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

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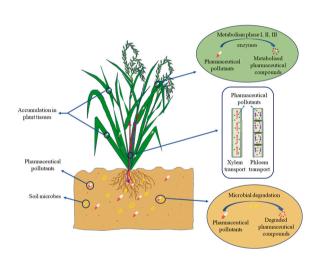
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HIGHLIGHTS

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.

G R A P H I C A L A B S T R A C T



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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

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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, logKow, 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 "micropollutants" (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 ₃ O ₃ S) | 253.3 | Switzerland | Altenrhein | Municipal wastewater primary effluent | 641 ± 4.0 | Göbel et al. (2004) |
| (010111113030) | | Sweden | Stockholm, Henriksdal | STP influent | 674 | Lindberg et al. (2005) |
| | | USA | Hagerman | Municipal wastewater | 1000 | Brown et al. (2006) |
| | | | | (influent or effluent not mentioned) | | |
| | | USA | Las Vegas | Municipal wastewater | 2060 | Vanderford and Snyder |
| | | 00.1 | zao vogao | (influent or effluent not mentioned) | 2000 | (2006) |
| | | Canada | Edmonton | – | 650 | McClure and Wong |
| | | UK | Colsech | WWTP influent | 20–274 (115) | (2007) Kasprzyk-Hordern |
| | | Australia | Brisbane | WWTP influent | 360 | et al. (2009) Watkinson et al. |
| | | | | | | (2007) |
| | | Croatia | Velicka Gorica | Raw wastewater | 4664 | Senta et al. (2008) |
| | | China (HK) | Stanley | WWTP influent | 220 538 | Li and Zhang (2011) Dinh (2012) |
| | | France | Limours | Municipal wastewater (influent or effluent not mentioned) | 336 | Diiii (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) |
| Analgesic and antipyretic | : | Bangladesh | Old Brahmaputra River | Surface water | LOD - 7.24 | Hossain et al. (2018) |
| Acetaminophen | 151.16 | Poland | Swarzewo | WWTP influent | 6.5 | Kołecka et al. (2020) |
| $(C_8H_9NO_2)$ | | 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) |
| 0.111 | | Mexico | Tula river | River water | 20,960.9 | Garduño-Jiménez et al. (2023) |
| Opioids Tramadol | 263.37 | Germany | Dresden | WWTP influent | 662.8 | Gurke et al. (2015) |
| $(C_{16}H_{25}NO_2)$ | | 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 EU-wide sampling | Bratislava WWTPs in EU countries | WWTP influent WWTP effluent | 860 ± 120 256 | Mackuľak et al. (2015) Loos et al. (2013) |
| | | campaign | | | | |
| | | 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 |
| | | I Trum commu | Danube | Direct restor committee | 1 44 969 4 | Püttmann (2012) |
| | | Hungary | | River water samples | 1.44–262.4 | Kondor et al. (2020) |
| | | Wales, UK | Pontypridd point, River Taff | River water samples | 244–5970 | Kasprzyk-Hordern |
| | | Wales, UK | Peterson-super-Ely point, | River water samples | 731–7731 | et al. (2008) |
| | | wates, UK | River Elv | Kiver water samples | /31-//31 | Kasprzyk-Hordern et al. (2008) |
| | | Germany | Conventional | WWTP influent | 470 | Wick et al. (2009) |
| | | Germany | WWTP | WWW. | 17.0 | Wick of the (2005) |
| Oxycodone | 315.36 | USA | Minnesota | Upstream, wastewater | 38.2-169.8 | Campos-Mañas et al. |
