26.2	–	–	–	–	–	–
pH	4.7–7.1	6.46	5.62–8.79	5.5–6.5	3.9	7.52	7.5	–	7.0–8.0	6.42	5.2–6.8	6.5–8.5	6–9.5
EC (μS/cm)	199–413.0	784.0	356.0–1275.0	–	–	–	3328	–	–	–	–	–	–
Turbidity	–	48.60	–	–	–	–	–	–	–	–	–	–	5
COD (mg/L)	80.0–110.0	525.51	1080.0–9504.0	15000.0–25000.0	23980.0	508.2	–	660	15365.0 ± 1214	20.14	7000 ± 800	–	–
BOD (mg/L)	22.0–60.0	–	180.0–1700.0	5000.0–9000.0	13430	–	–	290	–	–	3500 ± 500	–	–
Alkalinity (mg/L)	30.0–40.0	–	–	1000.0–2000.0	–	–	740.3	–	–	–	–	–	–
Salinity (mg/L)	0.02–0.03	–	–	–	–	–	1.7	–	–	–	–	–	–
Hardness (mg/L)	–	–	–	–	–	–	350	–	–	–	–	–	–
Ammonium nitrogen (mg/L)	–	–	–	300.0–500.0	–	49.13	–	–	–	988.6	–	–	–
Total nitrogen (mg/L)	–	–	3.05–20.32	–	444	–	–	57	1422 ± 173	2000.57	364 ± 50	–	–
Total phosphorus (mg/L)	–	–	0.77–8.75	–	–	–	–	33	–	400.2	–	–	–
TSS (mg/L)	30.0–70.0	–	370.0–2370.0	–	4915	119.2	–	200	–	–	–	–	–
TS (mg/L)	–	–	–	–	8512	–	–	–	–	–	–	–	–
TOC (mg/L)	–	–	–	–	–	67.67	–	–	7624 ± 710	–	–	–	–
TDS (mg/L)	134.0–277.0	–	–	–	–	–	2167	–	22168 ± 3757	–	–	500	<1200
Chloride (mg/L)	10.0–18.0	–	–	–	–	–	98.3	–	16134 ± 3971	–	–	250	250
Boron (mg/L)	–	–	–	–	–	–	–	–		–	–		
Sulphate (mg/L)	7.0–14.0	–	–	3000.0–4000.0	85	–	–	–	54 ± 5	–	2500 ± 500	250	500
Nitrate (mg/L)	1.52–3.31	–	–		–	–	–	–		–	–	10	50
Phosphate	0.08–0.16	–	–	70.0–200.0	270	–	–	–	176.3 ± 36.6	–	–	–	–
Fluoride (mg/L)	–	–	–		–	–	–	–	109 ± 29	–	–	–	–
References	James et al. (2014)	Kermet-Said and Moulai-Mostefa (2015)	Daouda et al. (2021)	Mullai and Vishali (2007)	Vanerkar et al. (2015)	Radjenovic et al. (2007)	Bhatti et al. (2017)	Estrada-Arriaga et al. (2016)	Ng et al. (2014)	Chen et al. (2014)	Chelliapan et al. (2011)	USEPA (1999)	WHO (2002)

4. Wastewater reuse and pharmaceutical pollution in agriculture

Wastewater reuse also known as reclaimed water use refers to the use of wastewater that undergoes treatment to meet defined water quality standards, to be utilized for a range of applications (USEPA, 2012). In the last few decades, adoption of reclaimed water for irrigation has become a common global practice. This is attributed to its numerous benefits, including alleviating pressure on other water resources, ensuring year-round reliability, changing weather patterns due to climate change, recovering nutrients for crops, and reducing disposal costs (Drechsel et al., 2022; Li et al., 2015; Holt-Giménez et al., 2012). The United Nations promotes water reuse through the 2030 Agenda for Sustainable Development to achieve the Sustainable Development Goals (United Nations, 2016). The agricultural sector, consuming 70% of the world's water, is crucial in integrated water management (WWAP - UNESCO World Water Assessment Programme, 2019). In dry regions, using treated sewage for crop irrigation is the major solution to sustain agriculture (Al-Hammad et al., 2014; Dery et al., 2019; Jaramillo and Restrepo, 2017; Tal, 2016).

The potential for reusing treated wastewater has not been fully exploited worldwide (Salgot and Folch, 2018). However, both developed and developing nations are increasingly viewing reclaimed water as a viable alternative resource (Caicedo et al., 2019). This practice has already begun in water-scarce areas, such as Mediterranean countries and other arid and semi-arid regions, where treated municipal wastewater is being recycled and reused (Cirelli et al., 2012). Studies indicate 1.6–6.3% of the world's treated sewage is used for irrigating agricultural land (Ungureanu et al., 2018). According to a 2017 United Nations report, nearly 50 countries worldwide utilize wastewater for irrigation (WWAP - UNESCO World Water Assessment Programme, United Nations World Water Development Report, 2017). Globally, around 15 million m^3 of reclaimed water is used daily for agricultural irrigation (Elgallal et al., 2016). The World Health Organization (2006) reported that over 10% of the global population consumes food irrigated with wastewater. By adopting wastewater reuse for agriculture, Israel has increased its production by 1600%, becoming a global benchmark (Tal, 2016). Wastewater reuse in agriculture as irrigation water has been reported to be ranging from 22 to 77 % in different countries such as Tunisia (Ait-Mouheb et al., 2018), China (Beijing) ((Lyu et al., 2016), Spain (Paranychianakis et al., 2015) and Southern Europe (Ricart and Rico, 2019). Thus, a significant portion of wastewater is reported to be reused for agricultural purposes worldwide.

Although wastewater reuse in agriculture as irrigation is higher in low-income countries compared to high-income countries, proper treatment and water quality standards are less maintained in low-income ones (Carter et al., 2019; Madikizela et al., 2017). The composition of reclaimed water varies depending on its sources and treatment processes. It may contain elevated concentrations of salts, heavy metals, pathogens, and emerging contaminants such as pharmaceuticals, illicit drugs, and pesticides (Masoner et al., 2023). The utilization of reclaimed water mainly the pollutants in it can potentially lead to adverse effects on soils and plants, directly influencing the suitability of the soil for cultivation and the availability of water resources. As such there is significant concern regarding potential health risks and environmental impacts arising from the agricultural use of reclaimed water throughout the world (Chen et al., 2011; Qadir et al., 2010). Gottschall et al. (2012) studied urban biosolids applied in agricultural sector in Ontario, Canada and found over 80 pharmaceuticals and personal care products in the studied samples. Section 2.3 above describes how these introduced pharmaceuticals behave in soil.

Continuous application of treated wastewater or biosolids in agricultural fields has the potential to elevate the concentration of pharmaceutical pollutants to levels higher than those present in the original sources (Li et al., 2019). A recent review article by Nguyen et al. (2023) provides the distribution of pharmaceutically active compounds at various concentrations in agricultural environments worldwide.

Pharmaceutical pollutants found in soil may enter plants through root uptake. The existence of crop plants contaminated with pharmaceuticals poses a potential threat to humans as these contaminants may enter the food chain. The movement of pharmaceutical pollutants from plants to the food consumed by humans raises concerns regarding potential health risks associated with the consumption of contaminated crops (Bartrons and Peñuelas, 2017).

5. Impacts of pharmaceuticals on plants

Once the pharmaceutical pollutants make their way into soils, plants can take up and accumulate these pollutants into their tissues. Different plants have been investigated for their ability to absorb over 100 different pharmaceuticals and personal care products in a range of countries (Fu et al., 2019; Al-Farsi et al., 2017). Several studies have confirmed the negative effect of pharmaceutical pollutants on different plants (Table 4), but whether the negative effects are a direct damage to the plant caused by the reported pharmaceutical pollutant or on the soil microbial community that helps in nutrient acquisition by plant is not clear (Grassi et al., 2013). For example, antimicrobial activity shown by the pharmaceuticals can slow down the decomposition rate in soil, resulting in slower denitrification and processing of nutrients (Fatta-Kassinos et al., 2011). Conversely, the phenomenon of hormesis or positive effect on plant growth and development has also been reported by several studies (Table 4). Along with plant impacts, there are also reports on potential human food chain contamination from the consumption of pharmaceutical contaminated food crops (Osuoha et al., 2023; Jayampathi et al., 2019; Wu et al., 2015b). Impact of pharmaceutical pollutants on plants and possible introduction of these pollutants in human food chain is represented in Fig. 3.

5.1. Plant uptake of pharmaceuticals

The uptake and accumulation of pharmaceuticals in plants are strongly affected by the physicochemical properties of the pollutants, such as hydrophobicity and ionization behaviour. Soil characteristics like pH, organic matter content, water quality, as well as the concentration and duration of exposure, are essential factors influencing this process (Bartrons and Peñuelas, 2017). Furthermore, the variation in the uptake and accumulation of pharmaceutical pollutants is associated with biotic factors such as species of plant, cultivar, variety, genotype, and the physiological stage of the plant (Ravichandran and Philip, 2021). The degradation of pharmaceuticals in soil is also influenced by microbial activities (Lin and Gan, 2011). A study by Langenhoff et al. (2013) demonstrated the mineralization and breakdown of ibuprofen and diclofenac by bacterial consortia. Bacteria and fungi are also reported to degrade and mineralize nearly all organic pollutants present in the environment. Plants can also uptake and accumulate the microbe degraded pharmaceutical pollutants from soil (Gworek et al., 2021). Antibiotics tend to be the most abundant among pharmaceuticals in plants, primarily due to their elevated concentrations in biosolids and animal manure commonly used as fertilizers in agricultural fields (Matamoros et al., 2012).

The entry of pharmaceutical pollutants into plants occurs through two main pathways: root uptake and foliar uptake, with root uptake being the predominant mechanism (Zhang and Zhu, 2009). Numerous studies have demonstrated that pharmaceuticals can be efficiently absorbed by roots, leading to accumulation in the roots. In other cases, pharmaceutical substances are translocated from the roots to above-ground tissues, including stems, leaves, and fruits, predominantly through passive diffusion (Fu et al., 2019).

Plants absorb organic pharmaceuticals through either active or passive mechanisms, influenced by the specific characteristics of the pollutants and the plants involved (Collins et al., 2006). Active absorption involves carriers and energy consumption, whereas passive

Table 4
Impact of pharmaceutical pollutants on plant growth.

Pharmaceutical pollutants	Impact on plant
Sulfamethoxazole	• Strawberry showed excitatory response to low-dose of SMX (1 mg/L), but root and photosynthetic efficiency were damaged under high level (Lv et al., 2021) • Increased Pakchoi (*Brassica chinensis* L.) plant height, root length, and fresh biomass at 50% minimum inhibitory concentration (MIC) but inhibited plant growth at MIC (Zhang et al., 2017) • Lower levels of SMX promoted the growth of ginger, but at higher dosages, the root growth and light energy utilization efficiency of ginger were impaired (Lv et al., 2020) • Negatively affected the seed germination and vegetable growth of both pakchoi and radish (Wang et al., 2016) • Inhibited seed germination of the three plants oat, rice and cucumber with the EC50 (effective concentrations) values (Liu et al., 2009) • Affected *Cyperus involucratus* plant growth (Xu et al., 2020)
Acetaminophen	• 20-day-old pea and maize plants exhibited decrease in biomass production (Zezulka et al., 2019) • Increasing paracetamol stress levels adversely affected the spinach plants' photosynthetic machinery, altering the chlorophyll fluorescence parameters, photosynthetic pigments and composition of essential nutrients and elements (Badar et al., 2022) • Application of paracetamol significantly decreased maize grains yield by up to 50% (Hammad et al., 2018) • Applied paracetamol concentrations, retarded the root and stem developments in seeds, and increased the electrolyte leakage and antioxidant enzyme activities in wheat plants (Türkoğlu et al., 2019) • The increased load of paracetamol in the environment may negatively affect the growth of duckweed (Hájková and Kummerová, 2014) • 1.0 ppm concentration of paracetamol induced oxidative stress via increasing levels of lipid peroxidation, and H_2O_2 accumulation in mung bean (*Vigna radiata*) plants (Almohisen, 2019) • Increased oxidative stress in duckweed (Kummerová et al., 2016) • Higher doses of paracetamol reduced the photosynthetic activity in lettuce (*Lactuca sativa*) (Kudrna et al., 2020)
Carbamazepine	• Increased carbamazepine uptake by zucchini (*Cucurbita pepo*) resulted in a decrease in above and below ground biomass (Carter et al., 2015) • Collard greens (*Brassica oleracea*) root and shoot biomass decreased with increasing CBZ concentration (Deng et al., 2017) • CBZ could be detected in soil, roots, and aerial plant parts but did not adversely affect the growth of ryegrass (Winker et al., 2010) • Bioaccumulation of CBZ by cucumber leaves, roots and fruits (Shenker et al., 2011) • CBZ was taken by the tomato plants and mainly stored in the leaves (Riemenschneider et al., 2017b)
Estrone (E1)	• Stimulative effect on the growth of isolated corn root tips (Fiedler, 1936) • Stimulated the growth of isolated pea embryos grown on a solid culture medium (Bonner and Axtman, 1937) • Increased germination of *Melandrium dioecum* seeds (Löve and Löve, 1945) • Increased biomass at lower concentrations in Alfalfa (Shore et al., 1992) • Even at low concentrations reduced potato tuber growth and overall tuber number (Brown, 2006) • In tomato seedlings, estrone and 17β-estradiol (as sulphate derivatives, at the concentration of 1 μM in nutrient solution), reduced root growth as well as root number in shoot cuttings (Guan and Roddick, 1988) • At 0.1 μM concentration decreased the number of generative plants in *Arabidopsis thaliana* (Janeczko et al., 2003)

Table 4 (*continued*)

Pharmaceutical pollutants	Impact on plant
17-β-Estradiol (E2)	• Inhibited pea shoot growth (Helmkamp and Bonner, 1953) • Application of low concentrations increased growth and photosynthesis, but high concentrations were found toxic in carrot tissue cultures (Gioelli, 1942), Alfalfa biomass growth (Shore et al., 1992) and Lettuce growth (Adeel et al., 2018) • Increased germination of *Melandrium dioecum* seeds (Löve and Löve, 1945) • Stimulated the flowering of broccoli curd cuttings grown in culture medium (Leshem, 1967) • Even at low concentrations reduced potato tuber growth and overall tuber number (Brown, 2006) • Improved chickpea plant growth under stressed conditions (Erdal and Dumlupinar, 2011) • Increased the inorganic element concentrations in Barley leaves (Dumlupinar et al., 2011) • In sunflower seedlings, increased shoot growth but inhibited root growth (Bhattacharya and Gupta, 1981) • At 0.1 μM concentration decreased the number of generative plants in *Arabidopsis thaliana* (Janeczko et al., 2003) • Maize seedling growth was consistently inhibited at 10 mg/L but was stimulated by 0.1 mg/L 17β-E2 (Bowlin, 2014) • In lentil, 17β-E2 treatment enhanced embryo growth and improved tolerance to cadmium and copper stress during germination (Chaoui and El Ferjani, 2013) • At 0.1 μM concentration decreased the number of generative plants in *Arabidopsis thaliana* (Janeczko et al., 2003)
Estriol (E3)	• Inhibitory effects on the development of *Lepidium sativum* seedlings (Euler, 1946) • Increase in the auxin content of dwarf pea and young pine seedlings (Kopcewicz, 1970a, 1970b) • Enhanced the number of flowers and increased the percentage of female flowers in *Ecballium ehterium* (Kopcewicz, 1971) • Even at low concentrations reduced potato tuber growth and overall tuber number (Brown, 2006) • At 0.1 μM concentration decreased the number of generative plants in *Arabidopsis thaliana* (Janeczko et al., 2003)
Ethinyl estradiol (EE2)	• The growth stimulation of dwarf pea seedlings (Kopcewicz, 1970a) • Flower promoting effects in *Callistepphus sinensis* (Castan and Chouard, 1937) • Induced flower buds of *Melandrium dioecum* to develop in a female or male direction (Löve and Löve, 1945) • In mung beans estrone and estradiol at low concentrations of 0.1 μM augmented germination and vegetative growth but were inhibitory at high concentrations (60 μM) (Guan and Roddick, 1988) • The negative effects of EE2 (at 7 μM) on growth and photosynthesis in the green alga, *Chlamydomonas reinhardtii* (Pocock and Falk, 2014) • Application of low concentrations increased growth, but higher concentrations were found toxic and induced stress in lettuce growth (Adeel et al., 2018)
Dexamethasone	• Promoted algal growth (Guo et al., 2017) • Application of dexamethasone to Arabidopsis mutant plants alleviates the dwarfism and sterility (Kim et al., 2014) • Induce gene expression in Arabidopsis, tobacco (Padidam, 2003) and citrus plants (Rossignol et al., 2014)
Triamcinolone	• Responsible for gene expression and does not retard rice plant growth (Samalova and Moore, 2021) • Triamcinolone acetonide expressed antagonistic activity against a soil-borne fungal plant pathogen *Fusarium oxysporum* (Nayana et al., 2023)

absorption is an energy-independent process that may or may not involve carriers (Zhan et al., 2010; Collins et al., 2006). For example, water enters cells through osmosis or aquaporin channels (Zhan et al., 2010). Chen et al. (2021) reported that aquaporin and anion channels participate in the uptake of steroid estrogens i.e., 17β-estradiol (17β-E2) in plants.

The hydrophobicity (reported as $LogK_{ow}$) also affects the ability of pollutants to cross membranes. Pharmaceuticals having a $LogK_{ow}$ between 0.5 and 3.5 are both water-soluble and lipophilic enough to penetrate the lipid bilayers of plant cell membranes and cell fluids (Dordio and Carvalho, 2013; Stottmeister et al., 2003; Schröder and Collins, 2002; Dietz and Schnoor, 2001). For instance, carbamazepine, with a $LogK_{ow}$ of 2.45, is readily taken up by *Typha* spp. roots and translocated from the roots to stems and leaves, accumulating predominantly in leaves (Dordio et al., 2011). In contrast, diclofenac, with a $LogK_{ow}$ higher than 3.5 (4.51), has limited uptake and translocation within the roots and shoots of *Scirpus validus* (Zhang et al., 2012).

Apart from the characteristics of the pharmaceuticals, crucial factors in plant uptake include plant characteristics like transpiration, as well as the lipids and proteins content (Liu et al., 2019; Zhu et al., 2007). Pharmaceuticals with a molecular weight below 1000 g/mol easily accumulate in plants by permeating cell membranes (Öztürk et al., 2015). For example, caffeine, lamotrigine, carbamazepine, and trimethoprim (MW < 300 g/mol) efficiently diffuse into lettuce roots and move to shoots or above ground plant parts (Chuang et al., 2019). Ionic pharmaceuticals, on the other hand, are only able to enter plant cells through integral proteins on biomembranes due to concentration gradients (Taiz et al., 2015; Wu et al., 2015b; Di et al., 2012).

Foliar uptake of pharmaceutical pollutants mainly occurs via stomata or cuticle on the leaf surface (Colon and Toor, 2016). In foliar uptake, aerial tissues absorb pharmaceuticals through the deposition of aerosols and volatilized compounds as well as direct interactions involving diffusion or ionic fraction absorption with irrigation or amendment materials (Trapp and Legind, 2011). Currently, there is no identification of specific transporters in plant cell membranes responsible for the uptake of pharmaceuticals, indicating a potential area for future research investigations.

5.2. Accumulation and transport of pharmaceuticals

The accumulation of pharmaceutical pollutants in roots can be characterized by the root concentration factor (RCF), a parameter determined by the ratio of the chemical concentration in roots to that in the surrounding environment. RCF values reported to span many magnitude orders, ranging from approximately 0.01 to around 1000 (Miller et al., 2016a). Root concentration factors for pharmaceuticals are influenced by multiple factors, including exposure duration, plant species, soil characteristics, humidity, temperature, and the concentrations of the chemicals involved (Bax, 1997). Additionally, the bioconcentration factor (BCF) is employed to assess the accumulation of pharmaceuticals in plant tissues (Bax, 1997). The calculation of BCF in hydroponic cultures involves calculating the ratio between the chemical concentration in the plant tissue and the nominal concentration in the growth medium, expressed as BCF (L/kg) = $C_{plant\ tissue}/C_{solution}$. This relationship can also be applied to estimate pharmaceutical concentrations in soil, using BCF (L/kg) = $C_{soil}/C_{solution}$. Furthermore, the translocation factor (TF) is used to represent the movement of pharmaceutical pollutants within plant tissues, defined as the ratio of concentration in leaves to that in roots ($TF = C_{leaf}/C_{root}$) (Guasch et al., 2012).

In the rhizosphere, pharmaceuticals become available for plant uptake through the epidermis at the root surface. Once inside the plant, pharmaceuticals are transported into or between plant cells through three main pathways: apoplastic (between cells along cell walls), symplastic (through cells via plasmodesmata), and transmembrane (through cells via cell membranes). The choice of pathway depends on the size and potentiality of the solute to cross membranes. Variations in the composition of plant cytoplasmic membranes across species and tissues can result in notable differences in how pharmaceuticals pass through lipid membranes (Pan et al., 2014; Mompelat et al., 2009; Pedersen et al., 2005; Bax, 1997).

Regardless of whether apoplastic, symplastic or transmembrane, the pharmaceuticals traverse the cortex to the endodermis. Within the endodermis, the apoplastic movement of pharmaceuticals is halted at the casparian strip. This strip, fortified with lignin and suberin accumulated on cell walls, acts as a hydrophobic barrier (Andersen et al., 2018; Miller et al., 2016a). Consequently, the water flow and solute flux are compelled to shift from the apoplastic pathway to the symplastic pathway (Cui and Schröder, 2016). Hydrophobic pharmaceuticals which are transported to vascular tissues through the apoplastic pathway tend to bind with membrane lipids and remain in the roots. In contrast, hydrophilic pharmaceuticals primarily follow the symplastic pathway (Zhang and Zhu, 2009) and cross to the casparian strip to the xylem where it is translocated to the leaves. Another situation occurs for ionic pharmaceuticals which are repelled by negatively charged cell walls and cytosol, and move toward the phloem, leading to increased accumulation in fruits (Goldstein et al., 2014).

Pharmaceutical pollutants can also enter aerial plant tissues by foliar irrigation through the stomatal pathway, where vapor-phase pharmaceuticals, along with carbon dioxide, infiltrate the leaf tissues and are subsequently transported to other plant parts via the phloem (Colon and Toor, 2016; Calderon-Preciado et al., 2012). Plant aerial portions or roots may also directly absorb gaseous pharmaceuticals from the air. Additionally, these gaseous compounds can dissolve in water or be sorbed by sludges/particles on plant surfaces, entering plants through diffusion (Hellstrom, 2004; O'Connor, 1996). Several factors, including vapor pressure, temperature, gas concentrations, Henry's law constant, and hydrophobicity, influence the overall absorption of pharmaceuticals from the air (Colon and Toor, 2016).

