Science of the Total Environment 939 (2024) 173634

Contents lists available at ScienceDirect

Science of the Total Environment

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

Treatment of pharmaceutical industry wastewater for water reuse in Jordan using hybrid constructed wetlands

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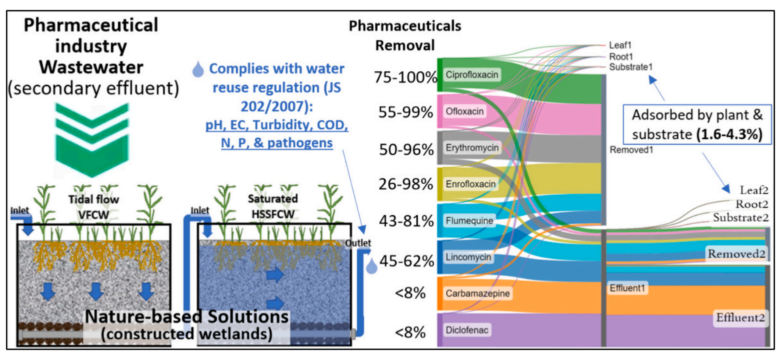
HIGHLIGHTS

- Constructed wetlands (CWs) can effectively treat pharmaceutical industry wastewater.
- The use of Jordanian zeolite and tidal flow operation enhanced treatment performance.
- The innovative hybrid CWs met the highest water reuse standards for effluent.
- Zeolite modification was not necessary in long-term operated CWs for treatment.
- Biodegradation of pharmaceuticals (up to 61 %) was the key removal pathway in CWs.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Modified zeolite
Micropollutants
Nature-based solution
Removal pathways
Tidal flow wetland
Treatment wetlands

ABSTRACT

Developing cost-efficient wastewater treatment technologies for safe reuse is essential, especially in developing countries simultaneously facing water scarcity. This study developed and evaluated a hybrid constructed wetlands (CWs) approach, incorporating tidal flow (TF) operation and utilising local Jordanian zeolite as a wetland substrate for real pharmaceutical industry wastewater treatment. Over 273 days of continuous monitoring, the results revealed that the first-stage TFCWs filled with either raw or modified zeolite performed significantly higher reductions in Chemical Oxygen Demand (COD, 58 %–60 %), Total Nitrogen (TN, 32 %–37 %), and Phosphate (PO_4, 46 %–64 %) compared to TFCWs filled with normal sand. Water quality further improved after the second stage of horizontal subsurface flow CWs treatment, achieving log removals of 1.09–2.47 for total coliform and 1.89–2.09 for *E. coli*. With influent pharmaceutical concentrations ranging from 275 to 2000 μg/L, the zeolite-filled hybrid CWs achieved complete removal (>98 %) for ciprofloxacin, ofloxacin, erythromycin, and enrofloxacin, moderate removal (43 %–81 %) for flumequine and lincomycin, and limited removal (<8 %) for carbamazepine and diclofenac. The overall accumulation of pharmaceuticals in plant tissue and substrate adsorption accounted for only 2.3 % and 4.3 %, respectively, of the total mass removal. Biodegradation of these pharmaceuticals (up to 61 %) through microbial-mediated processes or within plant tissues was identified as the key removal pathway. For both conventional pollutants and pharmaceuticals, modified zeolite wetland media could only slightly enhance treatment without a significant difference between the two treatment groups. The final effluent from all hybrid CWs complied with Jordanian treated industry wastewater reuse standards

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https://doi.org/10.1016/j.scitotenv.2024.173634
Received 14 January 2024; Received in revised form 19 May 2024; Accepted 28 May 2024
Available online 30 May 2024

(category III), and systems filled with raw or modified zeolite achieved over 95 % of samples meeting the highest water reuse category I. This study provides evidence of using hybrid CWs technology as a nature-based solution to address water safety and scarcity challenges.

1. Introduction

The persistent discharge of pharmaceuticals and personal care products (PPCPs) from domestic and industrial wastewater sources has resulted in significant detrimental impacts on human health, food security, and the global aquatic environment (Wilkinson et al., 2022). Conventional wastewater treatment plants are inefficient at removing such micropollutants (Comber et al., 2018), and the associated environmental risks are exacerbated in less developed countries due to the lack of economic investment in advanced wastewater treatment facilities. Moreover, in countries where the pharmaceutical sector is a key economic pillar and faces serious water scarcity, such as in Jordan (WHO/UNICEF, 2000), the presence of a large amount of pharmaceutical residues in water bodies poses even greater possibilities and risks (Al-Mashaqbeh et al., 2019). Hence, there is an urgent need to develop sustainable and cost-efficient technologies for treating pharmaceutical industry wastewater.

Constructed wetlands (CWs) can be designed as nature-based solutions that offer engineered systems for various wastewater treatment purposes while simultaneously providing additional benefits such as carbon sequestration and biodiversity enhancement (Dotro et al., 2017). Previous studies have demonstrated the effectiveness of CWs in remediating pharmaceuticals from wastewater, with microbe-mediated bioremediation playing a significant role (Matamoros et al., 2005; Zhang et al., 2017a, 2017b). The establishment and growth of biofilm in CWs rely heavily on the presence of suitable media/substrate. Although sand and gravel are commonly used due to their cost-effectiveness and easy availability (Dotro et al., 2017), recent advancements have explored more efficient substrates, such as biochar, seashells, and wood chips, to enhance treatment efficiency (Yang et al., 2018). In the context of pharmaceutical removal in CWs, the physical characteristics (e.g., porosity) and chemical properties (e.g., associated functional groups) of specialised substrates could also benefit the treatment process (Yang et al., 2018).