| (C ₁₈ H ₂₁ NO ₄) | | **** | | and downstream water | | (2019) |
| (-16214) | | 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 influent | 74.9 | Kamika et al. (2021) |
| | | | WWTP | | | |
| | | South Africa | Rietgat WWTP | WWTP influent | 177 | Kamika et al. (2021) |
| | | South Africa | Sandspruit | WWTP influent | 187 | Kamika et al. (2021) |
| | | | WWTP | | | |
| | | 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 | 7.2–286 | Castiglioni et al. |
| | | | | layer) | | (2018) |
| | | Canada | Grand river watershed in | DWTP effluent | 5.1 ± 0.7 | Davoli et al. (2019) |
| | | | southern Ontario | | | |
| Anticonvulsant | | | | | | |
| Carbamazepine | 236.3 | China | Beijing | Drinking water | 0.37–1.15 | Cai et al. (2015) |
| $(C_{15}H_{12}N_2O)$ | | Serbia | Novi Sad, Zrenjanin, Bečej, | Drinking water | <loq -="" 8.7<="" td=""><td>Petrović et al. (2014</td></loq> | Petrović et al. (2014 |
| | | | Vrbas and Obrenovac | | | |
| | | Italy | Milan | Drinking water wells | 1.05 | Riva et al. (2018) |
| | | Bangladesh | Old Brahamaputra river | River water | <lod -="" 8.80<="" td=""><td>Hossain et al. (2018)</td></lod> | 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, | Surface water | 0–35.5 | Petrović et al. (2014 |
| | | | Vrbas and Obrenovac | | | |
| | | Singapore | 5.1. | 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 | Skaneateles Lake, New York | Lake water | 0–0.17 | Subedi and Kannan |
| | | America | | 0.6 | 0.144.0.50 | (2015) |
| | | Vietnam | Hanoi | Surface water | <0.144-0.53 | Tran et al. (2014) |
| | | France | Orléans Drandon Kodita | WWTP influent | 51-937 | Thiebault et al. (201 |
| | | Germany | Dresden Kaditz All over | STP influent WWTP influent | 246–815 22–8200 | Gurke et al. (2015) Balakrishna et al. |
| | | India | All Over | vv vv 1 r iiiiiuelit | 44-04UU | (2017) |
| | | Canada | 5 different STPs across | STP influent | 757 | (2017) Lajeunesse et al. |
| | | Ganada | Canada | orr mindelit | 131 | (2012) |
| Antidepressant | | | Ganada | | | (2012) |
| Alprazolam | 308.8 | Mexico | 14 states of Mexico | WWTP effluent | 56 | Adhikari et al. (2023 |
| (C ₁₇ H ₁₃ ClN ₄) | 300.0 | Tehran | municipal wastewater | WWTP effluent | 2.21-6.46 | Golbaz et al. (2023) |
| (01/11/301144) | | - CIII (III | treatment plant in South | ciiiuciit | 2.21 0.10 | 5010ttz Ct til. (2023) |
| | | | Tehran | | | |
| | | 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<="" td=""><td>Goswami et al. (202</td></mdl> | Goswami et al. (202 |
| | | Spain | Castellon province | WWTP effluent | 0.01 | Gracia-Lor et al. |
| | | - F | F | | - · · · = | (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 | | ~ - | | | | m. (2020) |
| | 270.4 | China | Hanjiang river | Surface water | n.d. – 2.3 | Hu et al. (2019) |
| | | | 5 0 | Surface water | 0.21-0.91 | Zhang and Fent (201 |
| | | Switzerland | River Jona and Dachseggbach | Surface water | 0.21-0.91 | Lifally allu relit (20) |
| | | | River Jona and Dachseggbach Paris | Surface water | | |
| Estrone (C ₁₈ H ₂₂ O ₂) | | Switzerland France China | - | | 0.2–3.0 19.7–1330 | Cargouët et al. (2004 Liu et al. (2012) |
| | | France | Paris | Surface water | 0.2-3.0 | Cargouët et al. (200 |