5.3. Metabolism of pharmaceuticals

After being absorbed by plants, pharmaceutical pollutants undergo degradation, ultimately becoming incorporated into plant tissues (Zhang et al., 2014b). Contaminants absorbed and infiltrated into plant cells undergo enzymatic transformations, resulting in increased hydrophilicity and a simultaneous reduction in toxicity (Sandermann Jr, 1994). This is mainly because plants possess multiple detoxification mechanisms to reduce the harmful effects of contaminants and counteract the toxicity of various external chemicals, a concept referred to as the "green liver" model (Sandermann Jr, 1994). Transformed products typically diffuse within the vacuole, apoplasm, or cell wall (Sandermann Jr, 1994). Plant metabolism of pharmaceuticals involves three phases: I) chemical alteration; II) conjugation; III) isolating or separating conjugates (Fig. 2) (Wei et al., 2023; Pilon-Smits, 2005; Dietz and Schnoor, 2001). Plants can process xenobiotics through different phase I and phase II enzymatic modifications and molecular conjugations, converting these pollutants into less toxic and more water-soluble metabolites (Wei et al., 2023). In phase I, hydrophilic and reactive functional groups are added to pharmaceuticals to transform them into more reactive metabolites. Cytochrome P450 enzymes play a vital role in phase I metabolism, facilitating reactions like oxidation and hydroxylation. These reactions activate compounds for further conjugation in phase II. Moreover, cytochrome P450 monooxygenases are crucial in producing hydroxy metabolites, such as hydroxy-ibuprofen. They also mediate the transformation of diverse pharmaceuticals, including carbamazepine and enrofloxacin in plants (Pilon-Smits, 2005; Dietz and Schnoor, 2001). Moreover, peroxidase and laccase enzymes participate in the oxidation-reduction-reactions of different pharmaceuticals such as hydrolysis/dihydroxylation and carbonylation/decarbonylation in the plant cells (Morsi et al., 2020). Phase I reactions in plants, which activate xenobiotic compounds, do not always reduce toxicity and can

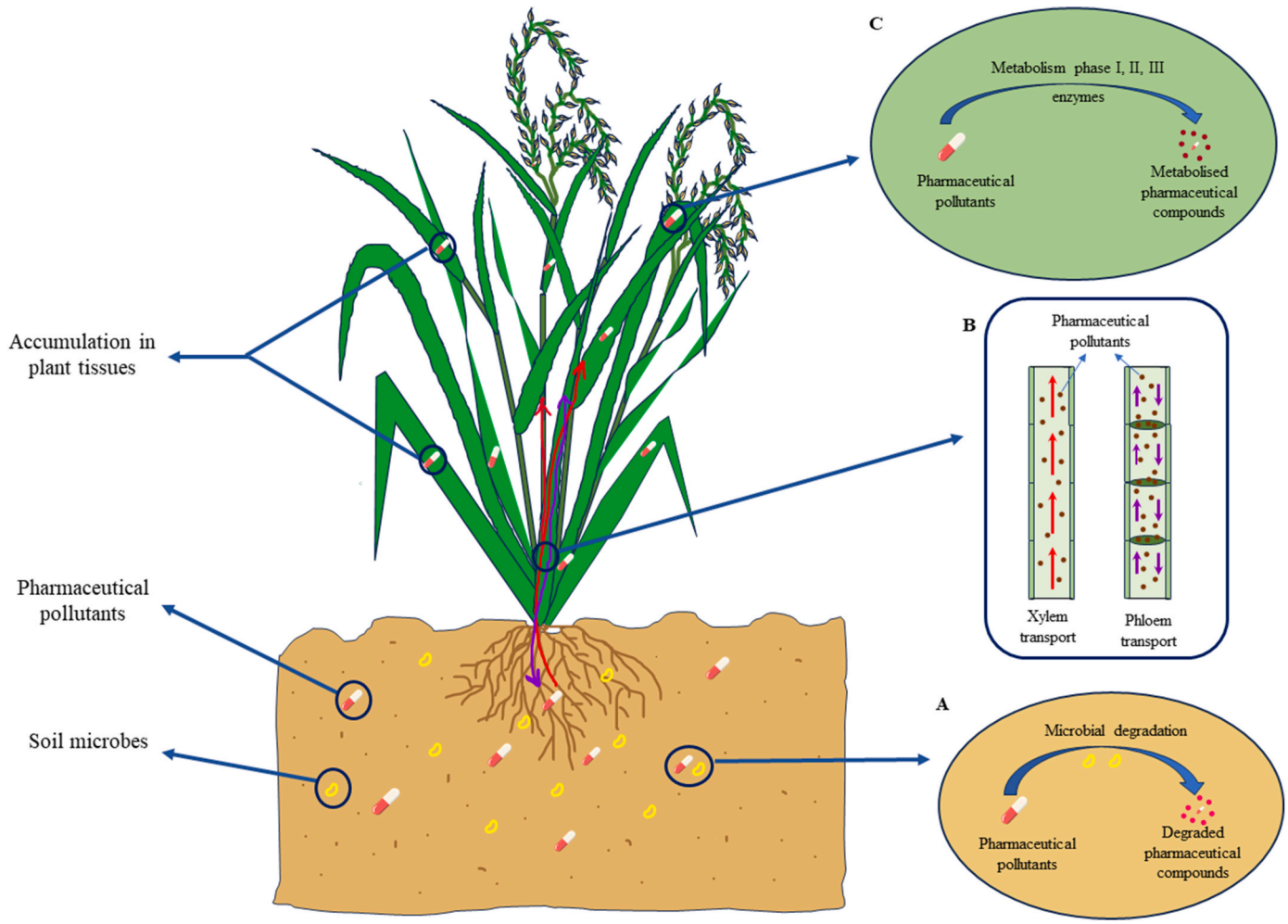


Fig. 2. Uptake and accumulation of pharmaceutical pollutants within plant tissues. In the soil, pharmaceutical pollutants are degraded by different microbes (A). The uptake pathways of pharmaceutical pollutants in plants involve the xylem and phloem transport (B). Within plant tissues, metabolic phase enzymes (I, II, III) transform pharmaceutical pollutants into different metabolized compounds (C).

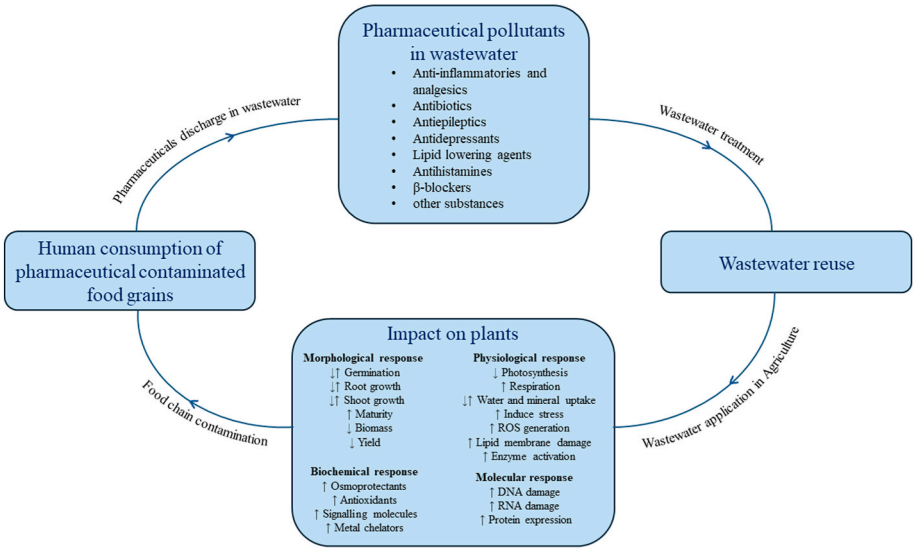


Fig. 3. Impact of pharmaceutical pollutants on plants and human food chain contamination from wastewater reuse in agriculture. Arrows indicate increase (↑) or decrease (↓) of respective traits in plants.

sometimes produce metabolites that are as toxic as or more toxic than the parent compounds (Coleman et al., 1997). A xenobiotic with a suitable functional group for phase II metabolism can be detoxified directly, skipping phase I (Coleman et al., 1997).

Conjugation with polar molecules occurs in phase II, converting pharmaceutical pollutants and/or their metabolites into more soluble compounds that are affixed to proteins, transporters, and enzymes (Pilon-Smits, 2005; Dietz and Schnoor, 2001). Phase II enzymes i.e., sulfotransferases (STs), glutathione-S-transferases (GST)s, and uridine diphosphate glycosyltransferases (UGTs), play a crucial role in detoxifying pharmaceuticals in plants by conjugating with biomolecules (Bartha et al., 2014). For example, in horseradish and *Typha latifolia*, diclofenac is mainly metabolized into glycosyl- and glutathionyl-conjugates (Huber et al., 2016; Bartha et al., 2014). In cucumber, phase II enzymes rapidly converts acetaminophen into GSH-acetaminophen through glutathione conjugation, reducing phytotoxicity (Sun et al., 2019). In contrast to phase I, which can generate phytotoxic metabolites, phase II produces compounds that are either nontoxic or less toxic than the original substance (Coleman et al., 1997). Therefore, in plants, phase II plays a vital protective role in the pharmaceutical detoxification process.

In phase III, conjugate metabolites are excreted from the cytoplasm as a result of the compounds' enhanced hydrophilicity by conjugation. These metabolites are then incorporated into plant vacuoles, cell wall components, or apoplast (Zheng and Guo, 2021; LeFevre et al., 2015). In a study by Macherius et al. (2012), the metabolism of triclocarban, triclosan, and methyl triclosan was investigated in carrot cell cultures and intact carrot plants. Triclocarban and methyl triclosan showed no metabolic changes in the cell cultures, while triclosan underwent fast metabolism, resulting in phase II conjugate metabolites. Furthermore, it was found that the overall amount of triclosan conjugates in whole carrot plants was five times greater than the amount of triclosan itself. In phase III, ATP-binding cassette (ABC) transporters actively transfer metabolites and conjugates produced during phase II, from the cytosol across membranes into the apoplast or vacuole, utilizing energy generated by ATP hydrolysis (Zheng and Guo, 2021; LeFevre et al., 2015; Davidson, 2007).

To date, the metabolic pathways and transformation products of only a few common pharmaceuticals have been thoroughly investigated within plants. This is due to the challenging nature of screening and identifying metabolites of pharmaceuticals within tissues. The difficulty arises from the limited structural information available for these products and interference from plant tissue matrices.

5.4. Plant responses to pharmaceuticals

Due to the bioactive nature of most pharmaceuticals and personal care products, their bioaccumulation and biotransformation in plants pose challenges to growth and development by altering plant physiology and key biochemical pathways (Sairam et al., 2023; Podlipná, 2022; Christou et al., 2018; Bartrons and Peñuelas, 2017). Exposure to pharmaceuticals can have direct impacts on seed germination, plant growth, and development. Physiological responses include inhibiting root activity, increasing reactive oxygen species (ROS), causing folic acid deficiency, elevating oxidative stress, inducing lipid peroxidation, and boosting glutathione content. Some of the reported impacts of pharmaceuticals on plants are highlighted in Table 4. These effects vary among plant species based on concentration and compound type. Root regions, being primary sites for pharmaceuticals, often exhibit more pronounced effects, compared to shoots (Madikizela et al., 2018; Sun et al., 2018; Amy-Sagers et al., 2017; Carvalho et al., 2014).

In the case of seed germination, effects of pharmaceuticals include delayed, accelerated or reduced germination rates. Mukhtar et al. (2020) reported the application of amoxicillin, ciprofloxacin, ofloxacin, levofloxacin, and ampicillin at 10 mg/L concentration resulted significant reduction in rice seed germination. Conversely, antibiotic ciprofloxacin at the rate of 0.2–2.0 mg/L enhanced germination in corn possibly by breaking dormancy (Gomes et al., 2019).

Interestingly, mammalian sex hormones at low doses have the capability to enhance plant functions (Agathokleous et al., 2018). Migliore et al. (2003) discovered that exposure to enrofloxacin had toxic effects at 5000 μg/L but exhibited hormesis at lower concentrations of 50 and 100 μg/L in *Cucumis sativus, Lactuca sativa*, *Phaseolus vulgaris* and *Raphanus sativus*. This was observed through significant alterations in root length, hypocotyl, cotyledons, and the number/length of leaves. A study by Carter et al. (2015) indicated that the uptake of carbamazepine and verapamil at concentrations ranging from 0.005 to 10 mg/kg led to notable changes in the concentrations of auxins, cytokinins, jasmonates, abscisic acid (ABA), and its glucose ester in zucchini leaves. These alterations could have significant effects on plant development because plant hormones play crucial roles in various plant growth processes and defence responses to both biotic and abiotic stressors.

Ciprofloxacin, an antibiotic, at concentrations equal to or exceeding 1.05 mg/L was found to impede electron flow through the respiratory electron transport chain (Gomes et al., 2017). This obstruction led to an over-production of reactive oxygen species (ROS), ultimately causing damage to the process of photosynthesis. Nutritional compositions can also be altered as result of plant exposure to pharmaceuticals. According to Mukhtar et al. (2020), treatment with ciprofloxacin, ofloxacin, levofloxacin, amoxicillin, and ampicillin at a concentration of 10 mg/kg resulted in reductions in the levels of phosphorus, iron, carbohydrates, and proteins in rice plants.

Additionally, pharmaceuticals have the potential to impact nitrogen fixation processes, secondary metabolism, and induce genotoxicity in plants. For example, Gomes et al. (2018) observed modifications in nitrogen fixation processes in the aquatic pteridophyte *Azolla* when exposed to ciprofloxacin at a concentration of 3.05 mg/L, leading to reduced photosynthetic and nitrogenase activities.

Therefore, plants show diverse responses to different class of pharmaceuticals they are exposed to. The findings mentioned above for plant exposure to pharmaceuticals studied much higher concentrations compared to environmentally relevant concentrations. Future research endeavours should prioritize the use of environmentally realistic exposure concentrations and comprehensive analysis of the complexity of phytotoxicity induced by individual as well as mixtures of pharmaceutical pollutants on plants.

6. Analytical methods for detection of pharmaceutical pollutants in plants

Analyzing pharmaceuticals in plant tissues poses additional challenges compared to examining water, soil, or sediment samples alone. This is because plant tissues contain pigments, fats, and waxy materials that can lead to significant matrix interferences. For precise and accurate analysis, sample preparations including pharmaceutical compound extraction and cleanup is essential. Key steps in pharmaceutical pollutants detection from plant samples involves sample preparation, data acquisition, analysis and interpretation (Fig. 4).

The investigation of plant uptake and metabolization of a specific pharmaceutical can be approached through targeted or untargeted analysis (Mlynek et al., 2021). In targeted analysis, specific metabolites are pre-selected for quantitation based on known plant metabolization pathways, studies on mammals or microbes, or in silico prediction tools (Kazmi et al., 2019). This method allows for optimized sample preparation and low quantitation limits, suitable for plants irrigated with reclaimed water (Mlynek et al., 2021; Kazmi et al., 2019).

In contrast, untargeted analysis aims to detect both known and unknown metabolites or transformed products using high-performance liquid chromatography coupled with high-resolution mass spectrometry (HPLC-HRMS) (Pezzatti et al., 2020; Gika et al., 2019; Nash and Dunn, 2019). Due to the focus on unknown metabolites, sample pretreatment cannot be fully optimized (Mlynek et al., 2021). While

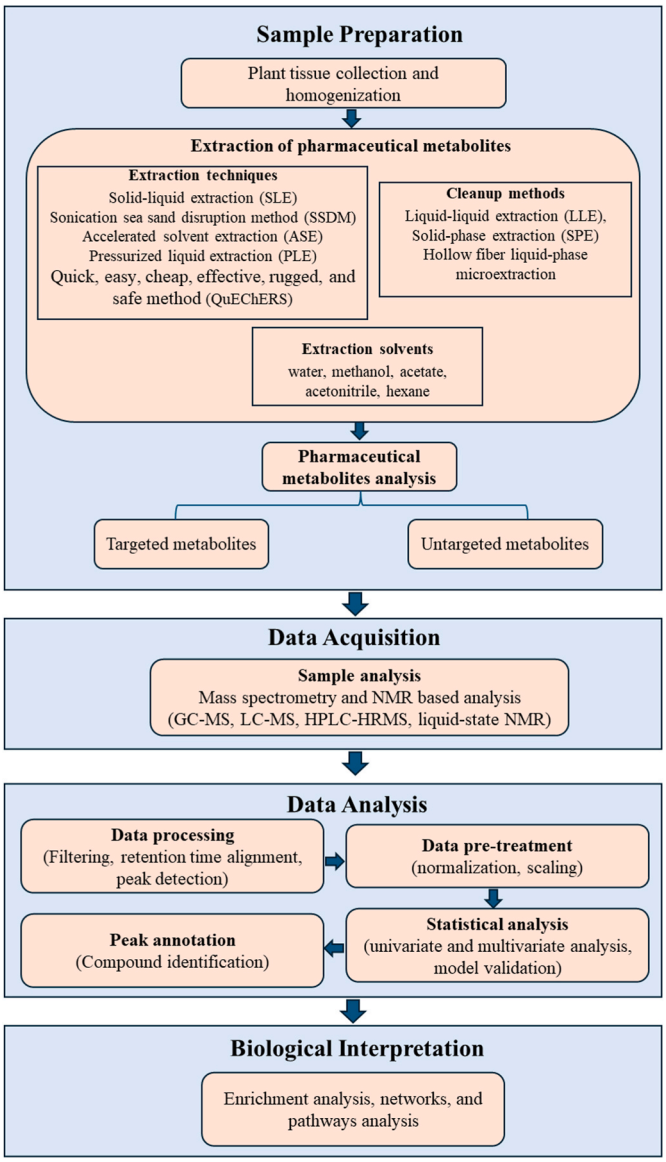


Fig. 4. Schematic workflow of targeted and non-targeted analysis of pharmaceutical metabolites in plant tissues.

untargeted metabolomics provides a broad overview of the metabolome and is invaluable for discovering new metabolites and biomarkers, it is often limited by the lack of specific standards for quantification and the challenges associated with metabolite identification (Dunn et al., 2013).

Multiple studies have employed diverse extracting methods, extraction solvents, cleanup techniques, and instrumental analyses to detect each group of pharmaceuticals (Miller et al., 2016b; Li, 2014; Malchi et al., 2014; Guasch et al., 2012; Jelic et al., 2011; Kümmerer, 2009b; Migliore et al., 2003; Liu et al., 2001). Extraction techniques utilized for extracting pharmaceuticals from plant tissues include solid-liquid extraction (SLE), sonication sea sand disruption method (SSDM), and accelerated solvent extraction (ASE) alternatively referred to as pressurized liquid extraction (PLE) or pressurized fluid extraction (PFE) (Fig. 4). Liquid chromatography (LC) combined with mass spectrometry (MS) stands out as the predominant instrument for analyzing various pharmaceuticals in plant tissue extraction (Kümmerer, 2009a). Additionally, some researchers have employed Gas Chromatography coupled with mass spectrometry (GC-MS) and Liquid Chromatography in conjunction with electrospray ionization (ESI), ultraviolet (UV), or fluorimeter for the analysis of pharmaceuticals. The mass spectrometry (MS) system commonly utilizes electrospray ionization (ESI) for better sensitivity, especially with certain pharmaceuticals like cyclophosphamide and ifosfamide (Kümmerer, 2009a).

Cleanup methods in extraction include liquid-liquid extraction (LLE), solid-phase extraction (SPE), and hollow fiber liquid-phase microextraction. A range of solvents including water, methanol, acetate, acetonitrile, hexane, and more are employed for extraction (Fig. 4). The diverse hydrophobicity of pharmaceuticals has led to the adoption of solid-phase extraction (SPE) as the preferred cleanup method. Hydrophilic–lipophilic-balanced (HLB) cartridges are commonly used in SPE to purify extracts of plant materials (Tanoue et al., 2012; Wu et al., 2012; Hu et al., 2010; Dolliver et al., 2007).

Instead of employing a conventional solvent extraction method, a modified QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) approach was utilized to extract parent drugs and their metabolites from plants (Riemenschneider et al., 2017a). This alternative method eliminates the need for solid-phase extraction (SPE) yet maintains effective limits of detection for both parent drugs and metabolites. Additionally, for ionic pharmaceuticals, ion-exchange SPE cartridges have been explored for sample cleanup (Emhofer et al., 2018; Riemenschneider et al., 2017a).

Coupled chromatography-MS systems enhance chemical analysis by providing both separation of mixtures and structural identification of individual components (Llewellyn et al., 2011). Another common technique employed for studying metabolic profile of a plant is the liquid-state nuclear magnetic resonance (NMR) spectroscopy which is a non-destructive method with low sensitivity and high reproducibility (Augustijn et al., 2021). Analyzing a diverse range of pharmaceuticals with different physicochemical properties can be challenging and also makes it difficult to achieve satisfactory recoveries for all compounds even with cleanup procedures. To address this, using isotope-labeled surrogates for each analyte or group is essential for accurate quantitative measurements. These surrogates compensate for analyte loss and potential interference during sample preparation and instrumental analysis by sharing similar physical and chemical properties with the analytes (Wu et al., 2012).

7. Conclusion and future remarks

The presence of pharmaceutical pollutants in water bodies represents a significant and complex challenge with implications for both human health and the environment. Reclaimed water obtained from treated wastewater or animal wastes used in agriculture poses a potential threat for pharmaceutical contamination in crop plants. The diverse physicochemical characteristics of these pollutants, their widespread occurrence, and potential impacts on different ecosystems highlight the urgency of addressing this issue. Uptake, accumulation, and enzymatic metabolism process of diverse pharmaceutical pollutants in plants are still unclear which has received more attention from research communities. Limited information is available on the toxicity and ultimate fate of transformation products resulting from the degradation of pharmaceuticals in plant tissues.

Recent studies have predicted exposure to individual pharmaceuticals in reclaimed water, but real-world scenarios likely involve multiple pharmaceuticals contaminating edible produce. There is a need for better prediction methods for simultaneous exposure to multiple pharmaceuticals. Current studies only measure extractable parent compounds, neglecting transformation products, conjugated compounds, and bound residues. While bound residues have reduced toxicity and are not bioavailable, conjugated compounds can be cleaved during metabolism and potentially exert biological effects. Thus, the health risks of these conjugated and transformed pharmaceuticals in plants need thorough evaluation. Additionally, field trials are essential for more accurate estimations of human exposure to pharmaceuticals through treated wastewater.

Accurate detection techniques, such as advanced analytical methods,

play a crucial role in identifying and quantifying pharmaceutical pollutants in plant tissues and water sources. However, continuous research and development of more sensitive and selective detection techniques are still needed to enhance monitoring capabilities and keep up with the emergence of new pharmaceutical pollutants. Comprehensive field-based data on pharmaceutical accumulation in plants, including crops, vegetables and fruit trees, is essential for accurately assessing human exposure through diet. Data from regions where treated wastewater are reused, will help analyze potential dietary risks and ensure safe adoption of these practices while protecting consumers. Also, due to the diversity of pharmaceuticals, it is important to develop a priority list of those with the highest plant uptake potential under realistic field conditions. This prioritization will focus research efforts, optimize investment in studies, and provide valuable information to guide future research.

Promoting greener practices in pharmaceutical manufacturing and encouraging the use of advanced wastewater treatment technologies are critical steps towards reducing the presence of pharmaceutical pollutants in water bodies. With proper treatment facilities and regulatory policies for wastewater reuse, the maximum potential of using wastewater as irrigation in agricultural field can be explored worldwide. Further research efforts should focus on identifying plant species that are efficient in removing a wide range of pharmaceuticals from contaminated water and studying the translocation of pollutants within plants for the development of sustainable phytoremediation strategies.