Zeolite is a microporous material with a large specific surface area, abundant functional groups (hydroxyl, carboxyl, and carbonyl), and active surface sites that promote pollutant adsorption and enhance biofilm development for biodegradation processes (Lu et al., 2022). Previous studies have demonstrated its superior performance in enhancing the removal of nutrients (Vera-Puerto et al., 2020), heavy metals (Guo et al., 2021), and in reducing greenhouse gas emissions (Zhao et al., 2022) in CWs for wastewater treatment. CWs equipped with zeolite have also shown better treatment performance for pharmaceuticals compared to CWs filled with normal gravel (Du et al., 2020; Zhang et al., 2018a). However, the hydrophilic and negatively charged surface of raw zeolite is less effective in trapping specific pharmaceutical compounds, such as carbamazepine (Al-Mashaqbeh et al., 2021). The adsorption affinities for pharmaceuticals can be improved through surface modifications, such as hydroxyl modification, of the zeolite (Cabrera-Lafaurie et al., 2014). Therefore, the application of modified zeolite in CWs is expected to extend the contact time between biofilms and pharmaceuticals, resulting in enhanced bioremediation efficiency.

Apart from the substrate, the design and operation strategies of CWs can influence microorganism growth and the treatment efficiency of pharmaceuticals. Artificial aeration can enhance O_2 transfer to the functional biofilm and has been incorporated into CWs, resulting in an approximate 33 % improvement in COD and NH_4^+-N removal (Nivala et al., 2020). The aerated CWs also showed significant improvements in pharmaceutical micropollutant removal (Ávila et al., 2021). However, artificial aeration relies on external energy input and demands additional maintenance efforts. Tidal flow operation, which mimics nature tidal scenarios, has been proven to be an efficient approach to augment O_2 availability in CWs, requiring only half the energy and area to treat the same wastewater volume compared to aerated wetlands (Austin and Nivala, 2009). While tidal flow CWs have been explored for treating various types of wastewater (Lv et al., 2013; Zhang et al., 2017a), there have been no studies focused on pharmaceutical removal.

Due to the distinct chemical characteristics of pharmaceuticals, certain compounds, such as ibuprofen, salicylic acid, and sulfamethoxazole, are primarily removed via aerobic biodegradation. In contrast, anaerobic biodegradation is more favourable for the removal of naproxen and caffeine (Li et al., 2014). Therefore, hybrid CWs, which combine a sequence of aerobic and anoxic/anaerobic conditions, are tested to enhance the treatment of wastewater containing a mixture of pharmaceutical compounds (Ávila et al., 2015, 2014). However, the use of tidal flow CWs as the first aerobic treatment stage remains unexplored, particularly in real pharmaceutical wastewater investigations, unlike the focus on artificial wastewater in numerous previous studies.

This is the first study of its kind in Jordan to develop and evaluate the effectiveness of a hybrid CWs strategy as a nature-based solution for treating real pharmaceutical industry wastewater. Three groups of mesocosm-scale hybrid CWs, consisting of tidal flow CWs and saturated horizontal subsurface flow CWs, were established. Modified and raw local zeolite were used as substrates for comparison with normal sand filled CWs in terms of pharmaceutical removal. The contributions of plant uptake, substrate adsorption, and biodegradation in pharmaceutical removal were assessed in all systems to explore removal pathways. Furthermore, the removal of pathogens (total coliforms and *E. coli*) was monitored to assess the effluent's compliance with regulations for treated industrial wastewater reuse. The results of this study could provide valuable evidence supporting the application of nature-based solutions for the effective treatment of pharmaceutical wastewater.

2. Materials and methods

2.1. Materials and reagents

All reagents utilised for Liquid Chromatography–Mass Spectrometry were of analytical grade. Acetonitrile, acetone, and methanol were acquired from Carlo Erba (99.9 % purity). Formic acid (≥98 % purity) and ammonium formate (99 % purity) were obtained from Scharlau and Merck, respectively.

2.2. Wetland substrate and zeolite surface modification

Local zeolite (Ø 6–10 mm) and river sand (Ø 5–10 mm) were purchased from Agriculture Green Zeolite CO., and Madar Water Technology Ltd., in Jordan, respectively. Both materials were washed with tap water and subsequently air-dried prior to use. Moreover, part of the clean raw zeolite was subjected to hydrophobic modification following the method reported by Al-Jammal et al. (2019). Briefly, a solution was prepared by mixing 708 mL of ultrapure water (Milli-Q Ultrapure, Millipore Sigma, Molsheim, France) with 375 mL of 0.5 M hydrochloric acid (HCl). Subsequently, 1.8 kg of raw zeolite was immersed in the solution for 24 h. The solid materials were then collected, rinsed with ultrapure water, and air-dried at ambient temperature for two days to obtain the modified zeolite. It is hypothesised that acid-modified zeolite could enhance effective cation exchange capability, thereby benefiting pollutant adsorption and consequently biodegradation.