Table 1 (continued)

| India Mexico Mexico Mexico Poland France Austria China Austria Belgium France Luxembourg Poland Spain Iran Italy China Tunisia | Yamuna river Xochimilco wetland Across the country Tula Valley Kraków Across the country Across the country Beijing and Tianjin Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, Spain | Surface water Surface water Surface water Irrigation water Ground water Ground water Ground water WWTP effluents Ground water Surface water Ground water Streams Ground water | 1781.8 ± 0.7 13000000 179.6 2.5 5.4 9.0 1.6 74 n.d 0.79 n.d < 0.13 n.d 1.3 | Biswas and Vellanki (2021) Díaz-Torres et al. (2013) De La Torre (2011) Chávez-Mejía et al. (2019) Rusiniak et al. (2021) Lopez et al. (2015) Hohenblum et al. (2004) Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mexico Mexico Poland France Austria China Austria Belgium France Luxembourg Poland Spain Iran Italy China | Across the country Tula Valley Kraków Across the country Across the country Beijing and Tianjin Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Surface water Irrigation water Ground water Ground water Ground water WWTP effluents Ground water Surface water Ground water Streams | 179.6 2.5 5.4 9.0 1.6 74 n.d 0.79 n.d < 0.13 n.d 1.3 | Díaz-Torres et al. (2013) De La Torre (2011) Chávez-Mejía et al. (2019) Rusiniak et al. (2021) Lopez et al. (2015) Hohenblum et al. (2004) Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
| Mexico Poland France Austria China Austria Belgium France Luxembourg Poland Spain Iran Italy China | Tula Valley Kraków Across the country Across the country Beijing and Tianjin Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Irrigation water Ground water Ground water Ground water WWTP effluents Ground water Surface water Ground water Streams | 2.5 5.4 9.0 1.6 74 n.d 0.79 n.d < 0.13 n.d 1.3 | De La Torre (2011) Chávez-Mejía et al. (2019) Rusiniak et al. (2021) Lopez et al. (2015) Hohenblum et al. (2004) Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
| Mexico Poland France Austria China Austria Belgium France Luxembourg Poland Spain Iran Italy China | Tula Valley Kraków Across the country Across the country Beijing and Tianjin Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Irrigation water Ground water Ground water Ground water WWTP effluents Ground water Surface water Ground water Streams | 2.5 5.4 9.0 1.6 74 n.d 0.79 n.d < 0.13 n.d 1.3 | Chávez-Mejía et al. (2019) Rusiniak et al. (2021) Lopez et al. (2015) Hohenblum et al. (2004) Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
| France Austria China Austria Belgium France Luxembourg Poland Spain Iran Italy China | Across the country Across the country Beijing and Tianjin Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Ground water Ground water WWTP effluents Ground water Surface water Ground water Streams | 9.0 1.6 74 n.d 0.79 n.d <0.13 n.d 1.3 | Rusiniak et al. (2021) Lopez et al. (2015) Hohenblum et al. (2004) Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
| France Austria China Austria Belgium France Luxembourg Poland Spain Iran Italy China | Across the country Across the country Beijing and Tianjin Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Ground water Ground water WWTP effluents Ground water Surface water Ground water Streams | 9.0 1.6 74 n.d 0.79 n.d <0.13 n.d 1.3 | Lopez et al. (2015) Hohenblum et al. (2004) Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
| China Austria Belgium France Luxembourg Poland Spain Iran Italy China | Across the country Beijing and Tianjin Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | WWTP effluents Ground water Surface water Ground water Streams | 74 n.d 0.79 n.d <0.13 n.d 1.3 | Hohenblum et al. (2004) Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
| Austria Belgium France Luxembourg Poland Spain Iran Italy China | Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Ground water Surface water Ground water Streams | n.d 0.79 n.d <0.13 n.d 1.3 | Lei et al. (2020) Hohenblum et al. (2004) Glineur et al. (2018) |
| Belgium France Luxembourg Poland Spain Iran Italy China | Across the country Different rivers Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Surface water Ground water Streams | n.d <0.13 n.d 1.3 | (2004) Glineur et al. (2018) |
| France Luxembourg Poland Spain Iran Italy China | Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Ground water Streams | n.d 1.3 | Glineur et al. (2018) |
| France Luxembourg Poland Spain Iran Italy China | Rhône-Alpes Pontpierre Kraków WWTP Quart, Catalonia, | Ground water Streams | n.d 1.3 | |
| Luxembourg Poland Spain Iran Italy China | Pontpierre Kraków WWTP Quart, Catalonia, | Streams | | Vulliet et al. (2008) |
| Poland Spain Iran Italy China | Kraków WWTP Quart, Catalonia, | Ground water | n.d 3.0 | Banzhaf et al. (2013) |
| Iran Italy China | | | n.d <0.2 | Rusiniak et al. (2021 |
| Italy China | -r | Raw wastewater | 6.05–8.72 | Čelić et al. (2017) |
| China | Ahvaz City | Slaughterhouse wastewater | 98.3 | Hassani et al. (2016) |
| China | Ticino River | Surface water | 34 | Merlo et al. (2020) |
| | Huangpu River | Surface water | 74.8 | Zhang et al. (2014a) |
| | 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 Ngqwa |
| South Africa | Bloukrans river | Upstream water | 16.3 | Farounbi and Ngqwa (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) |
| 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) |
| 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 14 WWTP across the country | WWTP effluent French WWTP effluent | 1.5–2 (1.77) 1.6–4.4 (2.7) | King et al. (2016) Gabet-Giraud et al. |
| France | Gwinnett County, GA | Wastewater reclamation | <10 | (2010) Yang et al. (2011a) |
| France USA | Various WWTPs | treatment plant effluent WWTPs effluents | <1-2.1 (0.9) | Janex-Habibi et al. (2009) |
| | Malaysia Turkey Australia Australia France USA France, Germany, | River, and the Youngsan River Malaysia Klang Valley Turkey in Istanbul Australia Southeast Queensland Australia Southeast Queensland France 14 WWTP across the country USA Gwinnett County, GA France, Various WWTPs Germany, | Korea Han River, the Nakdong River, and the Youngsan River Malaysia Klang Valley WWTP effluent Turkey in Istanbul WWTP effluent Australia Southeast Queensland Effluent from WWTP Australia Southeast Queensland WWTP effluent France 14 WWTP across the country French WWTP effluent USA Gwinnett County, GA Wastewater reclamation treatment plant effluent France, Various WWTPs WWTPs effluents | Korea Han River, the Nakdong River, and the Youngsan River Malaysia Klang Valley WWTP effluent 0.8 Turkey in Istanbul WWTP effluent 7 Australia Southeast Queensland Effluent from WWTP 1.14 Australia Southeast Queensland WWTP effluent 1.5–2 (1.77) France 14 WWTP across the country French WWTP effluent 1.6–4.4 (2.7) USA Gwinnett County, GA Wastewater reclamation treatment plant effluent France, Various WWTPs WWTPs effluents <1–2.1 (0.9) Germany, |