CRediT authorship contribution statement

Md Khaled Mosharaf: Writing – original draft, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Rachel L. Gomes:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Sarah Cook:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Mohammed S. Alam:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Amanda Rasmusssen:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Md Khaled Mosharaf reports financial support was provided by Commonwealth Scholarship Commission. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

The research reported here was funded by the Commonwealth Scholarship Commission and the Foreign, Commonwealth and Development Office in the UK. We are grateful for their support. All views expressed here are those of the authors not the funding body.

References

Adeel, M., Song, X., Wang, Y., Francis, D., Yang, Y., 2017. Environmental impact of estrogens on human, animal and plant life: a critical review. Environ. Int. 99, 107–119. https://doi.org/10.1016/j.envint.2016.12.010.

Adeel, M., Yang, Y.S., Wang, Y.Y., Song, X.M., Ahmad, M.A., Rogers, H.J., 2018. Uptake and transformation of steroid estrogens as emerging contaminants influence plant development. Environ. Pollut. 243, 1487–1497. https://doi.org/10.1016/j.envpol.2018.09.016.

Adhikari, S., Kumar, R., Driver, E.M., Bowes, D.A., Ng, K.T., Sosa-Hernandez, J.E., Oyervides-Muñoz, M.A., Melchor-Martínez, E.M., Martínez-Ruiz, M., Coronado-Apodaca, K.G., 2023. Occurrence of Z-drugs, benzodiazepines, and ketamine in wastewater in the United States and Mexico during the Covid-19 pandemic. Sci. Total Environ. 857, 159351 https://doi.org/10.1016/j.scitotenv.2022.159351.

Agathokleous, E., Kitao, M., Calabrese, E.J., 2018. Human and veterinary antibiotics induce hormesis in plants: scientific and regulatory issues and an environmental perspective. Environ. Int. 120, 489–495. https://doi.org/10.1016/j.envint.2018.08.035.

Ahmed, M.J., 2017. Adsorption of quinolone, tetracycline, and penicillin antibiotics from aqueous solution using activated carbons. Environ. Toxicol. Pharmacol. 50, 1–10. https://doi.org/10.1016/j.etap.2017.01.004.

Ait-Mouheb, N., Bahri, A., Thayer, B.B., Benyahia, B., Bourrié, G., Cherki, B., Condom, N., Declercq, R., Gunes, A., Héran, M., Kitir, N., Molle, B., Patureau, D., Pollice, A., Rapaport, A., Renault, P., Riahi, K., Romagny, B., Sari, T., Sinfort, C., Steyer, J.-P., Talozi, S., Topcuoglu, B., Turan, M., Wéry, N., Yıldırım, E., Harmand, J., 2018. The reuse of reclaimed water for irrigation around the Mediterranean Rim: a step towards a more virtuous cycle? Reg. Environ. Change 18, 693–705. https://doi.org/10.1007/s10113-018-1292-z.

Albaiges, J., Casado, F., Ventura, F., 1986. Organic indicators of groundwater pollution by a sanitary landfill. Water Res. 20, 1153–1159. https://doi.org/10.1016/0043-1354(86)90062-X.

Al-Farsi, R.S., Ahmed, M., Al-Busaidi, A., Choudri, B.S., 2017. Translocation of pharmaceuticals and personal care products (PPCPs) into plant tissues: a review. Emerging Contam. 3, 132–137. https://doi.org/10.1016/j.emcon.2018.02.001.

Al-Hammad, B.A., Abd El-Salam, M.M., Ibrahim, S.Y., 2014. Quality of wastewater reuse in agricultural irrigation and its impact on public health. Environ. Monitor. Aassess. 186, 7709–7718. https://doi.org/10.1007/s10661-014-3961-9.

Almazrouei, B., Islayem, D., Alskafi, F., Catacutan, M.K., Amna, R., Nasrat, S., Sizirici, B., Yildiz, I., 2023. Steroid hormones in wastewater: sources, treatments, environmental risks, and regulations. Emerging Contam. 9, 100210 https://doi.org/10.1016/j.emcon.2023.100210.

Almohisen, I.A., 2019. Effect of paracetamol on antioxidant system and osmoprotectants of mung bean (*Vigna radiata*). Appl. Ecol. Environ. Res. 17, 4297–4303. https://doi.org/10.15666/aeer/1702_42974303.

Al-Odaini, N.A., Zakaria, M.P., Yaziz, M.I., Surif, S., 2010. Multi-residue analytical method for human pharmaceuticals and synthetic hormones in river water and sewage effluents by solid-phase extraction and liquid chromatography–tandem mass spectrometry. J. Chromatogr. A 1217, 6791–6806. https://doi.org/10.1016/j.chroma.2010.08.033.

Al-Rifai, J.H., Gabelish, C.L., Schäfer, A.I., 2007. Occurrence of pharmaceutically active and non-steroidal estrogenic compounds in three different wastewater recycling schemes in Australia. Chemosphere 69, 803–815. https://doi.org/10.1016/j.chemosphere.2007.04.069.

Ammann, A.A., Macikova, P., Groh, K.J., Schirmer, K., Suter, M.J., 2014. LC-MS/MS determination of potential endocrine disruptors of cortico signalling in rivers and wastewaters. Anal. Bioanal. Chem. 406, 7653–7665. https://doi.org/10.1007/s00216-014-8206-9.

Amy-Sagers, C., Reinhardt, K., Larson, D.M., 2017. Ecotoxicological assessments show sucralose and fluoxetine affect the aquatic plant, *Lemna minor*. Aquat. Toxicol. 185, 76–85. https://doi.org/10.1016/j.aquatox.2017.01.008.

Andersen, H., Siegrist, H., Halling-Sørensen, B., Ternes, T.A., 2003. Fate of estrogens in a municipal sewage treatment plant. Environ. Sci. Technol. 37, 4021–4026. https://doi.org/10.1021/es026192a.

Andersen, T.G., Naseer, S., Ursache, R., Wybouw, B., Smet, W., De Rybel, B., Vermeer, J. E., Geldner, N., 2018. Diffusible repression of cytokinin signalling produces endodermal symmetry and passage cells. Nature 555, 529–533. https://doi.org/10.1038/nature25976.

Anjali, R., Shanthakumar, S., 2019. Insights on the current status of occurrence and removal of antibiotics in wastewater by advanced oxidation processes. J. Environ. Manag. 246, 51–62. https://doi.org/10.1016/j.jenvman.2019.05.090.

Antunes, E., Vuppaladadiyam, A.K., Sarmah, A.K., Varsha, S.S.V., Pant, K.K., Tiwari, B., Pandey, A., 2021. Chapter three - application of biochar for emerging contaminant mitigation. In: Sarmah, A.K. (Ed.), Advances in Chemical Pollution, Environmental Management and Protection. Elsevier, pp. 65–91. https://doi.org/10.1016/bs.apmp.2021.08.003.

Ashfaq, M., Khan, K.N., Rehman, M.S.U., Mustafa, G., Nazar, M.F., Sun, Q., Iqbal, J., Mulla, S.I., Yu, C.-P., 2017. Ecological risk assessment of pharmaceuticals in the receiving environment of pharmaceutical wastewater in Pakistan. Ecotoxical. Environ. Saf. 136, 31–39. https://doi.org/10.1016/j.ecoenv.2016.10.029.

Ashfaq, M., Li, Y., Wang, Y., Qin, D., Rehman, M.S.U., Rashid, A., Yu, C.-P., Sun, Q., 2018. Monitoring and mass balance analysis of endocrine disrupting compounds and their transformation products in an anaerobic-anoxic-oxic wastewater treatment system in Ciamen, China. Chemosphere 204, 170–177. https://doi.org/10.1016/j.chemosphere.2018.04.028.

Askey, H.E., Grayson, J.D., Tibbetts, J.D., Turner-Dore, J.C., Holmes, J.M., Kociok-Kohn, G., Wrigley, G.L., Cresswell, A.J., 2021. Photocatalytic hydroaminoalkylation of styrenes with unprotected primary alkylamines. J. Am. Chem. Soc. 143, 15936–15945. https://doi.org/10.1021/jacs.1c07401.

Augustijn, D., de Groot, H.J.M., Alia, A., 2021. HR-MAS NMR applications in plant metabolomics. Molecules 26, 931. https://doi.org/10.3390/molecules26040931.

aus der Beek, T., Weber, F.A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016. Pharmaceuticals in the environment—global occurrences and perspectives. Environ. Toxicol. Chem. 35, 823–835. https://doi.org/10.1002/etc.3339.

Babuponnusami, A., Sinha, S., Ashokan, H., Paul, M.V., Hariharan, S.P., Arun, J., Gopinath, K., Le, Q.H., Pugazhendhi, A., 2023. Advanced oxidation process (AOP) combined biological process for wastewater treatment: a review on advancements, feasibility and practicability of combined techniques. Environ. Res., 116944 https://doi.org/10.1016/j.envres.2023.116944.

Badar, Z., Shanableh, A., El-Keblawy, A., Mosa, K.A., Semerjian, L., Mutery, A.A., Hussain, M.I., Bhattacharjee, S., Tsombou, F.M., Ayyaril, S.S., 2022. Assessment of uptake, accumulation and degradation of paracetamol in spinach (*Spinacia oleracea* l.) under controlled laboratory conditions. Plants 11, 1626. https://doi.org/10.3390/plants11131626.

Bagheri, H., Afkhami, A., Noroozi, A., 2016. Removal of pharmaceutical compounds from hospital wastewaters using nanomaterials: a review. Anal. Bioanal. Chem. Res. 3, 1–18. https://doi.org/10.22036/abcr.2016.12655.

Bai, X., Lutz, A., Carroll, R., Keteles, K., Dahlin, K., Murphy, M., Nguyen, D., 2018. Occurrence, distribution, and seasonality of emerging contaminants in urban watersheds. Chemosphere 200, 133–142. https://doi.org/10.1016/j.chemosphere.2018.02.106.

Baker, D.R., Kasprzyk-Hordern, B., 2011. Multi-residue analysis of drugs of abuse in wastewater and surface water by solid-phase extraction and liquid chromatography–positive electrospray ionisation tandem mass spectrometry. J. Chromatogr. A 1218, 1620–1631. https://doi.org/10.1016/j.chroma.2011.01.060.

Baker, D.R., Kasprzyk-Hordern, B., 2013. Spatial and temporal occurrence of pharmaceuticals and illicit drugs in the aqueous environment and during wastewater treatment: new developments. Sci. Total Environ. 454, 442–456. https://doi.org/10.1016/j.scitotenv.2013.03.043.

Balakrishna, K., Rath, A., Praveenkumarreddy, Y., Guruge, K.S., Subedi, B., 2017. A review of the occurrence of pharmaceuticals and personal care products in Indian water bodies. Ecotoxical. Environ. Saf. 137, 113–120. https://doi.org/10.1016/j.ecoenv.2016.11.014.

Banzhaf, S., Krein, A., Scheytt, T., 2013. Using selected pharmaceutical compounds as indicators for surface water and groundwater interaction in the hyporheic zone of a low permeability riverbank. Hydrol. Process. 27, 2892–2902. https://doi.org/10.1002/hyp.9435.

Barnes, K.K., Kolpin, D.W., Furlong, E.T., Zaugg, S.D., Meyer, M.T., Barber, L.B., 2008. A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States—i) groundwater. Sci. Total Environ. 402, 192–200. https://doi.org/10.1016/j.scitotenv.2008.04.028.

Bartelt-Hunt, S.L., Snow, D.D., Kranz, W.L., Mader, T.L., Shapiro, C.A., Donk, S.J.v., Shelton, D.P., Tarkalson, D.D., Zhang, T.C., 2012. Effect of growth promotants on the occurrence of endogenous and synthetic steroid hormones on feedlot soils and in runoff from beef cattle feeding operations. Environ. Sci. Technol. 46, 1352–1360. https://doi.org/10.1021/es202680q.

Bartha, B., Huber, C., Schröder, P., 2014. Uptake and metabolism of diclofenac in *Typha latifolia*–how plants cope with human pharmaceutical pollution. Plant Sci. 227, 12–20. https://doi.org/10.1016/j.plantsci.2014.06.001.

Bartrons, M., Peñuelas, J., 2017. Pharmaceuticals and personal-care products in plants. Trends Plant Sci. 22, 194–203. https://doi.org/10.1016/j.tplants.2016.12.010.

Batt, A.L., Kim, S., Aga, D.S., 2007. Comparison of the occurrence of antibiotics in four full-scale wastewater treatment plants with varying designs and operations. Chemosphere 68, 428–435. https://doi.org/10.1016/j.chemosphere.2007.01.008.

Batt, A.L., Kincaid, T.M., Kostich, M.S., Lazorchak, J.M., Olsen, A.R., 2016. Evaluating the extent of pharmaceuticals in surface waters of the United States using a national-scale rivers and streams assessment survey. Environ. Toxicol. Chem. 35, 874–881. https://doi.org/10.1002/etc.3161.

Batt, A.L., Kostich, M.S., Lazorchak, J.M., 2008. Analysis of ecologically relevant pharmaceuticals in wastewater and surface water using selective solid-phase extraction and UPLC− MS/MS. Anal. Chem. 80, 5021–5030. https://doi.org/10.1021/ac800066n.

Bax, R.P., 1997. Antibiotic resistance: a view from the pharmaceutical industry. Clin. Infect. Dis. 24, S151–S153. https://doi.org/10.1093/clinids/24.Supplement_1.S151.

Bayen, S., Estrada, E.S., Juhel, G., Kit, L.W., Kelly, B.C., 2016. Pharmaceutically active compounds and endocrine disrupting chemicals in water, sediments and mollusks in mangrove ecosystems from Singapore. Mar. Pollut. Bull. 109, 716–722. https://doi.org/10.1016/j.marpolbul.2016.06.105.

Belhaj, D., Baccar, R., Jaabiri, I., Bouzid, J., Kallel, M., Ayadi, H., Zhou, J.L., 2015. Fate of selected estrogenic hormones in an urban sewage treatment plant in Tunisia (North Africa). Sci. Total Environ. 505, 154–160. https://doi.org/10.1016/j.scitotenv.2014.10.018.

Bhattacharya, B., Gupta, K., 1981. Steroid hormone effects on growth and apical dominance of sunflower. Phytochemistry (Elsevier) 20, 989–991. https://doi.org/10.1016/0031-9422(81)83014-2.

Bhatti, M.A., Almani, K.F., Mastoi, G.M., Qureshi, M.A., Qureshi, M.M., 2017. Physico-chemical study of effluents of pharmaceutical industries of Hyderabad division Sindh Pakistan. Int. J. Environ. Chem. 1, 28. https://doi.org/10.11648/j.ijec.20170102.12.

Biswas, P., Vellanki, B.P., 2021. Occurrence of emerging contaminants in highly anthropogenically influenced river Yamuna in India. Sci. Total Environ. 782, 146741 https://doi.org/10.1016/j.scitotenv.2021.146741.

Boleda, M.R., Galceran, M.T., Ventura, F., 2011. Behavior of pharmaceuticals and drugs of abuse in a drinking water treatment plant (DWTP) using combined conventional and ultrafiltration and reverse osmosis (UF/RO) treatments. Environ. Pollut. 159, 1584–1591. https://doi.org/10.1016/j.envpol.2011.02.051.

Bonner, J., Axtman, G., 1937. The growth of plant embryos in vitro. Preliminary experiments on the role of accessory substances. Proc. Natl. Acad. Sci. USA 23, 453–457. https://doi.org/10.1073/pnas.23.8.453.

Boogaerts, T., Degreef, M., Covaci, A., van Nuijs, A.L., 2019. Development and validation of an analytical procedure to detect spatio-temporal differences in antidepressant use through a wastewater-based approach. Talanta 200, 340–349. https://doi.org/10.1016/j.talanta.2019.03.052.

Bowlin, K.M., 2014. Effects of β-estradiol on Germination and Growth in *Zea mays* L. Department of Natural Sciences. Northwest Missouri State University Maryville, Missouri, USA. https://www.nwmissouri.edu/library/theses/2014/BowlinKelseyM.pdf.

Brown, G.S., 2006. The effects of estrogen on the growth and tuberization of potato plants (*Solanum tuberosum* cv. 'Iwa') grown in liquid tissue culture media. School of Biological Sciences. University of Canterbury, New Zealand. https://ir.canterbury.ac.nz/server/api/core/bitstreams/44ca29cd-378d-4432-a321-eb839df621a7/content.

Brown, K.D., Kulis, J., Thomson, B., Chapman, T.H., Mawhinney, D.B., 2006. Occurrence of antibiotics in hospital, residential, and dairy effluent, municipal wastewater, and the Rio Grande in New Mexico. Sci. Total Environ. 366, 772–783. https://doi.org/10.1016/j.scitotenv.2005.10.007.

Bu, Q., Shi, X., Yu, G., Huang, J., Wang, B., Wang, J., 2016. Pay attention to non-wastewater emission pathways of pharmaceuticals into environments. Chemosphere 165, 515–518. https://doi.org/10.1016/j.chemosphere.2016.09.078.

Cai, M.-Q., Wang, R., Feng, L., Zhang, L.-Q., 2015. Determination of selected pharmaceuticals in tap water and drinking water treatment plant by high-performance liquid chromatography-triple quadrupole mass spectrometer in Beijing, China. Environ. Sci. Pollut. Res. 22, 1854–1867. https://doi.org/10.1007/s11356-014-3473-8.

Caicedo, C., Rosenwinkel, K.H., Exner, M., Verstraete, W., Suchenwirth, R., Hartemann, P., Nogueira, R., 2019. *Legionella* occurrence in municipal and industrial wastewater treatment plants and risks of reclaimed wastewater reuse: review. Water Res. 149, 21–34. https://doi.org/10.1016/j.watres.2018.10.080.

Calderón, C.B., Sabundayo, B.P., 2007. Antimicrobial classifications: drugs for bugs. In: Schwalbe, R., Steele-Moore, L., Goodwin, A.C. (Eds.), Antimicrobial Susceptibility Testing Protocols. CRC Press. Taylor and Francis group.

Calderon-Preciado, D., Renault, Q., Matamoros, V., Canameras, N., Bayona, J.M., 2012. Uptake of organic emergent contaminants in spath and lettuce: an in vitro experiment. J. Agric. Food Chem. 60, 2000–2007. https://doi.org/10.1021/jf2046224.

Campos-Mañas, M.C., Ferrer, I., Thurman, E.M., Agüera, A., 2018. Opioid occurrence in environmental water samples—a review. Trends Environ. Anal. Chem. 20, e00059 https://doi.org/10.1016/j.teac.2018.e00059.

Campos-Mañas, M.C., Ferrer, I., Thurman, E.M., Pérez, J.A.S., Agüera, A., 2019. Identification of opioids in surface and wastewaters by LC/QTOF-MS using retrospective data analysis. Sci. Total Environ. 664, 874–884. https://doi.org/10.1016/j.scitotenv.2019.01.389.

Can, Z.S., Fırlak, M., Kerç, A., Evcimen, S., 2014. Evaluation of different wastewater treatment techniques in three WWTPs in Istanbul for the removal of selected EDCs in liquid phase. Environ. Monit. Assess. 186, 525–539. https://doi.org/10.1007/s10661-013-3397-7.

Cargouët, M., Perdiz, D., Mouatassim-Souali, A., Tamisier-Karolak, S., Levi, Y., 2004. Assessment of river contamination by estrogenic compounds in Paris area (France). Sci. Total Environ. 324, 55–66. https://doi.org/10.1016/j.scitotenv.2003.10.035.

Carter, L.J., Chefetz, B., Abdeen, Z., Boxall, A.B., 2019. Emerging investigator series: towards a framework for establishing the impacts of pharmaceuticals in wastewater irrigation systems on agro-ecosystems and human health. Environ. Sci.-Proc. Imp. 21, 605–622. https://doi.org/10.1039/c9em00020h.

Carter, L.J., Harris, E., Williams, M., Ryan, J.J., Kookana, R.S., Boxall, A.B.A., 2014. Fate and uptake of pharmaceuticals in soil–plant systems. J. Agric. Food Chem. 62, 816–825. https://doi.org/10.1021/jf404282y.

Carter, L.J., Williams, M., Böttcher, C., Kookana, R.S., 2015. Uptake of pharmaceuticals influences plant development and affects nutrient and hormone homeostases. Environ. Sci. Technol. 49, 12509–12518. https://doi.org/10.1021/acs.est.5b03468.

Carvalho, P.N., Basto, M.C.P., Almeida, C.M.R., Brix, H., 2014. A review of plant–pharmaceutical interactions: from uptake and effects in crop plants to phytoremediation in constructed wetlands. Environ. Sci. Pollut. Res. 21, 11729–11763. https://doi.org/10.1007/s11356-014-2550-3.

Castan, R., Chouard, P., 1937. Action of various hormones on the growth of plant seedlings and the development of their roots. C. R.. Soc. Biol. Paris 125, 751–754.

Castiglioni, S., Davoli, E., Riva, F., Palmiotto, M., Camporini, P., Manenti, A., Zuccato, E., 2018. Mass balance of emerging contaminants in the water cycle of a highly urbanized and industrialized area of Italy. Water Res. 131, 287–298. https://doi.org/10.1016/j.watres.2017.12.047.

Castiglioni, S., Zuccato, E., Chiabrando, C., Fanelli, R., Bagnati, R., 2008. Mass spectrometric analysis of illicit drugs in wastewater and surface water. Mass Spectrom. Rev. 27, 378–394. https://doi.org/10.1002/mas.20168.

Čelić, M., Insa, S., Škrbić, B., Petrović, M., 2017. Development of a sensitive and robust online dual column liquid chromatography-tandem mass spectrometry method for the analysis of natural and synthetic estrogens and their conjugates in river water and wastewater. Anal. Bioanal. Chem. 409, 5427–5440. https://doi.org/10.1007/s00216-017-0408-5.

Chacca, D.E.M., Maldonado, I., Vilca, F.Z., 2022. Environmental and ecotoxicological effects of drugs used for the treatment of COVID 19. Front. Environ. Sci. 10, 940975 https://doi.org/10.3389/fenvs.2022.940975.

Chang, H., Hu, J., Shao, B., 2007. Occurrence of natural and synthetic glucocorticoids in sewage treatment plants and receiving river waters. Environ. Sci. Technol. 41, 3462–3468. https://doi.org/10.1021/es062746o.

Chang, H., Wan, Y., Hu, J., 2009. Determination and source apportionment of five classes of steroid hormones in urban rivers. Environ. Sci. Technol. 43, 7691–7698. https://doi.org/10.1021/es803653j.

Chaoui, A., El Ferjani, E., 2013. B-estradiol protects embryo growth from heavy-metal toxicity in germinating lentil seeds. J. Plant Growth Regul. 32, 636–645. https://doi.org/10.1007/s00344-013-9332-x.

Chávez-Mejía, A.C., Magaña-López, R., Durán-Álvarez, J.C., Jiménez-Cisneros, B.E., 2019. The main removal mechanism of organic micropollutants and organisms in an irrigation system using untreated wastewater. Int. J. Environ. Agric. Biotech. 4, 436–443. https://doi.org/10.22161/ijeab/4.2.27.

Chelliapan, S., Wilby, T., Yuzir, A., Sallis, P.J., 2011. Influence of organic loading on the performance and microbial community structure of an anaerobic stage reactor treating pharmaceutical wastewater. Desalination 271, 257–264. https://doi.org/10.1016/j.desal.2010.12.045.

Chen, F., Ying, G.-G., Kong, L.-X., Wang, L., Zhao, J.-L., Zhou, L.-J., Zhang, L.-J., 2011. Distribution and accumulation of endocrine-disrupting chemicals and pharmaceuticals in wastewater irrigated soils in Hebei, China. Environ. Pollut. 159, 1490–1498. https://doi.org/10.1016/j.envpol.2011.03.016.