2.3. Experimental setup and operation

Three hybrid mesocosm-scale CWs were established at the Royal Scientific Society, Jordan. The whole system was placed outdoors under ambient conditions but shielded from precipitation (Fig. 1a–b). In each system, a vertical flow CW operated under tidal flow mode (TFCW) served as the first-stage treatment, followed by a saturated horizontal subsurface flow CW (HSSFCW) as the second-stage treatment (Fig. 1c). In each CW (H × L × W of 50 × 30 × 30 cm), a 5 cm layer of larger-sized gravel (Ø 3 cm) was placed at the bottom and PVC pipes with 10 holes (Ø5 mm) were buried to collect and drain the water. In the three first-stage TFCWs, different substrates, i.e. normal river sand (system 1), raw zeolite (system 2), and modified zeolite (system 3), were used as the main media. However, raw zeolite was used as the main media for all three second-stage HSSFCWs. The overall height of the media layer was approximately 45 cm in all CWs. The local wetland plant, *Typha angustifolia*, was collected from the Zarqa River and planted in all systems.

An activated sludge system was in operation at a local pharmaceutical factory for the treatment of its wastewater, mainly focusing on the removal of organics and ammonia. The effluent was transported every 1–2 weeks from the factory and stored in two 1 m^3 tanks for treatment (Fig. 1a). The three hybrid CWs received an identical average inflow rate of 120 mL/min, resulting in a hydraulic loading rate (HLR) of 1.92 m/d and a hydraulic retention time (HRT) of 1 d for each CW. Tidal operation in all three first-stage TFCWs was controlled by a peristaltic pump and a solenoid valve equipped with a timer. The flood and drain cycle occurred every 12 h. The effluent was then received by the second-stage HSSFCWs, maintaining a water level of approximately 40 cm. All systems were operated under these conditions for three months (September–December 2021), allowing for biofilm development and plant growth.

2.4. Sample collection and analysis

2.4.1. Water quality and pollutant analysis

Wastewater samples were collected weekly from the storage inlet tank and the outlet of each CW. The pH, electrical conductivity (EC), and turbidity were analysed using a multi-probe (Multi 9630 IDS WTW, Hach, Germany). Concentrations of chemical oxygen demand (COD), total nitrogen (TN) and phosphate (PO_4) were determined using spectrophotometer and test kits (XD 7000 (VIS), Lovibond, Germany). In total, 39 sampling campaigns were conducted over a period of 273 days (December 2021–September 2022), with triplicate samples collected for each sampling point prior to analysis.

2.4.2. Pharmaceutical analysis in water, plant tissue, and substrate

Pharmaceutical compounds in water samples were detected monthly according to the method developed by Al-Mashaqbeh et al. (2019). First, a polymeric HLB Oasis 6 cc cartridge (Milford, MA, USA) was conditioned by sequentially passing 6 mL of acetone and 6 mL of methanol, followed by 6 mL of deionised water. Then, a 50 mL water sample was passed through the Solid Phase Extraction (SPE) cartridge at a rate of ~10 mL/min. The cartridge was then rinsed with 5 mL of deionised water, and room air was allowed to flow through it under continued suction for at least 5 min to ensure proper drying. All extracted samples were eluted by adding 10 mL of methanol. The pharmaceuticals were analysed by Liquid Chromatography-Mass Spectrometry (AB SCIEX Triple Quad 5500, USA). The limits of detection for the compounds were 0.015 μg/L.

At the end of the experiment, plant leaves (aboveground biomass), roots (belowground biomass), and CW substrates were collected from all CWs for the analysis of accumulated pharmaceuticals. The leaves and roots were cleaned and the freeze-dried (Yamato, DC401, Japan) for 24 h before extracting pharmaceuticals following the method reported by Carvalho et al. (2018) with some modifications. In brief, 1.0 g of dried

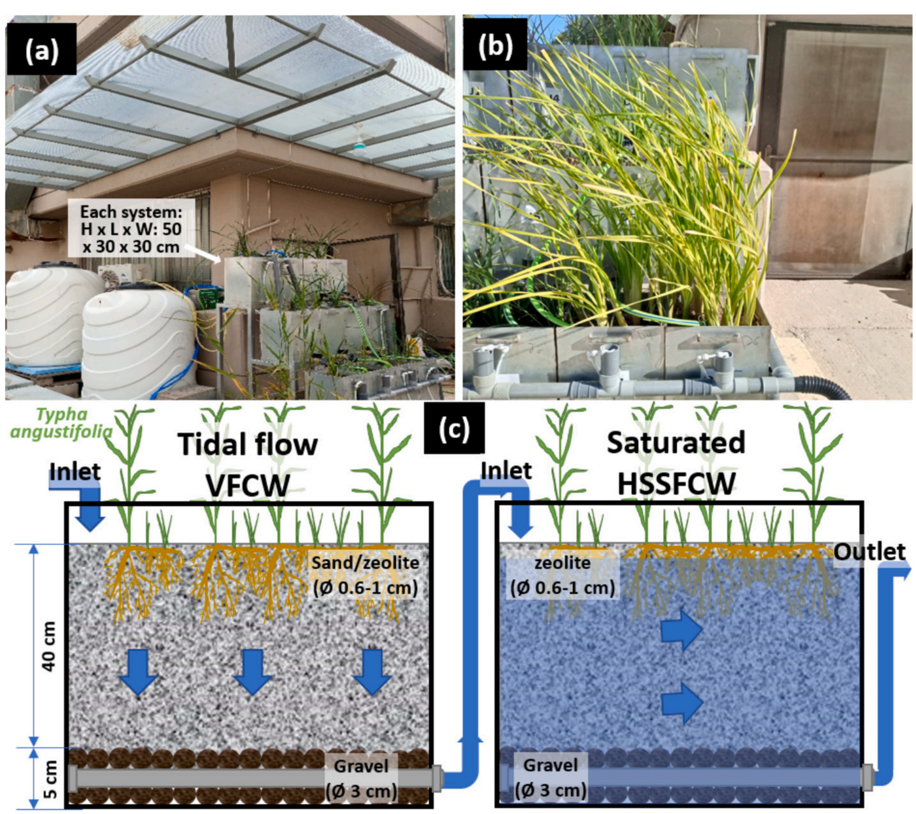

Fig. 1. The photo of the mesocosms-scale hybrid constructed wetland systems (CWs) set up at the beginning (a) and at the middle period (b) of the study. The schematic of each hybrid system (c) consisted of a tidal flow CW and a saturated horizontal flow CW.