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 | 392.5 | Hungary | Danube River | Surface water | 0.07 | Tölgyesi et al. (2010) |
| $(C_{22}H_{29}FO_5)$ | | Malaysia | Rivers in Selangor district | Surface water | 0.29 | Praveena et al. (2018) |
| (-22 25 - 37 | | 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, | 0-0.4 | Weizel et al. (2018) |
| | | Singapore | WWTP | Wastewater influent | 0.236 | Goh et al. (2018) |
| | | Siligapore South Africa | | Wastewater influent | | 1 1 |
| | | | Daspoort WWTW | Wastewater enfluents | 0.92 | Mhuka et al. (2020) |
| | | France | STP, downstream from Lyon | Treated wastewater, | 15 | Piram et al. (2008) |
| | | Italy | Pavia municipal waterworks, | rivers and streams. | 2–3 | Merlo et al. (2020) |
| | | Spain | Northern Italy surface waters Sewer of Girona University | Hospital effluents | 360 | Cruz-Morató et al. |
| | | | Hospital, Girona | p: d . 1 | 22 | (2014) |
| | | Spain | Katalan rivers (Ebre, Ter and Llobregat) and STPs located | River waters, influent and effluent sewage | <20 | Herrero et al. (2012) |
| Pulamain alama | 204.42 | China | in Tarragona area | Director | -0.E4.0.70 | Comp et al. (2010) |
| Triamcinolone | 394.43 | China | Pearl River system | River water | <0.54-0.79 | Gong et al. (2019) |
| $(C_{21}H_{27}FO_6)$ | | 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) |
| (021112803) | | 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) |
| Γrenbolone (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 | Surface water | <25 | Kolodziej and Sedlak (2007) |
| | | TICA | California | Deed and date of the | -0.0 | 0-11-4-1 (0011) |
| | | USA | north central Indiana | Beef and dairy effluent | <8.9 | Gall et al. (2011) |
| | | USA | University of Nebraska Haskell | Feedlot runoff from treated cattle shed | <115 | Bartelt-Hunt et al. (2012) |
| | | USA | Agricultural Laboratory near Concord Purdue Animal Science | Untreated lagoon water | 22–1720 | Khan and Lee (2012) |
| | | UJA | Research and Education Center | Chilicated lagoon water | 22-1/2U | Man 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 ₃ O ₃ S | 253.276 | 1.6, 5.7 | 0.89 | 6.42×10^{-13} | H ₂ N 0 N-0 | Patel et al. (2019) |
| Acetaminophen (Paracetamol) (103-90-2) | Analgesic/ antipyretic/ Human and veterinary use | C ₈ H ₉ NO ₂ | 151.16 | 9.38 | 0.46 | 8.93×10^{-10} | HO | 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 | H ₃ CO OH OH | 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} | O OH N | 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} | ONH ₂ | Patel et al. (2019) |
| Alprazolam (28981-97-7) | Benzodiazepine/ Anti-anxiety drug/Human use | $C_{17}H_{13}CIN_4$ | 308.769 | | 2.12 | 9.77 × 10 ⁻¹² | CI N N | 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} | H ₃ C 0 H H H | 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} | CH ₃ OH | 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} | HO OH | 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 | H ₃ C OH | 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 | HO CH ₃ OH CH ₃ | 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 | HO H ₃ C OH H ₃ C OH | 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 | HO HO OH | 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} | OH H H H | 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