Chen, X., Li, Y., Jiang, L., Hu, B., Wang, L., An, S., Zhang, X., 2021. Uptake, accumulation, and translocation mechanisms of steroid estrogens in plants. Sci. Total Environ. 753, 141979 https://doi.org/10.1016/j.scitotenv.2020.141979.

Chen, X., Li, Y., Jiang, L., Jiang, X., Hu, B., Wang, L., Zhang, S., Zhang, X., 2022. Uptake and transport of steroid estrogens in soil-plant systems and their dissipation in rhizosphere: influence factors and mechanisms. J. Hazard Mater. 428, 128171 https://doi.org/10.1016/j.jhazmat.2021.128171.

Chen, Z., Wang, Y., Li, K., Zhou, H., 2014. Effects of increasing organic loading rate on performance and microbial community shift of an up-flow anaerobic sludge blanket reactor treating diluted pharmaceutical wastewater. J. Biosci. Bioeng. 118, 284–288. https://doi.org/10.1016/j.jbiosc.2014.02.027.

Chimchirian, R.F., Suri, R.P., Fu, H., 2007. Free synthetic and natural estrogen hormones in influent and effluent of three municipal wastewater treatment plants. Water Environ. Res. 79, 969–974. https://doi.org/10.2175/106143007X175843.

Christou, A., Michael, C., Fatta-Kassinos, D., Fotopoulos, V., 2018. Can the pharmaceutically active compounds released in agroecosystems be considered as emerging plant stressors? Environ. Int. 114, 360–364. https://doi.org/10.1016/j.envint.2018.03.003.

Christou, A., Papadavid, G., Dalias, P., Fotopoulos, V., Michael, C., Bayona, J.M., Piña, B., Fatta-Kassinos, D., 2019. Ranking of crop plants according to their potential to uptake and accumulate contaminants of emerging concern. Environ. Res. 170, 422–432. https://doi.org/10.1016/j.envres.2018.12.048.

Chuang, Y.-H., Liu, C.-H., Sallach, J.B., Hammerschmidt, R., Zhang, W., Boyd, S.A., Li, H., 2019. Mechanistic study on uptake and transport of pharmaceuticals in lettuce from water. Environ. Int. 131, 104976 https://doi.org/10.1016/j.envint.2019.104976.

Cirelli, G.L., Consoli, S., Licciardello, F., Aiello, R., Giuffrida, F., Leonardi, C., 2012. Treated municipal wastewater reuse in vegetable production. Agril. Water Manage. 104, 163–170. https://doi.org/10.1016/j.agwat.2011.12.011.

Cizmas, L., Sharma, V.K., Gray, C.M., McDonald, T.J., 2015. Pharmaceuticals and personal care products in waters: occurrence, toxicity, and risk. Environ. Chem. Lett. 13, 381–394, 0.1007/s10311-015-0524-4.

Cohen, Y., Kirchmann, H., 2004. Increasing the pH of wastewater to high levels with different gases—CO_2 stripping. Water, Air, Soil Pollut. 159, 265–275. https://doi.org/10.1023/b:wate.0000049185.69759.b0.

Coleman, J., Blake-Kalff, M., Davies, E., 1997. Detoxification of xenobiotics by plants: chemical modification and vacuolar compartmentation. Trends Plant Sci. 2, 144–151. https://doi.org/10.1016/S1360-1385(97)01019-4.

Collins, C., Fryer, M., Grosso, A., 2006. Plant uptake of non-ionic organic chemicals. Environ. Sci. Technol. 40, 45–52. https://doi.org/10.1021/es0508166.

Colon, B., Toor, G., 2016. A review of uptake and translocation of pharmaceuticals and personal care products by food crops irrigated with treated wastewater. Adv. Agron. 140, 75–100. https://doi.org/10.1021/es0508166.

Cortez, F.S., da Silva Souza, L., Guimarães, L.L., Pusceddu, F.H., Maranho, L.A., Fontes, M.K., Moreno, B.B., Nobre, C.R., de Souza Abessa, D.M., Cesar, A., 2019. Marine contamination and cytogenotoxic effects of fluoxetine in the tropical brown mussel *Perna perna*. Mar. Pollut. Bull. 141, 366–372. https://doi.org/10.1016/j.marpolbul.2019.02.065.

Cruz-Morató, C., Lucas, D., Llorca, M., Rodriguez-Mozaz, S., Gorga, M., Petrovic, M., Barceló, D., Vicent, T., Sarrà, M., Marco-Urrea, E., 2014. Hospital wastewater treatment by fungal bioreactor: removal efficiency for pharmaceuticals and endocrine disruptor compounds. Sci. Total Environ. 493, 365–376. https://doi.org/10.1016/j.scitotenv.2014.05.117.

Cui, H., Schröder, P., 2016. Uptake, translocation and possible biodegradation of the antidiabetic agent metformin by hydroponically grown *Typha latifolia*. J. Hazard Mater. 308, 355–361. https://doi.org/10.1016/j.jhazmat.2016.01.054.

Dalkmann, P., Siebe, C., Amelung, W., Schloter, M., Siemens, J., 2014. Does long-term irrigation with untreated wastewater accelerate the dissipation of pharmaceuticals in soil? Environ. Sci. Technol. 48, 4963–4970. https://doi.org/10.1021/es501180x.

Daouda, M.M.A., Hounkpè, S.P., Djihouessi, M.B., Akowanou, A.O., Aïna, M.P., Drogui, P., 2021. Physicochemical assessment of urban wastewater of Cotonou (Benin). Water Sci. Technol. 83, 1499–1510. https://doi.org/10.2166/wst.2021.073.

Dasenaki, M.E., Thomaidis, N.S., 2015. Multianalyte method for the determination of pharmaceuticals in wastewater samples using solid-phase extraction and liquid chromatography–tandem mass spectrometry. Anal. Bioanal. Chem. 407, 4229–4245. https://doi.org/10.1007/s00216-015-8654-x.

Davidson, A.L., 2007. Abc transporters: how small machines do a big job. Trends Microbiol. 15, 448–455. https://doi.org/10.1016/j.tim.2007.09.005.

Davoli, E., Zuccato, E., Castiglioni, S., 2019. Illicit drugs in drinking water. Curr. Opin. Environ. Sci. Health 7, 92–97. https://doi.org/10.1016/j.coesh.2018.12.004.

De La Torre, R., 2011. Analysis of endocrine disrupting compounds in wastewater treatment plants: a perspective of trans-boundary waterborne pollution. Environ. Technol. 29, 279–286. https://doi.org/10.1080/09593330802099452.

Deegan, A., Shaik, B., Nolan, K., Urell, K., Oelgemöller, M., Tobin, J., Morrissey, A., 2011. Treatment options for wastewater effluents from pharmaceutical companies. Int. J. Environ. Sci. Technol. 8, 649–666. https://doi.org/10.1007/BF03326250.

Delli Compagni, R., Scana, F., Turolla, A., Polesel, F., Vezzaro, L., Antonelli, M., 2020. Assessing the impact of water reuse strategies using an integrated modelling approach. Proc. SETAC 2020, 30th Annual European Meeting (Open Science for Enhance Global Environmental Protection), pp. 1–2.

Deng, Y., Eitzer, B., White, J.C., Xing, B., 2017. Impact of multiwall carbon nanotubes on the accumulation and distribution of carbamazepine in collard greens (*Brassica oleracea*). Environ. Sci.: Nano 4, 149–159. https://doi.org/10.1039/c6en00419a.

Dery, J.L., Rock, C.M., Goldstein, R.R., Onumajuru, C., Brassill, N., Zozaya, S., Suri, M.R., 2019. Understanding grower perceptions and attitudes on the use of nontraditional water sources, including reclaimed or recycled water, in the semiarid Southwest United States. Environ. Res. 170, 500–509. https://doi.org/10.1016/j.envres.2018.12.039.

Desgens-Martin, V., Keller, A.A., 2021. COVID-19 treatment agents: do they pose an environmental risk? ACS ES&T Water 1, 1555–1565. https://doi.org/10.1021/acsestwater.1c00059.

Di, L., Artursson, P., Avdeef, A., Ecker, G.F., Faller, B., Fischer, H., Houston, J.B., Kansy, M., Kerns, E.H., Krämer, S.D., 2012. Evidence-based approach to assess passive diffusion and carrier-mediated drug transport. Drug Discov. Today 17, 905–912, 0.1016/j.drudis.2012.03.015.

Diaz-Camal, N., Cardoso-Vera, J.D., Islas-Flores, H., Gómez-Oliván, L.M., Mejía-García, A., 2022. Consumption and ocurrence of antidepressants (SSRIs) in pre-and post-COVID-19 pandemic, their environmental impact and innovative removal methods: a review. Sci. Total Environ. 829, 154656 https://doi.org/10.1016/j.scitotenv.2022.154656.

Diaz-Sosa, V.R., Tapia-Salazar, M., Wanner, J., Cardenas-Chavez, D.L., 2020. Monitoring and ecotoxicity assessment of emerging contaminants in wastewater discharge in the city of Prague (Czech Republic). Water 12, 1079. https://doi.org/10.3390/w12041079.

Díaz-Torres, E., Gibson, R., González-Farías, F., Zarco-Arista, A., Mazari-Hiriart, M., 2013. Endocrine disruptors in the Xochimilco wetland, Mexico city. Water, Air, Soil Pollut. 224, 1–11. https://doi.org/10.1007/s11270-013-1586-1.

Dietz, A.C., Schnoor, J.L., 2001. Advances in phytoremediation. Environ. Health Perspect. 109, 163–168. https://doi.org/10.1289/ehp.01109s1163.

Dinh, Q.T., 2012. Transferts et comportements d'antibiotiques à l'échelle du bassin versant élémentaire. Doctoral dissertation, Paris 6.

Dolliver, H., Kumar, K., Gupta, S., 2007. Sulfamethazine uptake by plants from manure-amended soil. J. Environ. Qual. 36, 1224–1230. https://doi.org/10.2134/jeq2006.0266.

Dordio, A., Ferro, R., Teixeira, D., Palace, A.J., Pinto, A.P., Dias, C.M., 2011. Study on the use of *Typha* spp. for the phytotreatment of water contaminated with ibuprofen. Int. J. Environ. Anal. Chem. 91, 654–667. https://doi.org/10.1080/03067311003782708.

Dordio, A.V., Carvalho, A.J.P., 2013. Organic xenobiotics removal in constructed wetlands, with emphasis on the importance of the support matrix. J. Hazard Mater. 252, 272–292. https://doi.org/10.1016/j.jhazmat.2013.03.008.

Drechsel, P., Qadir, M., Baumann, J., 2022. Water reuse to free up freshwater for higher-value use and increase climate resilience and water productivity. Irrigat. Drain. 71, 100–109. https://doi.org/10.1002/ird.2694.

Du, P., Zhou, Z., Wang, Z., Xu, Z., Zheng, Q., Li, X., He, J., Li, X., Cheng, H., Thai, P.K., 2021. Analysing wastewater to estimate fentanyl and tramadol use in major Chinese cities. Sci. Total Environ. 795, 148838 https://doi.org/10.1002/adfm.202003619.

Dumlupinar, R., Genisel, M., Erdal, S., Korkut, T., Taspinar, M.S., Taskin, M., 2011. Effects of progesterone, β-estradiol, and androsterone on the changes of inorganic element content in barley leaves. Biol. Trace Elem. Res. 143, 1740–1745. https://doi.org/10.1007/s12011-011-8980-6.

Dunn, K.E., Barrett, F.S., Fingerhood, M., Bigelow, G.E., 2017. Opioid overdose history, risk behaviors, and knowledge in patients taking prescribed opioids for chronic pain. Pain Med. 18, 1505–1515. https://doi.org/10.1093/pm/pnw228. Malden, Mass.

Dunn, W.B., Erban, A., Weber, R.J., Creek, D.J., Brown, M., Breitling, R., Hankemeier, T., Goodacre, R., Neumann, S., Kopka, J., Viant, M.R., 2013. Mass appeal: metabolite identification in mass spectrometry-focused untargeted metabolomics. Metabolomics 9, 44–66. https://doi.org/10.1007/s11306-012-0434-4.

Durhan, E.J., Lambright, C.S., Makynen, E.A., Lazorchak, J., Hartig, P.C., Wilson, V.S., Gray, L.E., Ankley, G.T., 2006. Identification of metabolites of trenbolone acetate in androgenic runoff from a beef feedlot. Environ. Health Perspect. 114, 65–68. https://doi.org/10.1289/ehp.8055.

Ebele, A.J., Abou-Elwafa Abdallah, M., Harrad, S., 2017. Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. Emerging Contam. 3, 1–16. https://doi.org/10.1016/j.emcon.2016.12.004.

Elgallal, M., Fletcher, L., Evans, B., 2016. Assessment of potential risks associated with chemicals in wastewater used for irrigation in arid and semiarid zones: a review. Agric. Water Manag. 177, 419–431. https://doi.org/10.1016/j.agwat.2016.08.027.

Emhofer, L., Himmelsbach, M., Buchberger, W., Klampfl, C.W., 2018. Insights into the uptake, metabolization, and translocation of four non-steroidal anti-inflammatory drugs in cress (*Lepidium sativum*) by HPLC-MS^2. Electrophoresis 39, 1294–1300. https://doi.org/10.1002/elps.201700438.

Erdal, S., Dumlupinar, R., 2011. Mammalian sex hormones stimulate antioxidant system and enhance growth of chickpea plants. Acta Physiol. Plant. 33, 1011–1017. https://doi.org/10.1007/s11738-010-0634-3.

Estrada-Arriaga, E.B., Cortés-Muñoz, J.E., González-Herrera, A., Calderón-Mólgora, C.G., de Lourdes Rivera-Huerta, M., Ramírez-Camperos, E., Montellano-Palacios, L., Gelover-Santiago, S.L., Pérez-Castrejón, S., Cardoso-Vigueros, L., 2016. Assessment of full-scale biological nutrient removal systems upgraded with physico-chemical processes for the removal of emerging pollutants present in wastewaters from Mexico. Sci. Total Environ. 571, 1172–1182. https://doi.org/10.1016/j.scitotenv.2016.07.118.

Euler, V.H., 1946. Influence of saponin and digitalis glycosides on seed germination and mitosis. Action of colchicine and x-rays. Arkiv Kemi, Mineral. Geol. 22, 1–10.

European Commission, 2018. Water Is Too Precious to Waste. European Commission.

Fairbairn, D.J., Karpuzcu, M.E., Arnold, W.A., Barber, B.L., Kaufenberg, E.F., Koskinen, W.C., Novak, P.J., Rice, P.J., Swackhamer, D.L., 2016. Sources and transport of contaminants of emerging concern: a two-year study of occurrence and spatiotemporal variation in a mixed land use watershed. Sci. Total Environ. 551–552, 605–613. https://doi.org/10.1016/j.scitotenv.2016.02.056.

Fang, F., Yang, M.-M., Wang, H., Yan, P., Chen, Y.-P., Guo, J.-S., 2018. Effect of high salinity in wastewater on surface properties of anammox granular sludge. Chemosphere 210, 366–375. https://doi.org/10.1016/j.chemosphere.2018.07.038.

Fang, T.Y., Praveena, S.M., Aris, A.Z., Ismail, S.N.S., Rasdi, I., 2019. Quantification of selected steroid hormones (17β-Estradiol and 17α-Ethynylestradiol) in wastewater treatment plants in Klang Valley (Malaysia). Chemosphere 215, 153–162. https://doi.org/10.1016/j.chemosphere.2018.10.032.

Farounbi, A.I., Ngqwala, N.P., 2020. Occurrence of selected endocrine disrupting compounds in the eastern cape province of South Africa. Environ. Sci. Pollut. Res. 27, 17268–17279. https://doi.org/10.1007/s11356-020-08082-y.

Fatta-Kassinos, D., Kalavrouziotis, I.K., Koukoulakis, P.H., Vasquez, M., 2011. The risks associated with wastewater reuse and xenobiotics in the agroecological environment. Sci. Total Environ. 409, 3555–3563. https://doi.org/10.1016/j.scitotenv.2010.03.036.

Feng, L., van Hullebusch, E.D., Rodrigo, M.A., Esposito, G., Oturan, M.A., 2013. Removal of residual anti-inflammatory and analgesic pharmaceuticals from aqueous systems by electrochemical advanced oxidation processes: a review. Chem. Eng. J. 228, 944–964. https://doi.org/10.1016/j.cej.2013.05.061.

Fick, J., Lindberg, R., Kai, L., Brorstoem-Lundén, E., 2011. Results from the Swedish National Screening Programme 2010 2011. IVL Swedish Environmental Research Institute, Stockholm, Sweden.

Fick, J., Söderström, H., Lindberg, R.H., Phan, C., Tysklind, M., Larsson, D.G.J., 2009. Contamination of surface, ground, and drinking water from pharmaceutical production. Environ. Toxicol. Chem. 28, 2522–2527. https://doi.org/10.1897/09-073.1.

Fiedler, H., 1936. Entwicklungs-und reizphysiologische untersuchungen an kulturen isolierter wurzelspitzen. Z. Bot. 33, 369–416.

Fu, Q., Malchi, T., Carter, L.J., Li, H., Gan, J., Chefetz, B., 2019. Pharmaceutical and personal care products: from wastewater treatment into agro-food systems. Environ. Sci. Technol. 53, 14083–14090. https://doi.org/10.1021/acs.est.9b06206.

Furuichi, T., Kannan, K., Giesy, J.P., Masunaga, S., 2004. Contribution of known endocrine disrupting substances to the estrogenic activity in Tama River water samples from Japan using instrumental analysis and in vitro reporter gene assay. Water Res. 38, 4491–4501. https://doi.org/10.1016/j.watres.2004.08.007.

Gabet-Giraud, V., Miege, C., Choubert, J., Ruel, S.M., Coquery, M., 2010. Occurrence and removal of estrogens and beta blockers by various processes in wastewater treatment plants. Sci. Total Environ. 408, 4257–4269. https://doi.org/10.1016/j.scitotenv.2010.05.023.

Gadipelly, C., Pérez-González, A., Yadav, G.D., Ortiz, I., Ibáñez, R., Rathod, V.K., Marathe, K.V., 2014. Pharmaceutical industry wastewater: review of the technologies for water treatment and reuse. Ind. Eng. Chem. Res. 53, 11571–11592. https://doi.org/10.1021/ie501210j.

Gago-Ferrero, P., Gros, M., Ahrens, L., Wiberg, K., 2017. Impact of on-site, small and large scale wastewater treatment facilities on levels and fate of pharmaceuticals, personal care products, artificial sweeteners, pesticides, and perfluoroalkyl substances in recipient waters. Sci. Total Environ. 601, 1289–1297. https://doi.org/10.1016/j.scitotenv.2017.05.258.

Gall, H.E., Sassman, S.A., Lee, L.S., Jafvert, C.T., 2011. Hormone discharges from a midwest tile-drained agroecosystem receiving animal wastes. Environ. Sci. Technol. 45, 8755–8764. https://doi.org/10.1021/es2011435.

Garduño-Jiménez, A.-L., Durán-Álvarez, J.-C., Ortori, C.A., Abdelrazig, S., Barrett, D.A., Gomes, R.L., 2023. Delivering on sustainable development goals in wastewater reuse for agriculture: initial prioritization of emerging pollutants in the Tula Valley, Mexico. Water Res. 238, 119903 https://doi.org/10.1016/j.watres.2023.119903.

Gika, H., Virgiliou, C., Theodoridis, G., Plumb, R.S., Wilson, I.D., 2019. Untargeted LC/MS-based metabolic phenotyping (metabonomics/metabolomics): the state of the art. J. Chromatogr. B 1117, 136–147. https://doi.org/10.1016/j.jchromb.2019.04.009.

Gioelli, F., 1942. Die wirkung des follikelhormons (ostradiol, dihydrofollikulin) auf kulturen pflanzlicher gewebe in vitro. Arch. Sci. Biol. 28, 311–316.

Glineur, A., Barbera, B., Nott, K., Carbonnelle, P., Ronkart, S., Lognay, G., Tyteca, E., 2018. Trace analysis of estrogenic compounds in surface and groundwater by ultra high performance liquid chromatography-tandem mass spectrometry as pyridine-3-sulfonyl derivatives. J. Chromatogr. A 1534, 43–54. https://doi.org/10.1016/j.chroma.2017.12.042.

Göbel, A., McArdell, C.S., Suter, M.J.-F., Giger, W., 2004. Trace determination of macrolide and sulfonamide antimicrobials, a human sulfonamide metabolite, and trimethoprim in wastewater using liquid chromatography coupled to electrospray tandem mass spectrometry. Anal. Chem. 76, 4756–4764. https://doi.org/10.1021/ac0496603.

Goeury, K., Duy, S.V., Munoz, G., Prévost, M., Sauvé, S., 2022. Assessment of automated off-line solid-phase extraction LC-MS/MS to monitor EPA priority endocrine disruptors in tap water, surface water, and wastewater. Talanta 241, 123216. https://doi.org/10.1016/j.talanta.2022.123216.

Goh, S.X.L., Goh, H.A., Lee, H.K., 2018. Automation of ionic liquid enhanced membrane bag-assisted-liquid-phase microextraction with liquid chromatography-tandem mass spectrometry for determination of glucocorticoids in water. Anal. Chim. Acta 1035, 77–86. https://doi.org/10.1373/clinchem.2008.103846.

Golbaz, S., Zamanzadeh, M., Yaghmaeian, K., Nabizadeh, R., Rastkari, N., Esfahani, H., 2023. Occurrence and removal of psychiatric pharmaceuticals in the tehran south municipal wastewater treatment plant. Environ. Sci. Pollut. Res. 30, 27041–27055. https://doi.org/10.1007/s11356-022-23667-5.

Goldstein, M., Shenker, M., Chefetz, B., 2014. Insights into the uptake processes of wastewater-borne pharmaceuticals by vegetables. Environ. Sci. Technol. 48, 5593–5600. https://doi.org/10.1021/es5008615.

Gomathy, S., Sridharan, R., Kumar, P.S., Gayathri, K.V., Al Farraj, D.A., Chen, T.-W., 2021. Application of alkaline MnP immobilized Luffa fibers in mixed azo dyes degradation. Environ. Technol. Innov. 24, 101964 https://doi.org/10.1016/j.eti.2021.101964.

Gomes, M.P., de Brito, J.C.M., Carvalho Carneiro, M.M.L., Ribeiro da Cunha, M.R., Garcia, Q.S., Figueredo, C.C., 2018. Responses of the nitrogen-fixing aquatic fern *Azolla* to water contaminated with ciprofloxacin: impacts on biofertilization. Environ. Pollut. 232, 293–299. https://doi.org/10.1016/j.envpol.2017.09.054.

Gomes, M.P., Gonçalves, C.A., de Brito, J.C.M., Souza, A.M., da Silva Cruz, F.V., Bicalho, E.M., Figueredo, C.C., Garcia, Q.S., 2017. Ciprofloxacin induces oxidative stress in duckweed (*Lemna minor* L.): implications for energy metabolism and antibiotic-uptake ability. J. Hazard Mater. 328, 140–149. https://doi.org/10.1016/j.jhazmat.2017.01.005.