samples was extracted with 20 mL of methanol using ultrasonic treatment (VWR, USC-THD, Malaysia) for 30 min at 10 °C. All extracted samples were then centrifuged at 3000 rpm for 20 min in a refrigerated centrifuge (Centurion K2015R Refrigerated Centrifuge, UK). The supernatant was decanted and evaporated using a Turbo-Vap until the volume reached 1 mL. Deionised water (20 mL) was added to the evaporated samples. Then, the aforementioned SPE method was applied to extract the samples from the liquid before analysis. For substrates, 20 g of dried samples were extracted with 20 mL of methanol by ultrasonication for 30 min. Then, the supernatant was collected in a glass test tube and evaporated using Turbo-Vap until the volume reached 5 mL. Furthermore, the measured above-ground plant mass and estimated below-ground plant mass at the end of the study were used to evaluate the mass balance of pharmaceutical compounds in each system.

2.4.3. Pathogen assessment

The presence of *Escherichia coli* (*E. coli*) in water samples is not only a statutory indicator of hygienic quality (Luo et al., 2017) but also an indicator for the surveillance of antimicrobial resistance (AMR) (Anjum et al., 2021). Both total coliforms and *E. coli* were evaluated in all water samples from the influent and final effluent of the three hybrid CWs. Water samples were enumerated by membrane filtration (0.45-μm pore size, 47-mm diameter sterile cellulose nitrate filter) and the plate count approach according to standard procedures (APHA, 2007). Filmplater™ *E. coli* and coliform count plates (Oasis Biochem, China) were used to quantify fecal indicators following incubation at 37 °C for 24 h.

2.5. Statistical analysis

Kruskal-Wallis tests were conducted to compare all water quality parameters and influent/effluent pollutant concentrations among the three hybrid CWs with a significance level of $p = 0.05$. To identify differences in treatment performance patterns between individual treatment stages and the three hybrid CWs, principal component analysis (PCA) was conducted using changes in water parameters, pollutants (nutrients, pharmaceuticals, and pathogen indicators) between influent and effluent. Prior to the PCA analysis, data were standardised using the autoscaling method to ensure that each variable had an equal influence in the analysis (Lyu et al., 2018). The PAST 4.03 software was used for statistical analysis. Moreover, Sankey diagrams were generated using the SankeyMATIC platform (https://sankeymatic.com/) to illustrate the removal pathways of pharmaceuticals in all CWs.

3. Results and discussion

3.1. Water quality and pollutant removal

Due to the challenge of water scarcity, Jordanian industries, regardless of their sector, are required to follow regulations governing the treatment of industrial wastewater for irrigation reuse (JS 202/2007). To meet the standard (based on annual average values), the effluent must have a pH level within the range of 6 to 9 and turbidity below 10 NTU (category III, or no specific requirement for other categories). Total dissolved solids (TDS) should be below 2000 mg/L, equivalent to an electrical conductivity (EC) of 4 mS/cm when converted to sodium chloride. The maximum allowable concentrations of TN, COD and PO_4 are 100, 500, and 30 mg/L, respectively. During the study period, the effluent from the activated sludge treatment system used by the industry (CW inlet in Fig. 2) met the standards for pH (7.2–8.1, Fig. 2b), EC (1.4–2.6 mS/cm, Fig. 2c), turbidity (5–72 NTU, Fig. 2d), and TN (6–30 mg/L, Fig. 2f). Although median values for COD (490 mg/L, Fig. 2e) and PO_4 (28 mg/L, Fig. 2g) were within regulatory limits, approximately 20 % of samples did not comply with the regulation. The results indicated that the current activated sludge system may be undersized or in need of updating.

The experiment was conducted outdoors, and the average water temperature varied with season changes, fluctuating between 0.5 °C to 32 °C (Fig. 2a). The effluent pH from the TFCW equipped with HCl-modified zeolite (system 3, Fig. 2b) was significantly lower than that from TFCW filled with normal sand (system 1) and raw zeolite (system 2), possibly due to the release of H^+ ions from the HCl-modified zeolite (Lu et al., 2022). However, the final effluent from all three hybrid CWs maintained a similar neutral pH range (7.1–8.4) compared to the influent, highlighting the capabilities of CWs in regulating pH during wastewater treatment (Ram and Vineet, 2015). Similar to previous studies that used CWs for treating pharmaceutical polluted water (Zhang