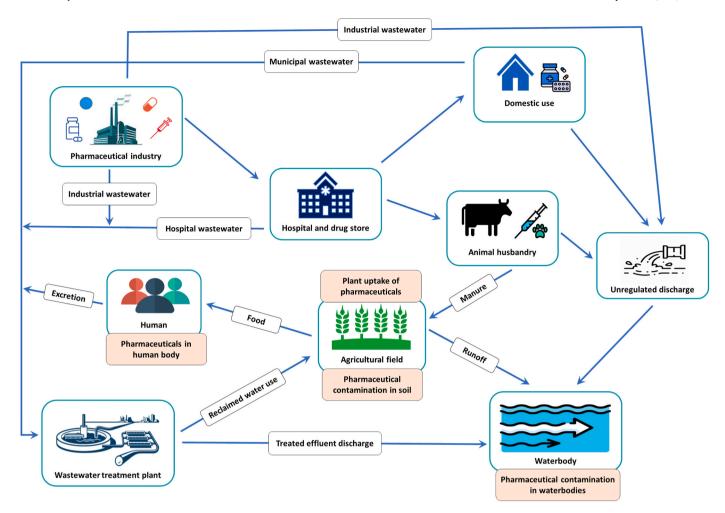


Fig. 1. The sources and pathways for the occurrence of pharmaceutical pollutants and their residues in the environment. Pharmaceutical industries serve as the main source of drugs for humans and animals and eventually end up in different environmental component as pollutants. Ultimately through the use 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 (logKow), 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 ($1 < logK_{ow} < 3$), 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' logKow 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 (log $K_{\rm ow}$) 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 $0.2~\mu g~kg^{-1}$, 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).

Chemosphere 364 (2024) 143055

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 | - | Antibiotics | - | Penicillin-G | Herbal | Mixed | Mixed | Mixed | Penicillin | - | - | | |
| type 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 m³ 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 lowincome 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 Penuelas, 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 (continued)

 Table 4

 Impact of pharmaceutical pollutants on plant growth.

| Impact of pharmaceut | ical pollutants on plant growth. | Pharmaceutical | Impact on plant | | | | |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|
| Pharmaceutical pollutants | Impact on plant | pollutants | | | | | |
| Pharmaceutical pollutants 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 (<i>Brassica chinensis</i> 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) | pollutants 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 | | | | |
| Acetaminophen | Affected <i>Cyperus involucratus</i> plant growth (Xu et al., 2020) 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 | | inhibited root growth (Bhattacharya and Gupta, 1981) At 0.1 μM concentration decreased the number of generative plants in <i>Arabidopsis thaliana</i> (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 <i>Arabidopsis thaliana</i> (Janeczko et al., | | | | |
| | 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 ₂ O ₂ accumulation in mung bean (<i>Vigna radiata</i>) plants (Almohisen, 2019) Increased oxidative stress in duckweed (Kummerová et al., 2016) Higher doses of paracetamol reduced the photosynthetic activity in lettuce (<i>Lactuca sativa</i>) (Kudrna et al., 2020) | Estriol (E3) | 2003) Inhibitory effects on the development of <i>Lepidium sativum</i> 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 <i>Ecballium ehterium</i> (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 <i>Arabidopsis thaliana</i> (Janeczko et al., 2003) | | | | |
| Carbamazepine | Increased carbamazepine uptake by zucchini (<i>Cucurbita pepo</i>) resulted in a decrease in above and below ground biomass (<i>Carter et al., 2015</i>) Collard greens (<i>Brassica oleracea</i>) 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 | 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 | | | | |
| Estrone (E1) | the leaves (Riemenschneider et al., 2017b) 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) | Dexamethasone | 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) 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) | | | | |
| | 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 <i>Arabidopsis thaliana</i> (Janeczko et al., 2003) | 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