Gomes, M.P., Richardi, V.S., Bicalho, E.M., da Rocha, D.C., Navarro-Silva, M.A., Soffiatti, P., Garcia, Q.S., Sant'Anna-Santos, B.F., 2019. Effects of ciprofloxacin and roundup on seed germination and root development of maize. Sci. Total Environ. 651, 2671–2678. https://doi.org/10.1016/j.scitotenv.2018.09.365.

Gong, J., Lin, C., Xiong, X., Chen, D., Chen, Y., Zhou, Y., Wu, C., Du, Y., 2019. Occurrence, distribution, and potential risks of environmental corticosteroids in surface waters from the Pearl River Delta, South China. Environ. Pollut. 251, 102–109. https://doi.org/10.1016/j.envpol.2019.04.110.

González-Alonso, S., Merino, L.M., Esteban, S., López de Alda, M., Barceló, D., Durán, J. J., López-Martínez, J., Aceña, J., Pérez, S., Mastroianni, N., Silva, A., Catalá, M., Valcárcel, Y., 2017. Occurrence of pharmaceutical, recreational and psychotropic drug residues in surface water on the northern Antarctic Peninsula region. Environ. Pollut. 229, 241–254. https://doi.org/10.1016/j.envpol.2017.05.060.

González-González, R.B., Sharma, A., Parra-Saldívar, R., Ramirez-Mendoza, R.A., Bilal, M., Iqbal, H.M.N., 2022. Decontamination of emerging pharmaceutical pollutants using carbon-dots as robust materials. J. Hazard Mater. 423, 127145 https://doi.org/10.1016/j.jhazmat.2021.127145.

Goswami, P., Guruge, K.S., Tanoue, R., Tamamura, Y.A., Jinadasa, K., Nomiyama, K., Kunisue, T., Tanabe, S., 2022. Occurrence of pharmaceutically active compounds and potential ecological risks in wastewater from hospitals and receiving waters in Sri Lanka. Environ. Toxicol. Chem. 41, 298–311. https://doi.org/10.1002/etc.5212.

Gottschall, N., Topp, E., Metcalfe, C., Edwards, M., Payne, M., Kleywegt, S., Russell, P., Lapen, D., 2012. Pharmaceutical and personal care products in groundwater, subsurface drainage, soil, and wheat grain, following a high single application of municipal biosolids to a field. Chemosphere 87, 194–203. https://doi.org/10.1016/j.chemosphere.2011.12.018.

Gracia-Lor, E., Sancho, J.V., Serrano, R., Hernández, F., 2012. Occurrence and removal of pharmaceuticals in wastewater treatment plants at the Spanish Mediterranean area of Valencia. Chemosphere 87, 453–462. https://doi.org/10.1016/j.chemosphere.2011.12.025.

Grassi, M., Rizzo, L., Farina, A., 2013. Endocrine disruptors compounds, pharmaceuticals and personal care products in urban wastewater: implications for agricultural reuse and their removal by adsorption process. Environ. Sci. Pollut. Res. 20, 3616–3628. https://doi.org/10.1007/s11356-013-1636-7.

Gros, M., Rodríguez-Mozaz, S., Barceló, D., 2013. Rapid analysis of multiclass antibiotic residues and some of their metabolites in hospital, urban wastewater and river water by ultra-high-performance liquid chromatography coupled to quadrupole-linear ion trap tandem mass spectrometry. J. Chromatogr. A 1292, 173–188. https://doi.org/10.1016/j.chroma.2012.12.072.

Guan, M., Roddick, J.G., 1988. Epibrassinolide-inhibition of development of excised, adventitious and intact roots of tomato (*Lycopersicon esculentum*): comparison with the effects of steroidal estrogens. Physiol. Plantarum 74, 720–726. https://doi.org/10.1111/j.1399-3054.1988.tb02043.x.

Guasch, H., Ginebreda, A., Geiszinger, A., 2012. Emerging and Priority Pollutants in Rivers: Bringing Science into River Management Plans. Springer Science & Business Media. https://doi.org/10.1007/978-3-642-25722-3.

Guo, Z., Guo, A., Guo, Q., Rui, M., Zhao, Y., Zhang, H., Zhu, S., 2017. Decomposition of dexamethasone by gamma irradiation: kinetics, degradation mechanisms and impact on algae growth. Chem. Eng. J. 307, 722–728. https://doi.org/10.1016/j.cej.2016.08.138.

Gurke, R., Rößler, M., Marx, C., Diamond, S., Schubert, S., Oertel, R., Fauler, J., 2015. Occurrence and removal of frequently prescribed pharmaceuticals and corresponding metabolites in wastewater of a sewage treatment plant. Sci. Total Environ. 532, 762–770. https://doi.org/10.1016/j.scitotenv.2015.06.067.

Gworek, B., Kijeńska, M., Wrzosek, J., Graniewska, M., 2021. Pharmaceuticals in the soil and plant environment: a review. Water Air Soil Pollut. 232, 1–17. https://doi.org/10.1007/s11270-020-04954-8.

Hájková, M., Kummerová, M., 2014. Growth Response of *Lemna Minor* L. To Paracetamol. MendelNet, pp. 457–462, 2014.

Hammad, H.M., Zia, F., Bakhat, H.F., Fahad, S., Ashraf, M.R., Wilkerson, C.J., Shah, G. M., Nasim, W., Khosa, I., Shahid, M., 2018. Uptake and toxicological effects of pharmaceutical active compounds on maize. Agric. Ecosyst. Environ. 258, 143–148. https://doi.org/10.1016/j.agee.2018.02.022.

Hassani, G., Babaei, A., Takdastan, A., Shirmardi, M., Yousefian, F., Mohammadi, M., 2016. Occurrence and fate of 17β-Estradiol in water resources and wastewater in Ahvaz, Iran. Global Nest J 18, 855–866. https://doi.org/10.30955/gnj.002053.

Hellstrom, A., 2004. Uptake of Organic Pollutants in Plants. Department of Environment and Assessments, Swedish University of Agricultural Sciences, Uppsala.

Helmkamp, G., Bonner, J., 1953. Some relationships of sterols to plant growth. Plant Physiol. 28, 428–436. https://doi.org/10.1104/pp.28.3.428.

Helwig, K., Hunter, C., McNaughtan, M., Roberts, J., Pahl, O., 2016. Ranking prescribed pharmaceuticals in terms of environmental risk: inclusion of hospital data and the importance of regular review. Environ. Toxicol. Chem. 35, 1043–1050. https://doi.org/10.1002/etc.3302.

Herrero, P., Borrull, F., Pocurull, E., Marcé, R., 2012. Determination of glucocorticoids in sewage and river waters by ultra-high performance liquid chromatography–tandem mass spectrometry. J. Chromatogr. A 1224, 19–26. https://doi.org/10.1016/j.chroma.2011.12.054.

Hilton, M.J., Thomas, K.V., 2003. Determination of selected human pharmaceutical compounds in effluent and surface water samples by high-performance liquid chromatography–electrospray tandem mass spectrometry. J. Chromatogr. A 1015, 129–141. https://doi.org/10.1016/s0021-9673(03)01213-5.

Hohenblum, P., Gans, O., Moche, W., Scharf, S., Lorbeer, G., 2004. Monitoring of selected estrogenic hormones and industrial chemicals in groundwaters and surface waters in Austria. Sci. Total Environ. 333, 185–193. https://doi.org/10.1016/j.scitotenv.2004.05.009.

Holt-Giménez, E., Shattuck, A., Altieri, M., Herren, H., Gliessman, S., 2012. We Already Grow Enough Food for 10 Billion People… and Still Can't End Hunger. Taylor & Francis, pp. 595–598. https://doi.org/10.1080/10440046.2012.695331.

Hossain, A., Nakamichi, S., Habibullah-Al-Mamun, M., Tani, K., Masunaga, S., Matsuda, H., 2017. Occurrence, distribution, ecological and resistance risks of antibiotics in surface water of finfish and shellfish aquaculture in Bangladesh. Chemosphere 188, 329–336. https://doi.org/10.1016/j.chemosphere.2017.08.152.

Hossain, A., Nakamichi, S., Habibullah-Al-Mamun, M., Tani, K., Masunaga, S., Matsuda, H., 2018. Occurrence and ecological risk of pharmaceuticals in river surface water of Bangladesh. Environ. Res. 165, 258–266. https://doi.org/10.1016/j.envres.2018.04.030.

Hu, X., Zhou, Q., Luo, Y., 2010. Occurrence and source analysis of typical veterinary antibiotics in manure, soil, vegetables and groundwater from organic vegetable bases, Northern China. Environ. Pollut. 158, 2992–2998. https://doi.org/10.1016/j.envpol.2010.05.023.

Hu, Y., Yan, X., Shen, Y., Di, M., Wang, J., 2019. Occurrence, behavior and risk assessment of estrogens in surface water and sediments from Hanjiang River, Central China. Ecotoxicology 28, 143–153. https://doi.org/10.1007/s10646-018-2007-4.

Hubbard, L.E., Kolpin, D.W., Givens, C.E., Blackwell, B.R., Bradley, P.M., Gray, J.L., Lane, R.F., Masoner, J.R., McCleskey, R.B., Romanok, K.M., Sandstrom, M.W., Smalling, K.L., Villeneuve, D.L., 2022. Food, beverage, and feedstock processing facility wastewater: a unique and underappreciated source of contaminants to U.S. streams. Environ. Sci. Technol. 56, 1028–1040. https://doi.org/10.1021/acs.est.1c06821.

Huber, C., Preis, M., Harvey, P.J., Grosse, S., Letzel, T., Schröder, P., 2016. Emerging pollutants and plants – metabolic activation of diclofenac by peroxidases. Chemosphere 146, 435–441. https://doi.org/10.1016/j.chemosphere.2015.12.059.

Hughes, S.R., Kay, P., Brown, L.E., 2013. Global synthesis and critical evaluation of pharmaceutical data sets collected from river systems. Environ. Sci. Technol. 47, 661–677.

Hummel, D., Löffler, D., Fink, G., Ternes, T.A., 2006. Simultaneous determination of psychoactive drugs and their metabolites in aqueous matrices by liquid chromatography mass spectrometry. Environ. Sci. Technol. 40, 7321–7328. https://doi.org/10.1021/es061740w.

Ilyas, H., van Hullebusch, E.D., 2020. Performance comparison of different types of constructed wetlands for the removal of pharmaceuticals and their transformation products: a review. Environ. Sci. Pollut. Res. 27, 14342–14364. https://doi.org/10.1007/s11356-020-08165-w.

Islam, R., Yu, R.M.K., Andrew-Priestley, M., Smith, N., Rahman, M.M., Tran, T.K.A., O'Connor, W.A., MacFarlane, G.R., 2021. Secondary treatment phase of tertiary wastewater treatment works significantly reduces estrogenic load. Water Res. 200, 117257 https://doi.org/10.1016/j.envpol.2019.02.056.

Ismail, N.A.H., Wee, S.Y., Haron, D.E.M., Kamarulzaman, N.H., Aris, A.Z., 2020. Occurrence of endocrine disrupting compounds in mariculture sediment of Pulau Kukup, Johor, Malaysia. Mar. Pollut. Bull. 150, 110735 https://doi.org/10.1016/j.marpolbul.2019.110735.

James, O.O., Oluwaleye, S.E., Saka, K.L., Olabanji, D.J., 2014. Physico-chemical characteristics of pharmaceutical effluents from Sango industrial area, Nigeria. Bull. Environ. Pharmacol. Life Sci. 3, 78–82.

Janeczko, A., Filek, W., Biesaga-Kościelniak, J., Marcińska, I., Janeczko, Z., 2003. The influence of animal sex hormones on the induction of flowering in *Arabidopsis thaliana*: comparison with the effect of 24-epibrassinolide. Plant Cell Tissue Organ Cult. 72, 147–151. https://doi.org/10.1023/A:1022291718398.

Janex-Habibi, M.-L., Huyard, A., Esperanza, M., Bruchet, A., 2009. Reduction of endocrine disruptor emissions in the environment: the benefit of wastewater treatment. Water Res. 43, 1565–1576. https://doi.org/10.1016/j.watres.2008.12.051.

Jank, L., Hoff, R.B., Costa, F.J.d., Pizzolato, T.M., 2014. Simultaneous determination of eight antibiotics from distinct classes in surface and wastewater samples by solid-phase extraction and high-performance liquid chromatography–electrospray ionisation mass spectrometry. Int. J. Environ. Anal. Chem. 94, 1013–1037. https://doi.org/10.1080/03067319.2014.914184.

Jaramillo, M.F., Restrepo, I., 2017. Wastewater reuse in agriculture: a review about its limitations and benefits. Sustainability 9, 1734. https://doi.org/10.3390/su9101734.

Jayampathi, T., Atugoda, T., Jayasinghe, C., 2019. Uptake and accumulation of pharmaceuticals and personal care products in leafy vegetables. In: Pharmaceuticals and Personal Care Products: Waste Management and Treatment Technology. Butterworth-Heinemann, pp. 87–113. https://doi.org/10.1016/B978-0-12-816189-0.00004-4.

Jelic, A., Gros, M., Ginebreda, A., Cespedes-Sánchez, R., Ventura, F., Petrovic, M., Barcelo, D., 2011. Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment. Water Res. 45, 1165–1176. https://doi.org/10.1016/j.watres.2010.11.010.

Jia, A., Wu, S., Daniels, K.D., Snyder, S.A., 2016. Balancing the budget: accounting for glucocorticoid bioactivity and fate during water treatment. Environ. Sci. Technol. 50, 2870–2880. https://doi.org/10.1021/acs.est.5b04893.

Jiménez-Bambague, E.M., Madera-Parra, C.A., Ortiz-Escobar, A.C., Morales-Acosta, P.A., Peña-Salamanca, E.J., Machuca-Martínez, F., 2020. High-rate algal pond for removal of pharmaceutical compounds from urban domestic wastewater under tropical conditions. Case study: Santiago de Cali, Colombia. Water Sci. Technol. 82, 1031–1043. https://doi.org/10.2166/wst.2020.362.

Jones, E.R., Van Vliet, M.T., Qadir, M., Bierkens, M.F., 2021. Country-level and gridded estimates of wastewater production, collection, treatment and reuse. Earth Syst. Sci. Data 13, 237–254. https://doi.org/10.5194/essd-13-237-2021.

K'Oreje, K.O., Vergeynst, L., Ombaka, D., De Wispelaere, P., Okoth, M., Van Langenhove, H., Demeestere, K., 2016. Occurrence patterns of pharmaceutical residues in wastewater, surface water and groundwater of Nairobi and Kisumu city, Kenya. Chemosphere 149, 238–244. https://doi.org/10.1016/j.chemosphere.2016.01.095.

Kallenborn, R., Brorström-Lundén, E., Reiersen, L.-O., Wilson, S., 2018. Pharmaceuticals and personal care products (PPCPs) in arctic environments: indicator contaminants for assessing local and remote anthropogenic sources in a pristine ecosystem in change. Environ. Sci. Pollut. Res. 25, 33001–33013. https://doi.org/10.1007/s11356-017-9726-6.

Kamika, I., Azizi, S., Muleja, A.A., Selvarajan, R., El-Liethy, M.A., Mamba, B.B., Nkambule, T.T., 2021. The occurrence of opioid compounds in wastewater treatment plants and their receiving water bodies in Gauteng Province, South Africa. Environ. Pollut. 290, 118048 https://doi.org/10.1016/j.envpol.2021.118048.

Kar, S., Sanderson, H., Roy, K., Benfenati, E., Leszczynski, J., 2020. Ecotoxicological assessment of pharmaceuticals and personal care products using predictive toxicology approaches. Green Chem. 22, 1458–1516. https://doi.org/10.1039/c9gc03265g.

Karimi-Maleh, H., Ayati, A., Davoodi, R., Tanhaei, B., Karimi, F., Malekmohammadi, S., Orooji, Y., Fu, L., Sillanpää, M., 2021. Recent advances in using of chitosan-based adsorbents for removal of pharmaceutical contaminants: a review. J. Clean. Prod. 291, 125880 https://doi.org/10.1016/j.jclepro.2021.125880.

Kasprzyk-Hordern, B., Dinsdale, R.M., Guwy, A.J., 2008. The occurrence of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs in surface water in South Wales. UK. Water Res 42, 3498–3518. https://doi.org/10.1016/j.watres.2008.04.026.

Kasprzyk-Hordern, B., Dinsdale, R.M., Guwy, A.J., 2009. The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. Water Res. 43, 363–380. https://doi.org/10.1016/j.watres.2008.10.047.

Kazmi, S.R., Jun, R., Yu, M.S., Jung, C., Na, D., 2019. In silico approaches and tools for the prediction of drug metabolism and fate: a review. Comput. Biol. Med. 106, 54–64. https://doi.org/10.1016/j.compbiomed.2019.01.008.

Keerthanan, S., Jayasinghe, C., Biswas, J.K., Vithanage, M., 2021. Pharmaceutical and personal care products (PPCPs) in the environment: plant uptake, translocation, bioaccumulation, and human health risks. Crit. Rev. Environ. Sci. Technol. 51, 1221–1258. https://doi.org/10.1080/10643389.2020.1753634.

Kermet-Said, H., Moulai-Mostefa, N., 2015. Optimization of turbidity and cod removal from pharmaceutical wastewater by electrocoagulation. Isotherm modeling and cost analysis. Pol. J. Environ. Stud. 24 https://doi.org/10.15244/PJOES/32334.

Khan, B., Lee, L.S., 2012. Estrogens and synthetic androgens in manure slurry from trenbolone acetate/estradiol implanted cattle and in waste-receiving lagoons used for irrigation. Chemosphere 89, 1443–1449. https://doi.org/10.1016/j.chemosphere.2012.06.015.

Khan, G.A., Berglund, B., Khan, K.M., Lindgren, P.-E., Fick, J., 2013. Occurrence and abundance of antibiotics and resistance genes in rivers, canal and near drug formulation facilities–a study in Pakistan. PLoS One 8, e62712. https://doi.org/10.1371/journal.pone.0062712.

Khasawneh, O.F.S., Palaniandy, P., 2021. Occurrence and removal of pharmaceuticals in wastewater treatment plants. Process Saf. Environ. Protect. 150, 532–556. https://doi.org/10.1016/j.psep.2021.04.045.

Kidd, K.A., Blanchfield, P.J., Mills, K.H., Palace, V.P., Evans, R.E., Lazorchak, J.M., Flick, R.W., 2007. Collapse of a fish population after exposure to a synthetic