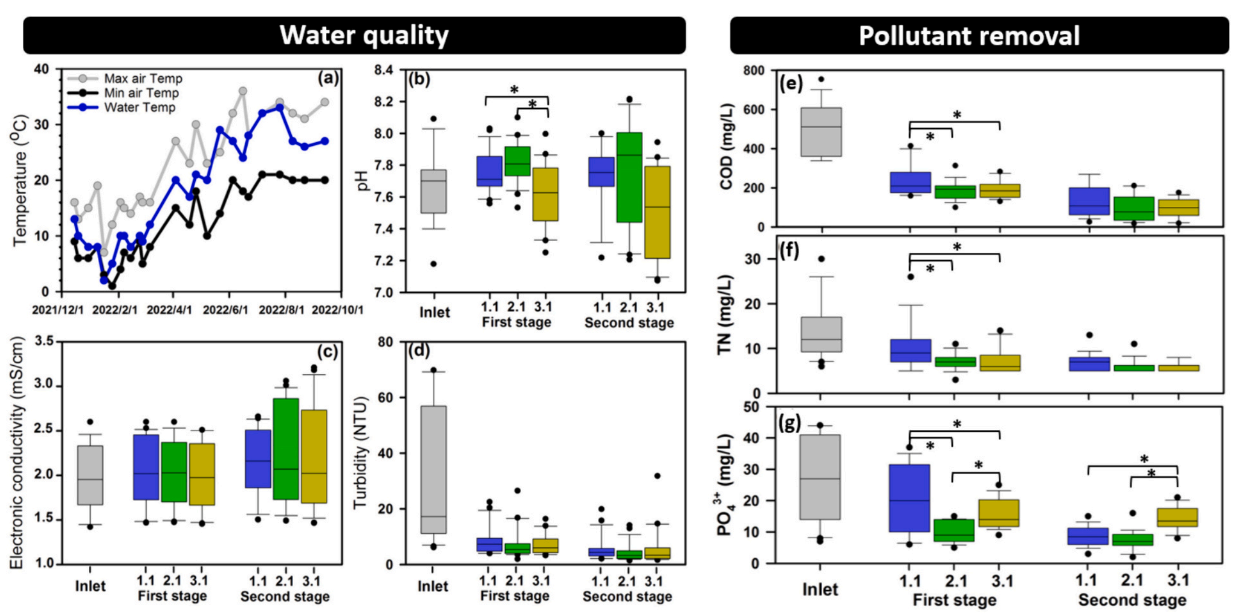

Fig. 2. The changes in water quality, including temperature (a), pH (b), electrical conductivity (c), and turbidity (d), in three hybrid constructed wetlands (CWs). The concentrations of COD (d), TN (f), and PO_4^{3-} (g) in the inlet and outlet of each CW. The stars above different bars represent statistical differences ($p < 0.05$). System 1.1, 2.1, and 3.1 represent tidal flow CWs filled with sand, raw zeolite, and modified zeolite, respectively. System 1.2, 2.2, and 3.2 represent horizontal subsurface flow CWs filled with raw zeolite.

et al., 2018b; Zhang et al., 2017b), EC values in the effluent did not significantly change after treatment in this study (Fig. 2c) and remained within the permissible limits. Nevertheless, all three systems significantly reduced turbidity, with median values reaching 5–6 NTU, and over 95 % of the samples met the highest category (I) target specified in the reuse regulations.

Attributed to the superior aerobic conditions in TFCWs (Kizito et al., 2017), significant COD removal (57 %–61 %) was achieved after the first stage treatment in all three groups, with an additional 16 %–20 % COD removal occurring in the second stage of HSSFCWs (Fig. 2e). The effluent COD concentration (median of 216 mg/L) in TFCWs filled with sand was significantly higher than that in the other two groups, owing to the lower adsorption capabilities of sand compared to microporous zeolite material. No significant difference in terms of the COD effluent concentration was observed between TFCWs filled with modified zeolite (202 mg/L) and raw zeolite (194 mg/L). Although final effluent concentrations of COD were not significantly different among the three hybrid systems (median of 98–122 mg/L), only the two hybrid systems filled with zeolite in the first stage had over 95 % of the samples below 100 mg/L and met the highest category of the regulation (JS 202/2007).

Similar to COD, significantly lower median effluent concentrations of TN (7.5–8.1 mg/L) and PO_4 (9.8–13.8 mg/L) were observed for the first stage TFCWs filled with modified/raw zeolite compared to the conventional sand-filled TFCWs (9.1 and 20.3 mg/L for TN and PO_4, respectively) (Fig. 2f and g). Previous studies have also demonstrated superior removal performances of organics and nutrients in both horizontal (Stefanakis et al., 2009; Vera et al., 2014) and vertical flow (Stefanakis and Tsihrintzis, 2012) CWs filled with zeolite compared to gravel due to the increased site and cation exchange capability for pollutant attachment and consequently biodegradation. In this study, the final effluent of TN (7.1–8.2 mg/L) and PO_4 (8.4–14.5 mg/L) from all three hybrid systems met the highest water reuse standard. In summary, the results support the idea that hybrid CWs equipped with Jordanian local zeolite can upgrade the pharmaceutical industry wastewater treatment to meet the highest standard for treated industrial wastewater reuse. However, the HCl-modified zeolite did not significantly benefit water quality improvement for COD and nutrient removal.