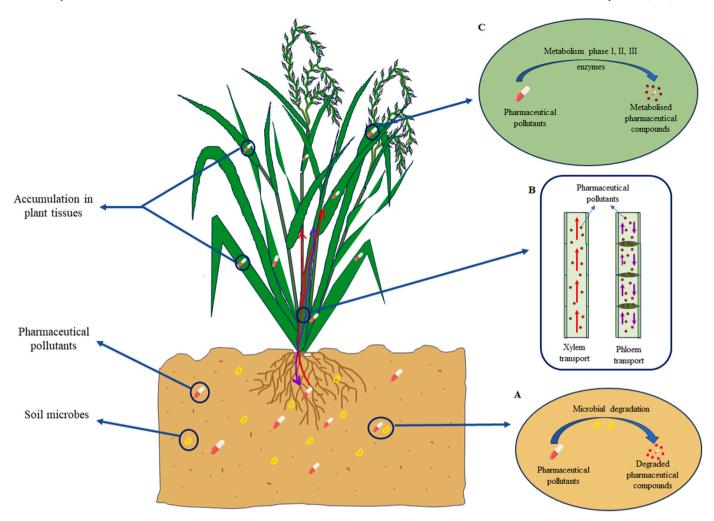


Fig. 2. Uptake and accumulation of pharmaceutical pollutants within plant tissues. In the soil, pharmaceutical pollutants are degraded by different microbes (A). The uptake pathways of pharmaceutical pollutants in plants involve the xylem and phloem transport (B). Within plant tissues, metabolic phase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

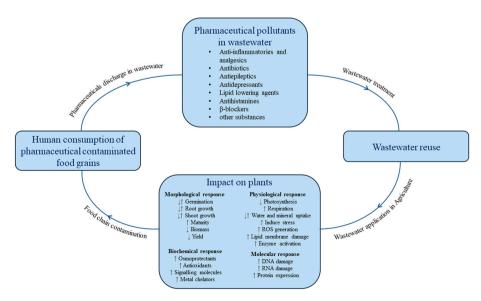


Fig. 3. Impact of pharmaceutical pollutants on plants and human food chain contamination from wastewater reuse in agriculture. Arrows indicate increase (†) or decrease (↓) of respective traits in plants.

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, glycosyldiclofenac is mainly metabolized into 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 $\mu g/L$ but exhibited hormesis at lower concentrations of 50 and 100 $\mu g/L$ 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

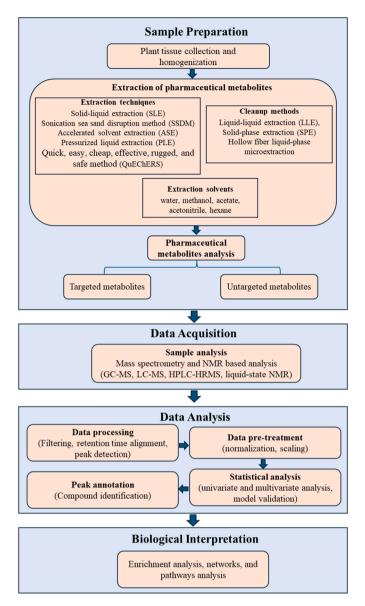


Fig. 4. Schematic workflow of targeted and non-targeted analysis of pharmaceutical metabolites in plant tissues.

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 micro-extraction. 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.

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