estrogen. Proc. Natl. Acad. Sci. U.S.A. 104, 8897–8901. https://doi.org/10.1073/pnas.0609568104.
Kim, J.I., Ciesielski, P.N., Donohoe, B.S., Chapple, C., Li, X., 2014. Chemically induced conditional rescue of the reduced epidermal fluorescence8 mutant of Arabidopsis reveals rapid restoration of growth and selective turnover of secondary metabolite pools. Plant Physiol. 164, 584–595. https://doi.org/10.1104/pp.113.229393.
Kim, S.D., Cho, J., Kim, I.S., Vanderford, B.J., Snyder, S.A., 2007. Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters. Water Res. 41, 1013–1021. https://doi.org/10.1016/j.watres.2006.06.034.
King, O.C., van de Merwe, J.P., McDonald, J.A., Leusch, F.D., 2016. Concentrations of levonorgestrel and ethinylestradiol in wastewater effluents: is the progestin also cause for concern? Environ. Toxicol. Chem. 35, 1378–1385. https://doi.org/10.1002/etc.3304.
Klatte, S., Schaefer, H.-C., Hempel, M., 2017. Pharmaceuticals in the environment – a short review on options to minimize the exposure of humans, animals and ecosystems. Sustain. Chem. Pharm. 5, 61–66. https://doi.org/10.1016/j.scp.2016.07.001.
Kleywegt, S., Pileggi, V., Yang, P., Hao, C., Zhao, X., Rocks, C., Thach, S., Cheung, P., Whitehead, B., 2011. Pharmaceuticals, hormones and bisphenol a in untreated source and finished drinking water in Ontario, Canada—occurrence and treatment efficiency. Sci. Total Environ. 409, 1481–1488. https://doi.org/10.1016/j.scitotenv.2011.01.010.
Knopp, G., Prasse, C., Ternes, T.A., Cornel, P., 2016. Elimination of micropollutants and transformation products from a wastewater treatment plant effluent through pilot scale ozonation followed by various activated carbon and biological filters. Water Res. 100, 580–592. https://doi.org/10.1016/j.watres.2016.04.069.
Kołecka, K., Gajewska, M., Cytawa, S., Stepnowski, P., Caban, M., 2020. Is sequential batch reactor an efficient technology to protect recipient against non-steroidal anti-inflammatory drugs and paracetamol in treated wastewater? Bioresour. Technol. 318, 124068 https://doi.org/10.1016/j.biortech.2020.124068.
Kolodziej, E.P., Sedlak, D.L., 2007. Rangeland grazing as a source of steroid hormones to surface waters. Environ. Sci. Technol. 41, 3514–3520. https://doi.org/10.1021/es063050y.
Kolok, A.S., Snow, D.D., Kohno, S., Sellin, M.K., Guillette Jr, L.J., 2007. Occurrence and biological effect of exogenous steroids in the Elkhorn River, Nebraska, USA. Sci. Total Environ. 388, 104–115. https://doi.org/10.1016/J.scitotenv.2007.08.001.
Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., Buxton, H.T., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in us streams, 1999− 2000: a national reconnaissance. Environ. Sci. Technol. 36, 1202–1211. https://doi.org/10.1021/es011055j.
Kondor, A.C., Jakab, G., Vancsik, A., Filep, T., Szeberényi, J., Szabó, L., Maász, G., Ferincz, Á., Dobosy, P., Szalai, Z., 2020. Dataset of pharmaceuticals in the Danube and related drinking water wells in the Budapest region. Data Brief 32, 106062. https://doi.org/10.1016/j.dib.2020.106062.
Kookana, R.S., Drechsel, P., Jamwal, P., Vanderzalm, J., 2020. Urbanisation and emerging economies: issues and potential solutions for water and food security. Sci. Total Environ. 732, 139057 https://doi.org/10.1016/j.scitotenv.2020.139057.
Kopcewicz, J., 1970a. Effect of estradiol-l7β, estrone and estriol on the endogenous auxins content in plants. Acta Soc. Bot. Pol. 39, 339–346. https://doi.org/10.5586/asbp.1970.026.
Kopcewicz, J., 1970b. Influence of estrogens on the auxins content in plants. Naturwissenschaften 57, 48. https://doi.org/10.1007/BF00593574.
Kopcewicz, J., 1971. Estrogens in developing bean (*Phaseolus vulgaris*) plants. Phytochemistry (Elsevier) 10, 1423–1427. https://doi.org/10.1016/0031-9422(71)85003-3.
Kovalakova, P., Cizmas, L., McDonald, T.J., Marsalek, B., Feng, M., Sharma, V.K., 2020. Occurrence and toxicity of antibiotics in the aquatic environment: a review. Chemosphere 251, 126351. https://doi.org/10.1016/j.chemosphere.2020.126351, 126351.
Kovalova, L., Siegrist, H., Singer, H., Wittmer, A., McArdell, C.S., 2012. Hospital wastewater treatment by membrane bioreactor: performance and efficiency for organic micropollutant elimination. Environ. Sci. Technol. 46, 1536–1545. https://doi.org/10.1021/es203495d.
Kudrna, J., Hnilicka, F., Kubes, J., Vachova, P., Hnilickova, H., Kuklova, M., 2020. Effect of acetaminophen (APAP) on physiological indicators in *Lactuca sativa*. Life 10, 303. https://doi.org/10.3390/life10110303.
Kumar, R., Sarmah, A.K., Padhye, L.P., 2019. Fate of pharmaceuticals and personal care products in a wastewater treatment plant with parallel secondary wastewater treatment train. J. Environ. Manag. 233, 649–659. https://doi.org/10.1016/j.jenvman.2018.12.062.
Kumar, V., Nakada, N., Yasojima, M., Yamashita, N., Johnson, A.C., Tanaka, H., 2011. The arrival and discharge of conjugated estrogens from a range of different sewage treatment plants in the UK. Chemosphere 82, 1124–1128. https://doi.org/10.1016/j.chemosphere.2010.11.040.
Kumari, M., Kumar, A., 2021. Can pharmaceutical drugs used to treat Covid-19 infection leads to human health risk? A hypothetical study to identify potential risk. Sci. Total Environ. 778, 146303 https://doi.org/10.1016/j.scitotenv.2021.146303.
Kümmerer, K., 2009a. Antibiotics in the aquatic environment–a review–part I. Chemosphere 75, 417–434. https://doi.org/10.1016/j.chemosphere.2008.11.086.
Kümmerer, K., 2009b. Antibiotics in the aquatic environment – a review – part II. Chemosphere 75, 435–441. https://doi.org/10.1016/j.chemosphere.2008.12.006.
Kümmerer, K., 2009c. The presence of pharmaceuticals in the environment due to human use – present knowledge and future challenges. J. Environ. Manag. 90, 2354–2366. https://doi.org/10.1016/j.jenvman.2009.01.023.
Kummerová, M., Zezulka, Š., Babula, P., Tříska, J., 2016. Possible ecological risk of two pharmaceuticals diclofenac and paracetamol demonstrated on a model plant *Lemna minor*. J. Hazard Mater. 302, 351–361. https://doi.org/10.1016/j.jhazmat.2015.09.057.
Laganà, A., Bacaloni, A., De Leva, I., Faberi, A., Fago, G., Marino, A., 2004. Analytical methodologies for determining the occurrence of endocrine disrupting chemicals in sewage treatment plants and natural waters. Anal. Chim. Acta 501, 79–88. https://doi.org/10.1016/j.aca.2003.09.020.
Lajeunesse, A., Smyth, S., Barclay, K., Sauvé, S., Gagnon, C., 2012. Distribution of antidepressant residues in wastewater and biosolids following different treatment processes by municipal wastewater treatment plants in Canada. Water Res. 46, 5600–5612. https://doi.org/10.1016/j.watres.2012.07.042.
Langenhoff, A., Inderfurth, N., Veuskens, T., Schraa, G., Blokland, M., Kujawa-Roeleveld, K., Rijnaarts, H., 2013. Microbial removal of the pharmaceutical compounds ibuprofen and diclofenac from wastewater. BioMed Res. Int. 2013, 325806 https://doi.org/10.1155/2013/325806.
Lapworth, D.J., Baran, N., Stuart, M.E., Ward, R.S., 2012. Emerging organic contaminants in groundwater: a review of sources, fate and occurrence. Environ. Pollut. 163, 287–303. https://doi.org/10.1016/j.envpol.2011.12.034.
Lee, C.M., Palaniandy, P., Dahlan, I., 2017. Pharmaceutical residues in aquatic environment and water remediation by TiO_2 heterogeneous photocatalysis: a review. Environ. Earth Sci. 76, 1–19. https://doi.org/10.1007/s12665-017-6924-y.
LeFevre, G.H., Müller, C.E., Li, R.J., Luthy, R.G., Sattely, E.S., 2015. Rapid phytotransformation of benzotriazole generates synthetic tryptophan and auxin analogs in *Arabidopsis*. Environ. Sci. Technol. 49, 10959–10968. https://doi.org/10.1021/acs.est.5b02749.
Lei, K., Lin, C.-Y., Zhu, Y., Chen, W., Pan, H.-Y., Sun, Z., Sweetman, A., Zhang, Q., He, M.-C., 2020. Estrogens in municipal wastewater and receiving waters in the Beijing-Tianjin-Hebei region, China: occurrence and risk assessment of mixtures. J. Hazard Mater. 389, 121891 https://doi.org/10.1016/j.jhazmat.2019.121891.
Leshem, Y., 1967. Physiological effects of animal steroid and gonadotropic hormones on curd cuttings of *Brassica oleracea* L var *cymosa*. Phyton 24, 25–29.
Li, B., Zhang, T., 2011. Mass flows and removal of antibiotics in two municipal wastewater treatment plants. Chemosphere 83, 1284–1289. https://doi.org/10.1016/j.chemosphere.2011.03.002.
Li, W.C., 2014. Occurrence, sources, and fate of pharmaceuticals in aquatic environment and soil. Environ. Pollut. 187, 193–201. https://doi.org/10.1016/j.envpol.2014.01.015.
Li, Y., Li, J., Zhao, W., Wang, Z., 2015. Review on irrigation technology applying sewage effluent-advances and prospects. Trans. Chin. Soc. Agric. Mach. 46, 102, 101.
Li, Y., Sallach, J.B., Zhang, W., Boyd, S.A., Li, H., 2019. Insight into the distribution of pharmaceuticals in soil-water-plant systems. Water Res. 152, 38–46. https://doi.org/10.1016/j.watres.2018.12.039.
Lin, K., Gan, J., 2011. Sorption and degradation of wastewater-associated non-steroidal anti-inflammatory drugs and antibiotics in soils. Chemosphere 83, 240–246. https://doi.org/10.1016/j.chemosphere.2010.12.083.
Lin, L., Yang, H., Xu, X., 2022. Effects of water pollution on human health and disease heterogeneity: a review. Front. Environ. Sci. 975 https://doi.org/10.3389/fenvs.2022.880246.
Lindberg, R.H., Wennberg, P., Johansson, M.I., Tysklind, M., Andersson, B.A., 2005. Screening of human antibiotic substances and determination of weekly mass flows in five sewage treatment plants in Sweden. Environ. Sci. Technol. 39, 3421–3429. https://doi.org/10.1021/es048143z.
Lindim, C., Van Gils, J., Georgieva, D., Mekenyan, O., Cousins, I.T., 2016. Evaluation of human pharmaceutical emissions and concentrations in Swedish river basins. Sci. Total Environ. 572, 508–519. https://doi.org/10.1016/j.scitotenv.2016.08.074.
Liu, F., Ying, G.-G., Tao, R., Zhao, J.-L., Yang, J.-F., Zhao, L.-F., 2009. Effects of six selected antibiotics on plant growth and soil microbial and enzymatic activities. Environ. Pollut. 157, 1636–1642. https://doi.org/10.1016/j.envpol.2008.12.021.
Liu, H., Lin, X., Xu, Y., Chen, S., Shi, J., Morisky, D., 2012. Emerging HIV epidemic among older adults in nanning, China. AIDS Patient Care STDS 26, 565–567. https://doi.org/10.1089/apc.2012.0227.
Liu, K.C., Racherla, U.S., 2019. Innovation, Economic Development, and Intellectual Property in India and China: Comparing Six Economic Sectors. Springer Singapore. https://doi.org/10.1007/978-981-13-8102-7.
Liu, Q., Wang, X., Yang, R., Yang, L., Sun, B., Zhu, L., 2019. Uptake kinetics, accumulation, and long-distance transport of organophosphate esters in plants: impacts of chemical and plant properties. Environ. Sci. Technol. 53, 4940–4947. https://doi.org/10.1021/acs.est.8b07189.
Liu, X., Lu, S., Guo, W., Xi, B., Wang, W., 2018. Antibiotics in the aquatic environments: a review of lakes. China. Sci. Total Environ. 627, 1195–1208. https://doi.org/10.1016/j.scitotenv.2018.01.271.
Liu, X.-Y., Yang, Q., Kamo, N., Miyake, J., 2001. Effect of liposome type and membrane fluidity on drug–membrane partitioning analyzed by immobilized liposome chromatography. J. Chromatogr. A 913, 123–131. https://doi.org/10.1016/S0021-9673(00)01266-8.
Llewellyn, N., Lloyd, P., Jürgens, M.D., Johnson, A.C., 2011. Determination of cyclophosphamide and ifosfamide in sewage effluent by stable isotope-dilution liquid chromatography–tandem mass spectrometry. J. Chromatogr. A 1218, 8519–8528. https://doi.org/10.1016/j.chroma.2011.09.061.
Loos, R., Carvalho, R., António, D.C., Comero, S., Locoro, G., Tavazzi, S., Paracchini, B., Ghiani, M., Lettieri, T., Blaha, L., 2013. EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. Water Res. 47, 6475–6487. https://doi.org/10.1016/j.watres.2013.08.024.
Lopez, B., Baran, N., Bourgine, B., 2015. An innovative procedure to assess multi-scale temporal trends in groundwater quality: example of the nitrate in the

Seine–Normandy basin, France. J. Hydrol. 522, 1–10. https://doi.org/10.1016/j.jhydrol.2014.12.002.
Löve, Á., Löve, D., 1945. Experiments on the effects of animal sex hormones on dioecious plants. Ark. Bot. 32A, 1–60.
Lozano, I., Pérez-Guzmán, C.J., Mora, A., Mahlknecht, J., Aguilar, C.L., Cervantes-Avilés, P., 2022. Pharmaceuticals and personal care products in water streams: occurrence, detection, and removal by electrochemical advanced oxidation processes. Sci. Total Environ. 827, 154348 https://doi.org/10.1016/j.scitotenv.2022.154348.
Lv, Y., Li, Y., Liu, X., Xu, K., 2021. Effect of soil sulfamethoxazole on strawberry (*Fragaria ananassa*): growth, health risks and silicon mitigation. Environ. Pollut. 286, 117321 https://doi.org/10.1016/j.envpol.2021.117321.
Lv, Y., Xu, J., Xu, K., Liu, X., Guo, X., Lu, S., Xi, B., 2020. Accumulation characteristics and biological response of ginger to sulfamethoxazole and ofloxacin. Environ. Pollut. 262, 114203 https://doi.org/10.1016/j.envpol.2020.114203.
Lyu, S., Chen, W., Zhang, W., Fan, Y., Jiao, W., 2016. Wastewater reclamation and reuse in China: opportunities and challenges. J. Environ. Sci. 39, 86–96. https://doi.org/10.1016/j.jes.2015.11.012.
Maasz, G., Molnar, E., Mayer, M., Kuzma, M., Takács, P., Zrinyi, Z., Pirger, Z., Kiss, T., 2021. Illicit drugs as a potential risk to the aquatic environment of a large freshwater lake after a major music festival. Environ. Toxicol. Chem. 40, 1491–1498. https://doi.org/10.1002/etc.4998.
Macherius, A., Eggen, T., Lorenz, W., Moeder, M., Ondruschka, J., Reemtsma, T., 2012. Metabolization of the bacteriostatic agent triclosan in edible plants and its consequences for plant uptake assessment. Environ. Sci. Technol. 46, 10797–10804. https://doi.org/10.1021/es3028378.
Macikova, P., Groh, K.J., Ammann, A.A., Schirmer, K., Suter, M.J.-F., 2014. Endocrine disrupting compounds affecting corticosteroid signaling pathways in Czech and Swiss waters: potential impact on fish. Environ. Sci. Technol. 48, 12902–12911. https://doi.org/10.1021/es502711c.
Mackuľak, T., Mosný, M., Škubák, J., Grabic, R., Birošová, L., 2015. Fate of psychoactive compounds in wastewater treatment plant and the possibility of their degradation using aquatic plants. Environ. Toxicol. Pharmacol. 39, 969–973. https://doi.org/10.1016/j.etap.2015.02.018.
Madikizela, L.M., Ncube, S., Chimuka, L., 2018. Uptake of pharmaceuticals by plants grown under hydroponic conditions and natural occurring plant species: a review. Sci. Total Environ. 636, 477–486. https://doi.org/10.1016/j.scitotenv.2018.04.297.
Madikizela, L.M., Tavengwa, N.T., Chimuka, L., 2017. Status of pharmaceuticals in African water bodies: occurrence, removal and analytical methods. J. Environ. Manag. 193, 211–220. https://doi.org/10.1016/j.jenvman.2017.02.022.
Majumder, A., Gupta, B., Gupta, A.K., 2019. Pharmaceutically active compounds in aqueous environment: a status, toxicity and insights of remediation. Environ. Res. 176, 108542 https://doi.org/10.1016/j.envres.2019.108542.
Malchi, T., Maor, Y., Tadmor, G., Shenker, M., Chefetz, B., 2014. Irrigation of root vegetables with treated wastewater: evaluating uptake of pharmaceuticals and the associated human health risks. Environ. Sci. Technol. 48, 9325–9333. https://doi.org/10.1021/es5017894.
Manallack, D.T., Prankerd, R.J., Yuriev, E., Oprea, T.I., Chalmers, D.K., 2013. The significance of acid/base properties in drug discovery. Chem. Soc. Rev. 42, 485–496. https://doi.org/10.1039/c2cs35348b.
Margot, J., Kienle, C., Magnet, A., Weil, M., Rossi, L., De Alencastro, L.F., Abegglen, C., Thonney, D., Chèvre, N., Schärer, M., 2013. Treatment of micropollutants in municipal wastewater: ozone or powdered activated carbon? Sci. Total Environ. 461, 480–498. https://doi.org/10.1016/j.scitotenv.2013.05.034.
Margot, J., Rossi, L., Barry, D.A., Holliger, C., 2015. A review of the fate of micropollutants in wastewater treatment plants. WIRES Water 2, 457–487. https://doi.org/10.1002/wat2.1090.
Masoner, J.R., Kolpin, D.W., Cozzarelli, I.M., Barber, L.B., Burden, D.S., Foreman, W.T., Forshay, K.J., Furlong, E.T., Groves, J.F., Hladik, M.L., Hopton, M.E., Jaeschke, J.B., Keefe, S.H., Krabbenhoft, D.P., Lowrance, R., Romanok, K.M., Rus, D.L., Selbig, W. R., Williams, B.H., Bradley, P.M., 2019. Urban stormwater: an overlooked pathway of extensive mixed contaminants to surface and groundwaters in the United States. Environ. Sci. Technol. 53, 10070–10081. https://doi.org/10.1021/acs.est.9b02867.
Masoner, J.R., Kolpin, D.W., Cozzarelli, I.M., Bradley, P.M., Arnall, B.B., Forshay, K.J., Gray, J.L., Groves, J.F., Hladik, M.L., Hubbard, L.E., Iwanowicz, L.R., Jaeschke, J.B., Lane, R.F., McCleskey, B.R., Polite, B.F., Roth, D.A., Pettijon, M.B., Wilson, M.C., 2023. Contaminant exposure and transport from three potential re-use waters within a single watershed. Environ. Sci. Technol. 57, 1353–1365. https://doi.org/10.1021/acs.est.2c07372.
Masoner, J.R., Kolpin, D.W., Furlong, E.T., Cozzarelli, I.M., Gray, J.L., 2016. Landfill leachate as a mirror of today's disposable society: pharmaceuticals and other contaminants of emerging concern in final leachate from landfills in the conterminous United States. Environ. Toxicol. Chem. 35, 906–918. https://doi.org/10.1002/etc.3219.
Matamoros, V., Calderón-Preciado, D., Domínguez, C., Bayona, J.M., 2012. Analytical procedures for the determination of emerging organic contaminants in plant material: a review. Anal. Chim. Acta 722, 8–20. https://doi.org/10.1016/j.aca.2012.02.004.
Mathenge, S.G., Wanjau, R.N., Kenji, G.M., 2017. Trimethoprim and sulfamethoxazole residues in untreated wastewater used for irrigation in peri-urban farms in Nairobi County, Kenya. Nat. Environ. Pollut. Technol. 16, 989–994.
McClure, E.L., Wong, C.S., 2007. Solid phase microextraction of macrolide, trimethoprim, and sulfonamide antibiotics in wastewaters. J. Chromatogr. A 1169, 53–62. https://doi.org/10.1016/j.chroma.2007.08.062.
Merlo, F., Speltini, A., Maraschi, F., Sturini, M., Profumo, A., 2020. HPLC-MS/MS multiclass determination of steroid hormones in environmental waters after preconcentration on the carbonaceous sorbent HA-C@ silica. Arab. J. Chem. 13, 4673–4680. https://doi.org/10.1016/j.arabjc.2019.10.009.
Meshram, N., Harane, S., Kale, V., Biyani, D., Umekar, M.J., 2023. Regulatory overview on new drugs and clinical trials rules, 2019. Int. J. Drug Regul. Aff. 11, 31–42. https://doi.org/10.22270/ijdra.v11i1.578.
Meyer, M.F., Powers, S.M., Hampton, S.E., 2019. An evidence synthesis of pharmaceuticals and personal care products (PPCPs) in the environment: imbalances among compounds, sewage treatment techniques, and ecosystem types. Environ. Sci. Technol. 53, 12961–12973. https://doi.org/10.1021/acs.est.9b02966.
Mhuka, V., Dube, S., Nindi, M.M., 2020. Occurrence of pharmaceutical and personal care products (PPCPs) in wastewater and receiving waters in South Africa using LC-orbitrap™ MS. Emerging Contam. 6, 250–258. https://doi.org/10.1016/j.emcon.2020.07.002.
Migliore, L., Cozzolino, S., Fiori, M., 2003. Phytotoxicity to and uptake of enrofloxacin in crop plants. Chemosphere 52, 1233–1244. https://doi.org/10.1016/S0045-6535(03)00272-8.
Miller, E.L., Nason, S.L., Karthikeyan, K., Pedersen, J.A., 2016a. Root uptake of pharmaceuticals and personal care product ingredients. Environ. Sci. Technol. 50, 525–541. https://doi.org/10.1021/acs.est.5b01546.
Miller, E.L., Nason, S.L., Karthikeyan, K.G., Pedersen, J.A., 2016b. Root uptake of pharmaceuticals and personal care product ingredients. Environ. Sci. Technol. 50, 525–541. https://doi.org/10.1021/acs.est.5b01546.
Minh, T.B., Leung, H.W., Loi, I.H., Chan, W.H., So, M.K., Mao, J.Q., Choi, D., Lam, J.C. W., Zheng, G., Martin, M., Lee, J.H.W., Lam, P.K.S., Richardson, B.J., 2009. Antibiotics in the Hong Kong metropolitan area: ubiquitous distribution and fate in Victoria Harbour. Mar. Pollut. Bull. 58, 1052–1062. https://doi.org/10.1016/j.marpolbul.2009.02.004.
Mlynek, F., Himmelsbach, M., Buchberger, W., Klampfl, C.W., 2021. Analytical approaches for the determination and identification of drug metabolites in plants after uptake. Interaction and Fate of Pharmaceuticals in Soil-Crop Systems: the Impact of Reclaimed Wastewater, pp. 493–523. https://doi.org/10.1007/698_2020_629.
Mohapatra, D.P., Brar, S.K., Tyagi, R.D., Picard, P., Surampalli, R.Y., 2014. Analysis and advanced oxidation treatment of a persistent pharmaceutical compound in wastewater and wastewater sludge-carbamazepine. Sci. Total Environ. 470, 58–75. https://doi.org/10.1016/j.scitotenv.2013.09.034.
Mompelat, S., Le Bot, B., Thomas, O., 2009. Occurrence and fate of pharmaceutical products and by-products, from resource to drinking water. Environ. Int. 35, 803–814. https://doi.org/10.1016/j.envint.2008.10.008.
Moreno-González, R., Rodríguez-Mozaz, S., Gros, M., Pérez-Cánovas, E., Barceló, D., León, V.M., 2014. Input of pharmaceuticals through coastal surface watercourses into a Mediterranean lagoon (Mar Menor, SE Spain): sources and seasonal variations. Sci. Total Environ. 490, 59–72. https://doi.org/10.1016/j.scitotenv.2014.04.097.
Morsi, R., Bilal, M., Iqbal, H.M., Ashraf, S.S., 2020. Laccases and peroxidases: the smart, greener and futuristic biocatalytic tools to mitigate recalcitrant emerging pollutants. Sci. Total Environ. 714, 136572 https://doi.org/10.1016/j.scitotenv.2020.136572.
Msigala, S.C., Mabiki, F.P., Styrishave, B., Mdegela, R.H., 2017. Pollution by endocrine disrupting estrogens in aquatic ecosystems in Morogoro urban and peri-urban areas in Tanzania. Afr. J. Environ. Sci. Technol. 11, 122–131. https://doi.org/10.5897/AJEST2016.2234.
Mukhtar, A., Manzoor, M., Gul, I., Zafar, R., Jamil, H.I., Niazi, A.K., Ali, M.A., Park, T.J., Arshad, M., 2020. Phytotoxicity of different antibiotics to rice and stress alleviation upon application of organic amendments. Chemosphere 258, 127353. https://doi.org/10.1016/j.chemosphere.2020.127353.
Mullai, P., Vishali, S., 2007. Biodegradation of penicillin-G wastewater using *Phanerochate chrysosporium*–an equilibrium and kinetic modeling. Afr. J. Biotechnol. 6, 1450–1454. https://doi.org/10.4314/AJB.V6I12.57570.
Mutuku, C., Gazdag, Z., Melegh, S., 2022. Occurrence of antibiotics and bacterial resistance genes in wastewater: resistance mechanisms and antimicrobial resistance control approaches. World J. Microbiol. Biotechnol. 38, 152. https://doi.org/10.1007/s11274-022-03334-0.
Nash, W.J., Dunn, W.B., 2019. From mass to metabolite in human untargeted metabolomics: recent advances in annotation of metabolites applying liquid chromatography-mass spectrometry data. TrAC, Trends Anal. Chem. 120, 115324 https://doi.org/10.1016/j.trac.2018.11.022.
Nayana, R.K., Nakkeeran, S., Saranya, N., Saravanan, R., Mahendra, K., Ashraf, S., Perveen, K., Alshaikh, N.A., Sayyed, R.Z., Show, P.L., 2023. Triamcinolone acetonide produced by *Bacillus velezensis* YEBBR6 exerts antagonistic activity against *Fusarium oxysporum* f. sp. *Cubense*: a computational analysis. Mol. Biotechnol. 1–19 https://doi.org/10.1007/s12033-023-00797-w.
Ng, K.K., Shi, X., Tang, M.K.Y., Ng, H.Y., 2014. A novel application of anaerobic bio-entrapped membrane reactor for the treatment of chemical synthesis-based pharmaceutical wastewater. Sep. Purif. Technol. 132, 634–643. https://doi.org/10.1016/j.seppur.2014.06.021.
Ng, K.T., Rapp-Wright, H., Egli, M., Hartmann, A., Steele, J.C., Sosa-Hernández, J.E., Melchor-Martínez, E.M., Jacobs, M., White, B., Regan, F., 2020. High-throughput multi-residue quantification of contaminants of emerging concern in wastewaters enabled using direct injection liquid chromatography-tandem mass spectrometry. J. Hazard Mater. 398, 122933 https://doi.org/10.1016/j.jhazmat.2020.122933.
Nguyen, M.-K., Lin, C., Nguyen, H.-L., Hung, N.T.Q., La, D.D., Nguyen, X.H., Chang, S.W., Chung, W.J., Nguyen, D.D., 2023. Occurrence, fate, and potential risk of pharmaceutical pollutants in agriculture: challenges and environmentally friendly solutions. Sci. Total Environ. 899, 165323 https://doi.org/10.1016/j.scitotenv.2023.165323.
Niemi, L., Taggart, M., Boyd, K., Zhang, Z., Gaffney, P.P., Pfleger, S., Gibb, S., 2020. Assessing hospital impact on pharmaceutical levels in a rural 'source-to-sink' water