3.2. Occurrence and removal of pharmaceuticals

Based on the pharmaceutical industry's production list, the top 22 pharmaceuticals with the highest production (Table S1) were detected through a single grab sampling before and after the existing activated sludge treatment system prior to this wetland study. All pharmaceuticals were found in the raw industrial wastewater, with the measured results indicating low removal efficiencies of <54 % (Table S2). This highlights the need for research into the proposed wetland treatment approach aimed at removing pharmaceuticals. In this study, water, plant, and substrate samples were collected from the CWs and analysed. Among these samples, eight pharmaceuticals were consistently found in all water samples (Table 1). The presence of the remaining compounds in plant tissue or substrate at the end of the study may be attributed to the accumulation process over the 273 days of CW operation. These eight compounds can be categorised into three types of medicine, including antiepileptic (carbamazepine), antibiotic (ciprofloxacin, erythromycin, ofloxacin, enrofloxacin, flumequine, and lincomycin), and analgesic (diclofenac). These compounds were selected as the targeted pharmaceuticals, with influent concentrations ranging between 275 and 2000 μg/L (Fig. 3), to assess the treatment performance of the CWs and evaluate removal pathways.

3.2.1. Completely removed compounds (ciprofloxacin, ofloxacin, erythromycin, enrofloxacin)

Under the average influent concentrations of 476, 481, 1844, and 378 μg/L for ciprofloxacin, ofloxacin, erythromycin, and enrofloxacin (Fig. 3a–d), most systems showed nearly complete removal (>98 %) of those four pharmaceuticals. The results align with the higher tier of reported values from a recent comprehensive review article by Ilyas

Table 1
Occurrence of pharmaceutical compounds in water, plant and substrate samples from three hybrid constructed wetland (CWs) along the experiment.

Pharmaceutical	System 1.1			System 1.2			System 2.1			System 2.2			System 3.1			System 3.2		
	water	plant	substrate	water	plant	substrate	water	plant	substrate	water	plant	substrate	water	plant	substrate	water	plant	substrate
Carbamazepine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cephapirin								X										
Ciprofloxacin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diclofenac	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enrofloxacin	X			X			X			X			X			X		
Erythromycin	X	X	X	X		X	X		X	X		X	X		X	X		X
Flumequine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lincomycin	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nalidixic acid		X	X		X	X		X	X		X	X		X	X		X	X
Norfloxacin					X						X			X			X	
Ofloxacin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oxytetracycline		X	X		X			X	X		X	X		X			X	
Pyrimthamine						X			X			X			X			X
Sulfadimidine		X			X	X		X	X		X	X		X	X		X	X
Sulfamerazine															X			
Sulfamethoxypyr-idiazine															X			X
Sulfamonometh-oxine															X			X
Sulfapyridine						X			X		X	X			X			X
Sulfaquinoxaline		X	X		X	X		X	X		X	X		X	X		X	X
Sulfamethoxazole		X	X		X	X		X	X		X	X		X	X		X	X
Thiamphenicol						X		X	X			X		X	X			X
Trimethoprim		X			X	X		X	X		X	X		X	X			X

Note: System 1.1, 2.1, and 3.1 represent tidal flow CWs filled with sand, raw zeolite, and modified zeolite, respectively. System 1.2, 2.2, and 3.2 represent horizontal subsurface flow CWs filled with raw zeolite. Grey highlighted pharmaceuticals are the eight targeted compounds continuously detected in water samples.

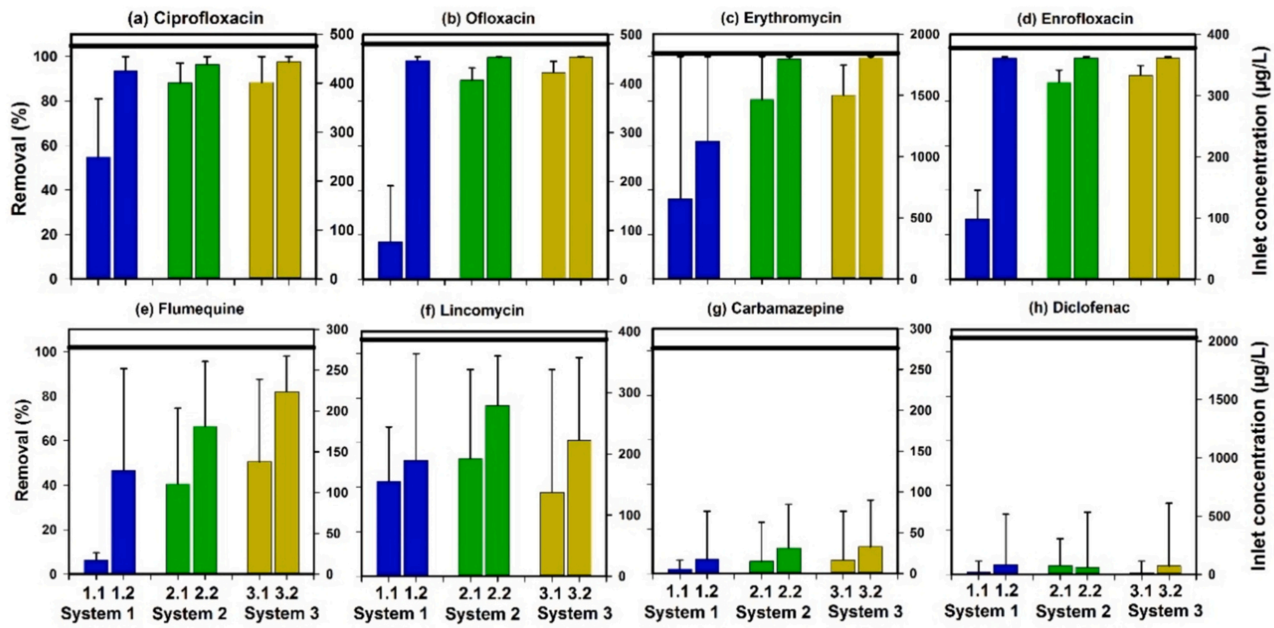

Fig. 3. The average influent concentrations (lines) and the removal efficiencies (bars) of pharmaceuticals, including ciprofloxacin (a), ofloxacin (b), erythromycin (c), enrofloxacin (d) flumequine (e), lincomycin (f), carbamazepine (g), and diclofenac (h), in each hybrid constructed wetland (CW). System 1.1, 2.1, and 3.1 represent tidal flow CWs filled with sand, raw zeolite, and modified zeolite, respectively. System 1.2, 2.2, and 3.2 indicate horizontal subsurface flow CWs filled with raw zeolite. Blue, green, and yellow bars represent the results from system 1, 2, and 3, respectively.

et al. (2020), which summarised the possible removal capabilities of ciprofloxacin (75 %–100 %), ofloxacin (55 %–99 %), erythromycin (50 %–96 %), and enrofloxacin (26 %–98 %) in different types of CWs. The removal efficiencies of the four pharmaceuticals through the first stage TFCWs filled raw zeolite (81 %–90 %) were similar to those (83–92 %) by the TFCWs filled with modified zeolite. The removal performances were significantly higher than those (17 %–53 %) by TFCWs filled with normal sand. It may be due to the microporous structures in zeolite providing a high surface area for chemical sorption and microbial attachment, while bridging hydroxyls (Si-OH) are catalytically active for various chemical reactions (Chen et al., 2016). The conclusions were also supported by the second stage HSSFCWs filled with zeolite in hybrid system 1, which accelerated the final removal of ciprofloxacin (92 %), ofloxacin (93 %), erythromycin (61 %), and enrofloxacin (97 %).

To compare the contributions of modified zeolite and raw zeolite, although the modified zeolite demonstrated better adsorption capabilities of pharmaceuticals in previous batch studies (Al-Mashaqbeh et al., 2021; Lu et al., 2022), such enhancement was not observed to significantly contribute in this long-term operated CWs study. This may be due to the excessive consecutive biodegradation overriding the function of improved adsorption. Both aerobic and anaerobic/anoxic biodegradation can help break down these compounds, however, aerobic biodegradation is more efficient and rapid in removing ciprofloxacin (Liu et al., 2013), ofloxacin, erythromycin (Chen et al., 2016), and enrofloxacin (Santos et al., 2019). Therefore, the first stage TFCWs filled with zeolite contributed the majority of the treatment, and the treatments in second-stage HSSFCWs were limited.

3.2.2. Moderately removed compounds (flumequine, and lincomycin)

The removal efficiencies of flumequine and lincomycin in all systems showed high variances, with final average removal efficiencies ranging between 43 % and 81 % under the average influent concentrations of 277 and 387 μg/L, respectively (Fig. 3e–f). Although previous studies on the removal of flumequine in CWs for wastewater treatment are lacking, phytoremediation of flumequine through plant uptake has been demonstrated (Carvalho et al., 2014), indicating the treatment potential of using CWs for flumequine. Similarly, previous studies on lincomycin removal in CWs also present large variations, ranging from negative removal (Hijosa-Valsero et al., 2011) to up to 81 % removal (Chen et al., 2016). The results demonstrated the necessity of further study and optimisation of CWs towards achieving high confidence in the removal of these two compounds.

Flumequine has a higher logKow value (1.85 to 2.63) than lincomycin (−1.7), indicating it tends to adsorb more readily to the substrate due to its high hydrophobicity and low affinity for water. This supports the observation that TFCWs equipped with zeolite performed significantly higher removal of flumequine (39 %–51 %) compared to the system filled with sand (8 %). However, the difference was not observed for lincomycin. Thus, adsorption probably plays a crucial role in flumequine removal in TFCWs, while other processes, such as bioremediation, contribute more to the removal of lincomycin. Notably, nearly half of the removed flumequine and lincomycin occurred in the second stage treatment in HSSFCWs, indicating that the removal of flumequine favours both aerobic (TFCWs) and anaerobic/anoxic (HSSFCWs) conditions.

3.2.3. Insufficiently removed compounds (carbamazepine, diclofenac)

The average influence concentrations of carbamazepine and diclofenac were 276 and 2013 μg/L, respectively (Fig. 3g–h), and the final removal efficiencies in all hybrid CWs were limited (<8 %). Carbamazepine is generally considered a recalcitrant compound, with <3 % removal occurring through the biodegradation process in CWs (Sharif et al., 2014; Zhang et al., 2013). The adsorption process by substrate/sediment in CWs was reported to be the key removal pathway (Park et al., 2018), however, the adsorbed compound can be released back into the water under changing operational/environmental conditions and resulted in low treatment performance. For diclofenac, considerable removal efficiencies (~90 %) have been reported in previous studies (Zhang et al., 2013), however, photodegradation was identified as the key removal pathway and contributed to ~80 % of the treatment. In this study, both stages of CWs were operated under subsurface conditions with a combination of anaerobic/anoxic tidal flow operation, which may have led to the low removal rates.