system. Sci. Total Environ. 737, 139618 https://doi.org/10.1016/j.scitotenv.2020.139618.
Nikolaou, A., Meric, S., Fatta, D., 2007. Occurrence patterns of pharmaceuticals in water and wastewater environments. Anal. Bioanal. Chem. 387, 1225–1234. https://doi.org/10.1007/s00216-006-1035-8.
Noguera-Oviedo, K., Aga, D.S., 2016. Lessons learned from more than two decades of research on emerging contaminants in the environment. J. Hazard Mater. 316, 242–251. https://doi.org/10.1016/j.jhazmat.2016.04.058.
Nunes, C.N., Pauluk, L.E., Dos Anjos, V.E., Lopes, M.C., Quináia, S.P., 2015. New approach to the determination of contaminants of emerging concern in natural water: study of alprazolam employing adsorptive cathodic stripping voltammetry. Anal. Bioanal. Chem. 407, 6171–6179. https://doi.org/10.1007/s00216-015-8792-1.
O'Connor, G.A., 1996. Organic compounds in sludge-amended soils and their potential for uptake by crop plants. Sci. Total Environ. 185, 71–81. https://doi.org/10.1016/0048-9697(95)05043-4.
O'Flynn, D., Lawler, J., Yusuf, A., Parle-McDermott, A., Harold, D., Mc Cloughlin, T., Holland, L., Regan, F., White, B., 2021. A review of pharmaceutical occurrence and pathways in the aquatic environment in the context of a changing climate and the COVID-19 pandemic. Anal. Methods 13, 575–594. https://doi.org/10.1039/d0ay02098b.
Okuda, T., Kobayashi, Y., Nagao, R., Yamashita, N., Tanaka, H., Tanaka, S., Fujii, S., Konishi, C., Houwa, I., 2008. Removal efficiency of 66 pharmaceuticals during wastewater treatment process in Japan. Water Sci. Technol. 57, 65–71. https://doi.org/10.2166/wst.2008.822.
Olatunji, O.S., Fatoki, O.S., Opeolu, B.O., Ximba, B.J., Chitongo, R., 2017. Determination of selected steroid hormones in some surface water around animal farms in Cape Town using HPLC-DAD. Environ. Monit. Assess. 189, 1–10. https://doi.org/10.1007/s10661-017-6070-8.
Osuoha, J.O., Anyanwu, B.O., Ejileugha, C., 2023. Pharmaceuticals and personal care products as emerging contaminants: need for combined treatment strategy. J. Hazard. Mater. Adv. 9, 100206 https://doi.org/10.1016/j.hazadv.2022.100206.
Osytek, A., Biesaga, M., Pyrzynska, K., Szewczyńska, M., 2008. Quantification of some active compounds in air samples at pharmaceutical workplaces by HPLC. J. Biochem. Biophys. Methods 70, 1283–1286. https://doi.org/10.1016/j.jbbm.2007.10.003.
Öztürk, M., Ashraf, M., Aksoy, A., Ahmad, M.S.A., Hakeem, K.R., 2015. Plants, Pollutants and Remediation. Springer. https://doi.org/10.1007/978-94-017-7194-8.
Padidam, M., 2003. Chemically regulated gene expression in plants. Curr. Opin. Plant Biol. 6, 169–177. https://doi.org/10.1016/S1369-5266(03)00005-0.
Paiga, P., Santos, L.H., Ramos, S., Jorge, S., Silva, J.G., Delerue-Matos, C., 2016. Presence of pharmaceuticals in the Lis river (Portugal): sources, fate and seasonal variation. Sci. Total Environ. 573, 164–177. https://doi.org/10.1016/j.scitotenv.2016.08.089.
Pal, A., Gin, K.Y.-H., Lin, A.Y.-C., Reinhard, M., 2010. Impacts of emerging organic contaminants on freshwater resources: review of recent occurrences, sources, fate and effects. Sci. Total Environ. 408, 6062–6069. https://doi.org/10.1016/j.scitotenv.2010.09.026.
Pan, M., Wong, C.K., Chu, L., 2014. Distribution of antibiotics in wastewater-irrigated soils and their accumulation in vegetable crops in the Pearl River Delta, southern China. J. Agric. Food Chem. 62, 11062, 11069. 10.1021/jf503850v.
Paranychianakis, N.V., Salgot, M., Snyder, S.A., Angelakis, A.N., 2015. Water reuse in EU states: necessity for uniform criteria to mitigate human and environmental risks. Crit. Rev. Environ. Sci. Technol. 45, 1409–1468. https://doi.org/10.1080/10643389.2014.955629.
Parida, V.K., Saidulu, D., Majumder, A., Srivastava, A., Gupta, B., Gupta, A.K., 2021. Emerging contaminants in wastewater: a critical review on occurrence, existing legislations, risk assessment, and sustainable treatment alternatives. J. Environ. Chem. Eng. 9, 105966 https://doi.org/10.1016/j.jece.2021.105966.
Patel, M., Kumar, R., Kishor, K., Mlsna, T., Pittman Jr., C.U., Mohan, D., 2019. Pharmaceuticals of emerging concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chem. Rev. 119, 3510–3673. https://doi.org/10.1021/acs.chemrev.8b00299.
Peck, M., Gibson, R.W., Kortenkamp, A., Hill, E.M., 2004. Sediments are major sinks of steroidal estrogens in two United Kingdom rivers. Environ. Toxicol. Chem. 23, 945–952. https://doi.org/10.1897/03-41.
Pedersen, J.A., Soliman, M., Suffet, I., 2005. Human pharmaceuticals, hormones, and personal care product ingredients in runoff from agricultural fields irrigated with treated wastewater. J. Agric. Food Chem. 53, 1625–1632. https://doi.org/10.1021/jf049228m.
Pei, M., Zhang, B., He, Y., Su, J., Gin, K., Lev, O., Shen, G., Hu, S., 2019. State of the art of tertiary treatment technologies for controlling antibiotic resistance in wastewater treatment plants. Environ. Int. 131, 105026 https://doi.org/10.1016/j.envint.2019.105026.
Petrović, M., Škrbić, B., Živančev, J., Ferrando-Climent, L., Barcelo, D., 2014. Determination of 81 pharmaceutical drugs by high performance liquid chromatography coupled to mass spectrometry with hybrid triple quadrupole–linear ion trap in different types of water in Serbia. Sci. Total Environ. 468, 415–428. https://doi.org/10.1016/j.scitotenv.2013.08.079.
Pezzatti, J., Boccard, J., Codesido, S., Gagnebin, Y., Joshi, A., Picard, D., González-Ruiz, V., Rudaz, S., 2020. Implementation of liquid chromatography–high resolution mass spectrometry methods for untargeted metabolomic analyses of biological samples: a tutorial. Anal. Chim. Acta 1105, 28–44. https://doi.org/10.1016/j.aca.2019.12.062.
Phillips, P.J., Smith, S.G., Kolpin, D.W., Zaugg, S.D., Buxton, H.T., Furlong, E.T., Esposito, K., Stinson, B., 2010. Pharmaceutical formulation facilities as sources of opioids and other pharmaceuticals to wastewater treatment plant effluents. Environ. Sci. Technol. 44, 4910–4916. https://doi.org/10.1021/es100356f.
Picó, Y., Alvarez-Ruiz, R., Alfarhan, A.H., El-Sheikh, M.A., Alobaid, S.M., Barceló, D., 2019. Uptake and accumulation of emerging contaminants in soil and plant treated with wastewater under real-world environmental conditions in the Al Hayer area (Saudi Arabia). Sci. Total Environ. 652, 562–572. https://doi.org/10.1016/j.scitotenv.2018.10.224.
Pilon-Smits, E., 2005. Phytoremediation. Annu. Rev. Plant Biol. 56, 15–39. https://doi.org/10.1146/annurev.arplant.56.032604.144214.
Piram, A., Salvador, A., Gauvrit, J.-Y., Lanteri, P., Faure, R., 2008. Development and optimisation of a single extraction procedure for the LC/MS/MS analysis of two pharmaceutical classes residues in sewage treatment plant. Talanta 74, 1463–1475. https://doi.org/10.1016/j.talanta.2007.09.038.
Pocock, T., Falk, S., 2014. Negative impact on growth and photosynthesis in the green alga *Chlamydomonas reinhardtii* in the presence of the estrogen 17α-Ethynylestradiol. PLoS One 9, e109289. https://doi.org/10.1371/journal.pone.0109289.
Podlipná, R., 2022. Benzimidazoles and plants: uptake, transformation and effect. Toxics 10, 135. https://doi.org/10.3390/toxics10030135.
Praveena, S.M., Shaifuddin, S.N.M., Sukiman, S., Nasir, F.A.M., Hanafi, Z., Kamarudin, N., Ismail, T.H.T., Aris, A.Z., 2018. Pharmaceuticals residues in selected tropical surface water bodies from Selangor (Malaysia): occurrence and potential risk assessments. Sci. Total Environ. 642, 230–240. https://doi.org/10.1016/j.scitotenv.2018.06.058.
Qadir, M., Wichelns, D., Raschid-Sally, L., McCornick, P.G., Drechsel, P., Bahri, A., Minhas, P., 2010. The challenges of wastewater irrigation in developing countries. Agric. Water Manag. 97, 561–568. https://doi.org/10.1016/j.agwat.2008.11.004.
Quesada, H.B., Baptista, A.T.A., Cusioli, L.F., Seibert, D., de Oliveira Bezerra, C., Bergamasco, R., 2019. Surface water pollution by pharmaceuticals and an alternative of removal by low-cost adsorbents: a review. Chemosphere 222, 766–780. https://doi.org/10.1016/j.chemosphere.2019.02.009.
Racz, L., Goel, R.K., 2010. Fate and removal of estrogens in municipal wastewater. J. Environ. Monit. 12, 58–70. https://doi.org/10.1039/B917298J.
Radjenovic, J., Petrovic, M., Barceló, D., 2007. Analysis of pharmaceuticals in wastewater and removal using a membrane bioreactor. Anal. Bioanal. Chem. 387, 1365–1377. https://doi.org/10.1007/s00216-006-0883-6.
Rajendran, S., Priya, A., Kumar, P.S., Hoang, T.K., Sekar, K., Chong, K.Y., Khoo, K.S., Ng, H.S., Show, P.L., 2022. A critical and recent developments on adsorption technique for removal of heavy metals from wastewater-a review. Chemosphere 303, 135146. https://doi.org/10.1016/j.chemosphere.2022.135146.
Ramírez-Morales, D., Masís-Mora, M., Montiel-Mora, J.R., Cambronero-Heinrichs, J.C., Briceño-Guevara, S., Rojas-Sánchez, C.E., Méndez-Rivera, M., Arias-Mora, V., Tormo-Budowski, R., Brenes-Alfaro, L., 2020. Occurrence of pharmaceuticals, hazard assessment and ecotoxicological evaluation of wastewater treatment plants in Costa Rica. Sci. Total Environ. 746, 141200 https://doi.org/10.1016/j.scitotenv.2020.141200.
Rana, R.S., Singh, P., Kandari, V., Singh, R., Dobhal, R., Gupta, S., 2017. A review on characterization and bioremediation of pharmaceutical industries' wastewater: an Indian perspective. Appl. Water Sci. 7, 1–12. https://doi.org/10.1007/s13201-014-0225-3.
Rathi, B.S., Kumar, P.S., Vo, D.V.N., 2021. Critical review on hazardous pollutants in water environment: occurrence, monitoring, fate, removal technologies and risk assessment. Sci. Total Environ. 797, 149134 https://doi.org/10.1016/j.scitotenv.2021.149134.
Ravichandran, M.K., Philip, L., 2021. Insight into the uptake, fate and toxic effects of pharmaceutical compounds in two wetland plant species through hydroponics studies. Chem. Eng. J. 426, 131078 https://doi.org/10.1016/j.cej.2021.131078.
Rehman, M.S.U., Rashid, N., Ashfaq, M., Saif, A., Ahmad, N., Han, J.-I., 2015. Global risk of pharmaceutical contamination from highly populated developing countries. Chemosphere 138, 1045–1055. https://doi.org/10.1016/j.chemosphere.2013.02.036.
Riaz, L., Mahmood, T., Khalid, A., Rashid, A., Ahmed Siddique, M.B., Kamal, A., Coyne, M.S., 2018. Fluoroquinolones (FQs) in the environment: a review on their abundance, sorption and toxicity in soil. Chemosphere 191, 704–720. https://doi.org/10.1016/j.chemosphere.2017.10.092.
Ricart, S., Rico, A.M., 2019. Assessing technical and social driving factors of water reuse in agriculture: a review on risks, regulation and the yuck factor. Agric. Water Manag. 217, 426–439. https://doi.org/10.1016/j.agwat.2019.03.017.
Riemenschneider, C., Seiwert, B., Goldstein, M., Al-Raggad, M., Salameh, E., Chefetz, B., Reemtsma, T., 2017a. An LC-MS/MS method for the determination of 28 polar environmental contaminants and metabolites in vegetables irrigated with treated municipal wastewater. Anal. Methods 9, 1273–1281. https://doi.org/10.1039/c6ay02984a.
Riemenschneider, C., Seiwert, B., Moeder, M., Schwarz, D., Reemtsma, T., 2017b. Extensive transformation of the pharmaceutical carbamazepine following uptake into intact tomato plants. Environ. Sci. Technol. 51, 6100–6109. https://doi.org/10.1021/acs.est.6b06485.
Riva, F., Castiglioni, S., Fattore, E., Manenti, A., Davoli, E., Zuccato, E., 2018. Monitoring emerging contaminants in the drinking water of Milan and assessment of the human risk. Int. J. Hyg Environ. Health 221, 451–457. https://doi.org/10.1016/j.ijheh.2018.01.008.
Rivera-Utrilla, J., Sánchez-Polo, M., Ferro-García, M.Á., Prados-Joya, G., Ocampo-Pérez, R., 2013. Pharmaceuticals as emerging contaminants and their removal from water. A review. Chemosphere 93, 1268–1287. https://doi.org/10.1016/j.chemosphere.2013.07.059.

Roberts, P.H., Thomas, K.V., 2006. The occurrence of selected pharmaceuticals in wastewater effluent and surface waters of the lower Tyne catchment. Sci. Total Environ. 356, 143–153. https://doi.org/10.1016/j.scitotenv.2005.04.031.

Rosman, N., Salleh, W., Mohamed, M.A., Jaafar, J., Ismail, A., Harun, Z., 2018. Hybrid membrane filtration-advanced oxidation processes for removal of pharmaceutical residue. J. Colloid Interface Sci. 532, 236–260. https://doi.org/10.1016/j.jcis.2018.07.118.

Rossignol, P., Orbović, V., Irish, V.F., 2014. A dexamethasone-inducible gene expression system is active in Citrus plants. Sci. Hortic. 172, 47–53. https://doi.org/10.1016/j.scienta.2014.02.041.

Rossmann, J., Schubert, S., Gurke, R., Oertel, R., Kirch, W., 2014. Simultaneous determination of most prescribed antibiotics in multiple urban wastewater by SPE-LC–MS/MS. J. Chromatogr. B 969, 162–170. https://doi.org/10.1016/j.jchromb.2014.08.008.

Rúa-Gómez, P.C., Püttmann, W., 2012. Impact of wastewater treatment plant discharge of lidocaine, tramadol, venlafaxine and their metabolites on the quality of surface waters and groundwater. J. Environ. Monit. 14, 1391–1399. https://doi.org/10.1039/c2em10950f.

Rusiniak, P., Kmiecik, E., Wątor, K., Duda, R., Bugno, R., 2021. Pharmaceuticals and personal care products in the urban groundwater–preliminary monitoring (case study: kraków, Southern Poland). Urban Water J. 18, 364–374. https://doi.org/10.1080/1573062X.2021.1893354.

Sairam, M., Maitra, S., Praharaj, S., Nath, S., Shankar, T., Sahoo, U., Santosh, D.T., Sagar, L., Panda, M., Shanthi Priya, G., Ashwini, T.R., Gaikwad, D.J., Hossain, A., Pramanick, B., Jatav, H.S., Gitari, H.I., Aftab, T., 2023. An insight into the consequences of emerging contaminants in soil and water and plant responses. In: Aftab, T. (Ed.), Emerging Contaminants and Plants: Interactions, Adaptations and Remediation Technologies. Springer International Publishing, Cham, pp. 1–27. https://doi.org/10.1007/978-3-031-22269-6_1.

Salgot, M., Folch, M., 2018. Wastewater treatment and water reuse. Curr. Opin. Environ. Sci. Health 2, 64–74. https://doi.org/10.1016/j.coesh.2018.03.005.

Samalova, M., Moore, I., 2021. The steroid-inducible pOp6/LhGR gene expression system is fast, sensitive and does not cause plant growth defects in rice (*Oryza sativa*). BMC Plant Biol. 21, 1–15. https://doi.org/10.1186/s12870-021-03241-w.

Sandermann Jr, H., 1994. Higher plant metabolism of xenobiotics: the 'green liver' concept. Pharmacogenetics 4, 225–241. https://doi.org/10.1097/00008571-199410000-00001.

Saravanan, A., Kumar, P.S., Jeevanantham, S., Anubha, M., Jayashree, S., 2022. Degradation of toxic agrochemicals and pharmaceutical pollutants: effective and alternative approaches toward photocatalysis. Environ. Pollut. 298, 118844. https://doi.org/10.1016/j.envpol.2022.118844, 118844.

Sathishkumar, P., Meena, R.A.A., Palanisami, T., Ashokkumar, V., Palvannan, T., Gu, F. L., 2020. Occurrence, interactive effects and ecological risk of diclofenac in environmental compartments and biota - a review. Sci. Total Environ. 698, 134057 https://doi.org/10.1016/j.scitotenv.2019.134057.

Schellenberg, T., Subramanian, V., Ganeshan, G., Tompkins, D., Pradeep, R., 2020. Wastewater discharge standards in the evolving context of urban sustainability–the case of India. Front. Environ. Sci. 8 https://doi.org/10.3389/fenvs.2020.00030.

Schiffer, B., Daxenberger, A., Meyer, K., Meyer, H., 2001. The fate of trenbolone acetate and melengestrol acetate after application as growth promoters in cattle: environmental studies. Environ. Health Perspect. 109, 1145–1151. https://doi.org/10.1289/ehp.011091145.

Schriks, M., van Leerdam, J.A., van der Linden, S.C., van der Burg, B., van Wezel, A.P., de Voogt, P., 2010. High-resolution mass spectrometric identification and quantification of glucocorticoid compounds in various wastewaters in The Netherlands. Environ. Sci. Technol. 44, 4766–4774. https://doi.org/10.1021/es100013x.

Schröder, P., Collins, C., 2002. Conjugating enzymes involved in xenobiotic metabolism of organic xenobiotics in plants. Int. J. Phytoremediation 4, 247–265. https://doi.org/10.1080/15226510208500086.

Scott, T.M., Phillips, P.J., Kolpin, D.W., Colella, K.M., Furlong, E.T., Foreman, W.T., Gray, J.L., 2018. Pharmaceutical manufacturing facility discharges can substantially increase the pharmaceutical load to US wastewaters. Sci. Total Environ. 636, 69–79. https://doi.org/10.1016/j.scitotenv.2018.04.160.

Segura, P.A., Takada, H., Correa, J.A., El Saadi, K., Koike, T., Onwona-Agyeman, S., Ofosu-Anim, J., Sabi, E.B., Wasonga, O.V., Mghalu, J.M., 2015. Global occurrence of anti-infectives in contaminated surface waters: impact of income inequality between countries. Environ. Int. 80, 89–97. https://doi.org/10.1016/j.envint.2015.04.001.

Sengupta, A., Lyons, J.M., Smith, D.J., Drewes, J.E., Snyder, S.A., Heil, A., Maruya, K.A., 2014. The occurrence and fate of chemicals of emerging concern in coastal urban rivers receiving discharge of treated municipal wastewater effluent. Environ. Toxicol. Chem. 33, 350–358. https://doi.org/10.1002/etc.2457.

Senta, I., Terzić, S., Ahel, M., 2008. Simultaneous determination of sulfonamides, fluoroquinolones, macrolides and trimethoprim in wastewater and river water by LC-tandem-MS. Chromatographia 68, 747–758. https://doi.org/10.1365/s10337-008-0780-6.

Sharma, V.K., Jinadatha, C., Lichtfouse, E., Decroly, E., Van Helden, J., Choi, H., Chatterjee, P., 2021. COVID-19 epidemiologic surveillance using wastewater. Environ. Chem. Lett. 19, 1911–1915. https://doi.org/10.1007/s10311-021-01188-w.

Shenker, M., Harush, D., Ben-Ari, J., Chefetz, B., 2011. Uptake of carbamazepine by cucumber plants–a case study related to irrigation with reclaimed wastewater. Chemosphere 82, 905–910. https://doi.org/10.1016/j.chemosphere.2010.10.052.

Sher, F., Hanif, K., Iqbal, S.Z., Imran, M., 2020. Implications of advanced wastewater treatment: electrocoagulation and electroflocculation of effluent discharged from a wastewater treatment plant. J. Water Process Eng. 33, 101101 https://doi.org/10.1016/j.jwpe.2019.101101.

Shore, L.S., Kapulnik, Y., Ben-Dor, B., Fridman, Y., Wininger, S., Shemesh, M., 1992. Effects of estrone and 17 β-estradiol on vegetative growth of *Medicago sativa*. Physiol. Plantarum 84, 217–222. https://doi.org/10.1111/j.1399-3054.1992.tb04656.x.

Singh, A., 2021. A review of wastewater irrigation: environmental implications. Resour. Conserv. Recycl. 168, 105454 https://doi.org/10.1016/j.resconrec.2021.105454.

Skees, A.J., Foppe, K.S., Loganathan, B., Subedi, B., 2018. Contamination profiles, mass loadings, and sewage epidemiology of neuropsychiatric and illicit drugs in wastewater and river waters from a community in the Midwestern United States. Sci. Total Environ. 631, 1457–1464. https://doi.org/10.1016/j.scitotenv.2018.03.060.

Sodré, F.F., Pescara, I.C., Montagner, C.C., Jardim, W.F., 2010. Assessing selected estrogens and xenoestrogens in Brazilian surface waters by liquid chromatography–tandem mass spectrometry. Microchem. J. 96, 92–98. https://doi.org/10.1016/J.MICROC.2010.02.012.

Stackelberg, P.E., Gibs, J., Furlong, E.T., Meyer, M.T., Zaugg, S.D., Lippincott, R.L., 2007. Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds. Sci. Total Environ. 377, 255–272. https://doi.org/10.1016/j.scitotenv.2007.01.095.

Stottmeister, U., Wießner, A., Kuschk, P., Kappelmeyer, U., Kästner, M., Bederski, O., Müller, R., Moormann, H., 2003. Effects of plants and microorganisms in constructed wetlands for wastewater treatment. Biotechnol. Adv. 22, 93–117. https://doi.org/10.1016/j.biotechadv.2003.08.010.

Subedi, B., Balakrishna, K., Sinha, R.K., Yamashita, N., Balasubramanian, V.G., Kannan, K., 2015a. Mass loading and removal of pharmaceuticals and personal care products, including psychoactive and illicit drugs and artificial sweeteners, in five sewage treatment plants in India. J. Environ. Chem. Eng. 3, 2882–2891. https://doi.org/10.1016/j.chemosphere.2016.10.026.

Subedi, B., Codru, N., Dziewulski, D.M., Wilson, L.R., Xue, J., Yun, S., Braun-Howland, E., Minihane, C., Kannan, K., 2015b. A pilot study on the assessment of trace organic contaminants including pharmaceuticals and personal care products from on-site wastewater treatment systems along Skaneateles Lake in New York State, USA. Water Res. 72, 28–39. https://doi.org/10.1016/j.watres.2014.10.049.

Subedi, B., Kannan, K., 2015. Occurrence and fate of select psychoactive pharmaceuticals and antihypertensives in two wastewater treatment plants in New York State, USA. Sci. Total Environ. 514, 273. https://doi.org/10.1016/j.scitotenv.2015.01.0980, 28.

Sun, C., Dudley, S., McGinnis, M., Trumble, J., Gan, J., 2019. Acetaminophen detoxification in cucumber plants via induction of glutathione S-transferases. Sci. Total Environ. 649, 431–439. https://doi.org/10.1016/j.scitotenv.2018.08.346.

Sun, C., Dudley, S., Trumble, J., Gan, J., 2018. Pharmaceutical and personal care products-induced stress symptoms and detoxification mechanisms in cucumber plants. Environ. Pollut. 234, 39–47. https://doi.org/10.1016/j.envpol.2017.11.041.

Sunyer-Caldú, A., Sepúlveda-Ruiz, P., Salgot, M., Folch-Sánchez, M., Barcelo, D., Diaz-Cruz, M.S., 2022. Reclaimed water in agriculture: a plot-scale study assessing crop uptake of emerging contaminants and pathogens. J. Environ. Chem. Eng. 10, 108831 https://doi.org/10.1016/j.jece.2022.108831.

Taiz, L., Zeiger, E., Møller, I.M., Murphy, A., 2015. Plant Physiology and Development. Sinauer Associates Incorporated, p. 761.

Tal, A., 2016. Rethinking the sustainability of Israel's irrigation practices in the drylands. Water Res. 90, 387–394. https://doi.org/10.1016/j.watres.2015.12.016.

Tanoue, R., Sato, Y., Motoyama, M., Nakagawa, S., Shinohara, R., Nomiyama, K., 2012. Plant uptake of pharmaceutical chemicals detected in recycled organic manure and reclaimed wastewater. J. Agric. Food Chem. 60, 10203–10211. https://doi.org/10.1021/jf303142t.

Thebo, A.L., Drechsel, P., Lambin, E., Nelson, K., 2017. A global, spatially-explicit assessment of irrigated croplands influenced by urban wastewater flows. Environ. Res. Lett. 12, 074008 https://doi.org/10.1088/1748-9326/aa75d1.

Thiebault, T., Boussafir, M., Le Milbeau, C., 2017. Occurrence and removal efficiency of pharmaceuticals in an urban wastewater treatment plant: mass balance, fate and consumption assessment. J. Environ. Chem. Eng. 5, 2894–2902. https://doi.org/10.1016/j.jece.2017.05.039.

Tiwari, B., Sellamuthu, B., Ouarda, Y., Drogui, P., Tyagi, R.D., Buelna, G., 2017. Review on fate and mechanism of removal of pharmaceutical pollutants from wastewater using biological approach. Bioresour. Technol. 224, 1–12. https://doi.org/10.1016/j.biortech.2016.11.042.

Togola, A., Budzinski, H., 2008. Multi-residue analysis of pharmaceutical compounds in aqueous samples. J. Chromatogr. A 1177, 150–158. https://doi.org/10.1016/j.chroma.2007.10.105.

Tölgyesi, Á., Verebey, Z., Sharma, V.K., Kovacsics, L., Fekete, J., 2010. Simultaneous determination of corticosteroids, androgens, and progesterone in river water by liquid chromatography–tandem mass spectrometry. Chemosphere 78, 972–979. https://doi.org/10.1016/j.chemosphere.2009.12.025.

Tran, N.H., Reinhard, M., Gin, K.Y.-H., 2018. Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions- a review. Water Res. 133, 182–207. https://doi.org/10.1016/j.watres.2017.12.029.

Tran, N.H., Urase, T., Ta, T.T., 2014. A preliminary study on the occurrence of pharmaceutically active compounds in hospital wastewater and surface water in Hanoi, Vietnam. CLEAN–Soil. Air, Water 42, 267–275. https://doi.org/10.1002/clen.201300021.

Trapp, S., Legind, C.N., 2011. Uptake of organic contaminants from soil into vegetables and fruits. Dealing with Contaminated Sites: from Theory towards Practical Application. Springer, Dordrecht, pp. 369–408. https://doi.org/10.1007/978-90-481-9757-6_9.

Türkoğlu, E., Osma, E., Elveren, M., 2019. Effects of acetaminophen (paracetamol) and gemfibrozil on seed development and antioxidant enzyme activities in different

wheat varieties. Iran. J. Sci. Technol. Trans. A Sci. 43, 2075–2082. https://doi.org/10.1007/s40995-017-0386-7.
Tyumina, E.A., Bazhutin, G.A., Cartagena Gómez, A.d.P., Ivshina, I.B., 2020. Nonsteroidal anti-inflammatory drugs as emerging contaminants. Microbiol. 89, 148–163. https://doi.org/10.1134/S0026261720020125.
UNESCO, W., 2020. Water and climate change. The UN World Water Development Report 2020.
Ungureanu, N., Vlăduț, V., Dincă, M., Zăbavă, B.Ș., 2018. Reuse of wastewater for irrigation, a sustainable practice in arid and semi-arid regions. In: Renewable Energy and Rural Development (TE-RE-RD). Drobeta-Turnu Severin, Romania, pp. 379–384.
United Nations, 2016. General Assembly Resolution 70/1, Transforming Our World: the 2030 Agenda for Sustainable Development. A/70/L. 1.
USEPA, 1999. National Recommended Water Quality Criteria-correction. Technical Report. US Environmental Protection Agency. Office of Water Office of Science and Technology, Washington DC.
USEPA, 2012. Guide-lines for Water Reuse. US Environmental Protection Agency, Washington, DC, USA. EPA 600-R-612-618.
Van Boeckel, T.P., Brower, C., Gilbert, M., Grenfell, B.T., Levin, S.A., Robinson, T.P., Teillant, A., Laxminarayan, R., 2015. Global trends in antimicrobial use in food animals. Proc. Natl. Acad. Sci. USA 112, 5649–5654. https://doi.org/10.1073/pnas.1503141112.
Van der Linden, S.C., Heringa, M.B., Man, H.-Y., Sonneveld, E., Puijker, L.M., Brouwer, A., Van der Burg, B., 2008. Detection of multiple hormonal activities in wastewater effluents and surface water, using a panel of steroid receptor CALUX bioassays. Environ. Sci. Technol. 42, 5814–5820. https://doi.org/10.1021/es702897y.
Vanderford, B.J., Snyder, S.A., 2006. Analysis of pharmaceuticals in water by isotope dilution liquid chromatography/tandem mass spectrometry. Environ. Sci. Technol. 40, 7312–7320. https://doi.org/10.1021/es0613198.
Vanerkar, A.P., Fulke, A.B., Lokhande, S.K., Giripunje, M.D., Satyanarayan, S., 2015. Recycling and treatment of herbal pharmaceutical wastewater using Scenedesmus quadricuada. Curr. Sci. 979–983 https://doi.org/10.18520/CS/V108/I5/979-983.
Veiga-Gómez, M., Nebot, C., Franco, C.M., Miranda, J.M., Vázquez, B., Cepeda, A., 2017. Identification and quantification of 12 pharmaceuticals in water collected from milking parlors: food safety implications. J. Dairy Sci. 100, 3373–3383. https://doi.org/10.3168/jds.2016-12227.
Vergili, I., Kaya, Y., Gönder, Z.B., Boergers, A., Tuerk, J., 2019. Occurrence and prioritization of pharmaceutical active compounds in domestic/municipal wastewater treatment plants. Bull. Environ. Contam. Toxicol. 102, 252–258. https://doi.org/10.1007/s00128-019-02550-z.
Verliefde, A.R., Heijman, S., Cornelissen, E., Amy, G., Van der Bruggen, B., Van Dijk, J., 2008. Rejection of trace organic pollutants with high pressure membranes (NF/RO). Environ. Prog. 27, 180–188. https://doi.org/10.1002/EP.10272.
Vieno, N.M., Härkki, H., Tuhkanen, T., Kronberg, L., 2007. Occurrence of pharmaceuticals in river water and their elimination in a pilot-scale drinking water treatment plant. Environ. Sci. Technol. 41, 5077–5084. https://doi.org/10.1021/es062720x.
Vulliet, E., Wiest, L., Baudot, R., Grenier-Loustalot, M.-F., 2008. Multi-residue analysis of steroids at sub-ng/L levels in surface and ground-waters using liquid chromatography coupled to tandem mass spectrometry. J. Chromatogr. A 1210, 84–91. https://doi.org/10.1016/j.chroma.2008.09.034.
Wang, J., Lin, H., Sun, W., Xia, Y., Ma, J., Fu, J., Zhang, Z., Wu, H., Qian, M., 2016. Variations in the fate and biological effects of sulfamethoxazole, norfloxacin and doxycycline in different vegetable–soil systems following manure application. J. Hazard Mater. 304, 49–57. https://doi.org/10.1016/j.jhazmat.2015.10.038.
Wang, K., Zhuang, T., Su, Z., Chi, M., Wang, H., 2021. Antibiotic residues in wastewaters from sewage treatment plants and pharmaceutical industries: occurrence, removal and environmental impacts. Sci. Total Environ. 788, 147811 https://doi.org/10.1016/j.scitotenv.2021.147811.
Wang, L., Zhang, X., Tam, N., 2010. Analysis and occurrence of typical endocrine-disrupting chemicals in three sewage treatment plants. Water Sci. Technol. 62, 2501–2509. https://doi.org/10.2166/wst.2010.533.
Water, U., 2018. UN World Water Development Report 2018, Nature-Based Solutions for Water.
Watkinson, A., Murby, E., Costanzo, S., 2007. Removal of antibiotics in conventional and advanced wastewater treatment: implications for environmental discharge and wastewater recycling. Water Res. 41, 4164–4176. https://doi.org/10.1016/j.watres.2007.04.005.
Watkinson, A.J., Murby, E.J., Kolpin, D.W., Costanzo, S.D., 2009. The occurrence of antibiotics in an urban watershed: from wastewater to drinking water. Sci. Total Environ. 407, 2711–2723. https://doi.org/10.1016/j.scitotenv.2008.11.059.
Wei, H., Tang, M., Xu, X., 2023. Mechanism of uptake, accumulation, transport, metabolism and phytotoxic effects of pharmaceuticals and personal care products within plants: a review. Sci. Total Environ. 892, 164413 https://doi.org/10.1016/j.scitotenv.2023.164413.
Weizel, A., Schlüsener, M.P., Dierkes, G., Ternes, T.A., 2018. Occurrence of glucocorticoids, mineralocorticoids, and progestogens in various treated wastewater, rivers, and streams. Environ. Sci. Technol. 52, 5296–5307. https://doi.org/10.1021/acs.est.7b06147.
WFD, 2000. Water Framework Directive (2000/60/ec).
WHO- World Health Organization, 2001. Water Quality: Guidelines, Standards and Health: Assessment of Risk and Risk Management for Water-Related Infectious Disease.
WHO- World Health Organization, 2002. Guidelines for drinking-water quality. World Health Organization.
WHO- World Health Organization, 2006. Guidelines for the safe use of wastewater, excreta and greywater. Wastewater Use in Agriculture. World Health Organization.
WHO- World Health Organization, 2014. Antimicrobial Resistance: Global Report on Surveillance. World Health Organization.
Wick, A., Fink, G., Joss, A., Siegrist, H., Ternes, T.A., 2009. Fate of beta blockers and psycho-active drugs in conventional wastewater treatment. Water Res. 43, 1060–1074. https://doi.org/10.1016/j.watres.2008.11.031.
Wilkinson, J.L., Boxall, A.B.A., Kolpin, D.W., Leung, K.M.Y., Lai, R.W.S., Galbán-Malagón, C., Adell, A.D., Mondon, J., Metian, M., Marchant, R.A., Bouzas-Monroy, A., Cuni-Sanchez, A., Coors, A., Carriquiriborde, P., Rojo, M., Gordon, C., Cara, M., Moermond, M., Luarte, T., Petrosyan, V., Perikhanyan, Y., Mahon, C.S., McGurk, C.J., Hofmann, T., Kormoker, T., Iniguez, V., Guzman-Otazo, J., Tavares, J. L., Gildasio De Figueiredo, F., Razzolini, M.T.P., Dougnon, V., Gbaguidi, G., Traoré, O., Blais, J.M., Kimpe, L.E., Wong, M., Wong, D., Ntchantcho, R., Pizarro, J., Ying, G.-G., Chen, C.-E., Páez, M., Martínez-Lara, J., Otamonga, J.-P., Poté, J., Ifo, S. A., Wilson, P., Echeverría-Sáenz, S., Udikovic-Kolic, N., Milakovic, M., Fatta-Kassinos, D., Ioannou-Ttofa, L., Belušová, V., Vymazal, J., Cárdenas-Bustamante, M., Kassa, B.A., Garric, J., Chaumot, A., Gibba, P., Kunchulia, I., Seidensticker, S., Lyberatos, G., Halldórsson, H.P., Melling, M., Shashidhar, T., Lamba, M., Nastiti, A., Supriatin, A., Pourang, N., Abedini, A., Abdullah, O., Gharbia, S.S., Pilla, F., Chefetz, B., Topaz, T., Yao, K.M., Aubakirova, B., Beisenova, R., Olaka, L., Mulu, J. K., Chatanga, P., Ntuli, V., Blama, N.T., Sherif, S., Aris, A.Z., Looi, L.J., Niang, M., Traore, S.T., Oldenkamp, R., Ogunbanwo, O., Ashfaq, M., Iqbal, M., Abdeen, Z., O'Dea, A., Morales-Saldaña, J.M., Custodio, M., de la Cruz, H., Navarrete, I., Carvalho, F., Gogra, A.B., Koroma, B.M., Cerkvenik-Flajs, V., Gombač, M., Thwala, M., Choi, K., Kang, H., Ladu, J.L.C., Rico, A., Amerasinghe, P., Sobek, A., Horlitz, G., Zenker, A.K., King, A.C., Jiang, J.-J., Kariuki, R., Tumbo, M., Tezel, U., Onay, T.T., Lejju, J.B., Vystavna, Y., Vergeles, Y., Heinzen, H., Pérez-Parada, A., Sims, D.B., Figy, M., Good, D., Teta, C., 2022. Pharmaceutical pollution of the world's rivers. Proc. Natl. Acad. Sci. USA 119, e2113947119. https://doi.org/10.1073/pnas.2113947119.
Winker, M., Clemens, J., Reich, M., Gulyas, H., Otterpohl, R., 2010. Ryegrass uptake of carbamazepine and ibuprofen applied by urine fertilization. Sci. Total Environ. 408, 1902–1908. https://doi.org/10.1016/j.scitotenv.2010.01.028.
Writer, J.H., Ryan, J.N., Keefe, S.H., Barber, L.B., 2012. Fate of 4-nonylphenol and 17β-estradiol in the redwood river of Minnesota. Environ. Sci. Technol. 46, 860–868. https://doi.org/10.1021/es2031664.
Wu, M., Xiang, J., Que, C., Chen, F., Xu, G., 2015a. Occurrence and fate of psychiatric pharmaceuticals in the urban water system of Shanghai, China. Chemosphere 138, 486–493. https://doi.org/10.1016/j.chemosphere.2015.07.002.
Wu, S., Jia, A., Daniels, K.D., Park, M., Snyder, S.A., 2019. Trace analysis of corticosteroids (CSs) in environmental waters by liquid chromatography–tandem mass spectrometry. Talanta 195, 830–840. https://doi.org/10.1016/j.talanta.2018.11.113.
Wu, W., Ma, M., Hu, Y., Yu, W., Liu, H., Bao, Z., 2021. The fate and impacts of pharmaceuticals and personal care products and microbes in agricultural soils with long term irrigation with reclaimed water. Agric. Water Manag. 251, 106862 https://doi.org/10.1016/j.agwat.2021.106862.
Wu, X., Conkle, J.L., Gan, J., 2012. Multi-residue determination of pharmaceutical and personal care products in vegetables. J. Chromatogr. A 1254, 78–86. https://doi.org/10.1016/j.chroma.2012.07.041.
Wu, X., Dodgen, L.K., Conkle, J.L., Gan, J., 2015b. Plant uptake of pharmaceutical and personal care products from recycled water and biosolids: a review. Sci. Total Environ. 536, 655–666. https://doi.org/10.1016/j.scitotenv.2015.07.129.
WWAP - UNESCO World Water Assessment Programme, 2017. The United Nations World Water Development Report, 2017. Wastewater: the Untapped Resource. UNESCO, Paris, p. 2017.
WWAP - UNESCO World Water Assessment Programme, 2019. The United Nations World Water Development Report 2019: Leaving No One behind. UNESCO, Paris.
Xu, J., Liu, X., Lv, Y., Guo, X., Lu, S., 2020. Response of *Cyperus involucratus* to sulfamethoxazole and ofloxacin-contaminated environments: growth physiology, transportation, and microbial community. Ecotoxicol. Environ. Saf. 206, 111332 https://doi.org/10.1016/j.ecoenv.2020.111332.
Xu, M., Huang, H., Li, N., Li, F., Wang, D., Luo, Q., 2019. Occurrence and ecological risk of pharmaceuticals and personal care products (PPCPs) and pesticides in typical surface watersheds, China. Ecotoxicol. Environ. Saf. 175, 289–298. https://doi.org/10.1016/j.ecoenv.2019.01.131.
Xu, W., Yan, W., Huang, W., Miao, L., Zhong, L., 2014. Endocrine-disrupting chemicals in the Pearl River Delta and coastal environment: sources, transfer, and implications. Environ. Geochem. Health 36, 1095–1104. https://doi.org/10.1007/s10653-014-9618-3.
Yamamoto, H., Nakamura, Y., Moriguchi, S., Nakamura, Y., Honda, Y., Tamura, I., Hirata, Y., Hayashi, A., Sekizawa, J., 2009. Persistence and partitioning of eight selected pharmaceuticals in the aquatic environment: laboratory photolysis, biodegradation, and sorption experiments. Water Res. 43, 351–362. https://doi.org/10.1016/j.watres.2008.10.039.
Yang, X., Flowers, R.C., Weinberg, H.S., Singer, P.C., 2011a. Occurrence and removal of pharmaceuticals and personal care products (PPCPs) in an advanced wastewater reclamation plant. Water Res. 45, 5218–5228. https://doi.org/10.1016/j.watres.2011.07.026.
Yang, Y., Fu, J., Peng, H., Hou, L., Liu, M., Zhou, J.L., 2011b. Occurrence and phase distribution of selected pharmaceuticals in the Yangtze Estuary and its coastal zone. J. Hazard Mater. 190, 588–596. https://doi.org/10.1016/j.jhazmat.2011.03.092.
Ying, G.-G., Kookana, R.S., Kumar, A., Mortimer, M., 2009. Occurrence and implications of estrogens and xenoestrogens in sewage effluents and receiving waters from South

East Queensland. Sci. Total Environ. 407, 5147–5155. https://doi.org/10.1016/j.scitotenv.2009.06.002.

Ying, G.-G., Kookana, R.S., Ru, Y.-J., 2002. Occurrence and fate of hormone steroids in the environment. Environ. Int. 28, 545–551. https://doi.org/10.1016/S0160-4120(02)00075-2.

Yuan, S., Jiang, X., Xia, X., Zhang, H., Zheng, S., 2013. Detection, occurrence and fate of 22 psychiatric pharmaceuticals in psychiatric hospital and municipal wastewater treatment plants in Beijing, China. Chemosphere 90, 2520–2525. https://doi.org/10.1016/j.chemosphere.2012.10.089.

Zezulka, Š., Kummerová, M., Babula, P., Hájková, M., Oravec, M., 2019. Sensitivity of physiological and biochemical endpoints in early ontogenetic stages of crops under diclofenac and paracetamol treatments. Environ. Sci. Pollut. Res. 26, 3965–3979. https://doi.org/10.1007/s11356-018-3930-x.

Zhan, X.-H., Ma, H.-L., Zhou, L.-X., Liang, J.-R., Jiang, T.-H., Xu, G.-H., 2010. Accumulation of phenanthrene by roots of intact wheat (*Triticum acstivnm L.*) seedlings: passive or active uptake? BMC Plant Biol. 10, 1–8. https://doi.org/10.1186/1471-2229-10-52.

Zhang, A., Li, Y., Chen, L., 2014a. Distribution and seasonal variation of estrogenic endocrine disrupting compounds, N-nitrosodimethylamine, and N-nitrosodimethylamine formation potential in the Huangpu River, China. J. Environ. Sci. 26, 1023–1033. https://doi.org/10.1016/S1001-0742(13)60530-6.

Zhang, D., Gersberg, R.M., Ng, W.J., Tan, S.K., 2014b. Removal of pharmaceuticals and personal care products in aquatic plant-based systems: a review. Environ. Pollut. 184, 620–639. https://doi.org/10.1016/j.envpol.2013.09.009.

Zhang, D.Q., Hua, T., Gersberg, R.M., Zhu, J., Ng, W.J., Tan, S.K., 2012. Fate of diclofenac in wetland mesocosms planted with *Scirpus validus*. Ecol. Eng. 49, 59–64. https://doi.org/10.1016/j.ecoleng.2012.08.018.

Zhang, H., Li, X., Yang, Q., Sun, L., Yang, X., Zhou, M., Deng, R., Bi, L., 2017. Plant growth, antibiotic uptake, and prevalence of antibiotic resistance in an endophytic system of pakchoi under antibiotic exposure. Int. J. Environ. Res. Publ. Health 14, 1336. https://doi.org/10.3390/ijerph14111336.

Zhang, K., Fent, K., 2018. Determination of two progestin metabolites (17α-hydroxypregnanolone and pregnanediol) and different classes of steroids (androgens, estrogens, corticosteroids, progestins) in rivers and wastewaters by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Sci. Total Environ. 610, 1164–1172. https://doi.org/10.1016/j.scitotenv.2017.08.114.

Zhang, M., Zhu, L., 2009. Sorption of polycyclic aromatic hydrocarbons to carbohydrates and lipids of ryegrass root and implications for a sorption prediction model. Environ. Sci. Technol. 43, 2740–2745. https://doi.org/10.1021/es802808q.

Zhang, Y., Geißen, S.-U., Gal, C., 2008. Carbamazepine and diclofenac: removal in wastewater treatment plants and occurrence in water bodies. Chemosphere 73, 1151–1161. https://doi.org/10.1016/j.chemosphere.2008.07.086.

Zheng, W., Guo, M., 2021. Soil–plant transfer of pharmaceuticals and personal care products. Curr. Pollut. Rep. 7, 510–523. https://doi.org/10.1007/s40726-021-00207-2.

Zhu, Y., Zhang, S., Zhu, Y.-G., Christie, P., Shan, X., 2007. Improved approaches for modeling the sorption of phenanthrene by a range of plant species. Environ. Sci. Technol. 41, 7818–7823. https://doi.org/10.1021/es071305h.