3.3. Removal pathways of pharmaceuticals

3.3.1. Accumulation in plant tissue and substrate

Previous studies have demonstrated that pharmaceutical compounds can be uptake, translocated, and accumulated in wetland plants. It is generally agreed that compounds with higher hydrophilic (lower logKow) are more easily taken up by plants (Ilyas et al., 2020; Zhang et al., 2017b). Therefore, the accumulation of the targeted eight compounds in plants should theoretically follow the order: ofloxacin > ciprofloxacin > lincomycin > enrofloxacin > carbamazepine > flumequine > erythromycin > diclofenac (logKow of −2, 0.28, 0.56, 0.7, 2.45, 2.6, 3.06, and 4.51, respectively). In this study, the highest plant accumulation of ofloxacin and ciprofloxacin was found in TFCWs filled with sand (Table 2). Different from this logKow-based assumption, lincomycin and enrofloxacin showed the lowest plant accumulation, which may be attributed to their relatively larger chemical structures hindering their uptake by plants (Carvalho et al., 2013). The loading of the pharmaceuticals could also affect the accumulated pharmaceuticals in various plants (Hijosa-Valsero et al., 2011). Although a similar trend in plant accumulation of all eight pharmaceuticals was observed in all three second stage HSSFCWs, system 1 showed high values compared to the other two groups, possibly due to higher loading (less removal in the first stage) (Fig. 3). Moreover, lower plant accumulation of the compounds was observed in both CWs filled with zeolite compared to the system filled with sand. The results indicated that the enhanced binding between pharmaceuticals and the special substrate could negatively affect removal functions through direct plant uptake processes.

It is clear that the highest substrate-accumulated pharmaceuticals were found in TFCWs filled with modified zeolite, followed by the system filled with raw zeolite and normal sand (Table 2), indicating the superior performance of microporous zeolite for the compounds' adsorption. The modification can benefit this process. Besides, the substrate adsorption of different chemicals has been reported to be driven by the soil organic carbon–water partitioning coefficient Koc (adsorption coefficient) (Ilyas and van Hullebusch, 2020; Liu et al., 2019). Thus, the targeted compounds, i.e., erythromycin, carbamazepine, and diclofenac (Koc of 570–3871 L/kg), showed the highest substrate accumulation in all systems, regardless of the two treatment stages. Other compounds with lower Koc values (35.51–83.49 L/kg) showed much lower or undetectable concentrations accumulated in the substrate.

3.3.2. Mass balance of pharmaceuticals during treatment

The pharmaceuticals mass balance calculations were further conducted to quantify the removal pathways of the compounds in CWs and visualised in the Sankey diagram (Fig. 4). Despite the considerable accumulation of pharmaceuticals identified in plant tissue and substrate (Table 2), the directly contributions of overall pharmaceuticals mass removal by plant uptake and substrate adsorption were below 2.3 % and 4.3 % in first stage TFCWs, and 1.6 % and 3.6 % in second stage HSSFCWs, respectively. Since the systems operated in subsurface mode and all pharmaceuticals were non-violated compounds, pathways such as photodegradation and evapotranspiration were limited. Thus, the majority of the removed mass after the 1st stage (up to 61 %) and 2nd stage treatment (up to 37 %) would primarily be through biodegradation (Fig. 4).

The results align with numerous previous studies that demonstrated plant accumulation and substrate adsorption constituted only up to <1 %–7 % (Delgado et al., 2020; Ravichandran and Philip, 2021; Zhang et al., 2016), and <0.17 %–6.6 % (Delgado et al., 2020; Matamoros et al., 2008; Zhang et al., 2017b), respectively, in pharmaceuticals removal in CWs. Considering the possibility that up to 50 % of the updated pharmaceuticals can be metabolised inside the plant (Ravichandran and Philip, 2021), the indirect contributions of plant update on their removal could be higher, although quantification was not possible in this study. Overall, it can be concluded that biodegradation of the compounds through microbial-mediated processes and within plant tissues were the key removal pathways in CWs.

3.4. Implementation potential and recommendations

3.4.1. Pathogen removal and safety

Ensuring the safety of treated industrial effluent for irrigation reuse extends beyond addressing chemical risks to tackle pathogenic contaminants. According to JS202/2007, three categories define the three categories of reuse standards for *E. coli*, i.e. <100, <1000 MPN/100 mL,

Table 2
The plant uptake of pharmaceuticals in plant leaves, roots and substrate (μg/Kg) during the experiment.

CW systems	Pharmaceuticals	System 1.1			System 1.2		
		Leaf	Root	Substrate	Leaf	Root	Substrate
Hybrid CW 1	Ciprofloxacin	15,048.5	55,902.6	267.7	620.3	10,837.7	9.5
	Ofloxacin	8079.9	26,511.4	213.6	39.3	6567.1	6.1
	Erythromycin	116.2	<5	44.1	<5	<5	2709.8
	Enrofloxacin	<5	<5	<5	<5	<5	<5
	Flumequine	4462.6	20,018.9	164.0	141.8	15,744.6	196.3
	Lincomycin	1914.7	9.6	<5	209.3	55.4	640.3
	Carbamazepine	24,383.0	5835.1	45.9	12,714.3	1752.7	446.8
	Diclofenac	1653.0	4790.4	86.3	134.2	5376.8	1872
Hybrid CW 2	Ciprofloxacin	58.3	1354.8	<5	106.9	761.1	<5
	Ofloxacin	79.8	719.8	<5	17.1	395.9	<5
	Erythromycin	<5	<5	1090.3	<5	<5	779.8
	Enrofloxacin	<5	<5	<5	<5	<5	<5
	Flumequine	100.9	12,387.7	75.3	119.4	9596.7	78.4
	Lincomycin	700.4	7.9	19.1	345.7	9.5	202.5
	Carbamazepine	9222.5	815.3	148.8	8157.7	1228.8	206.6
	Diclofenac	45.4	1444.1	128.6	46.8	4304.4	263.3
Hybrid CW 3	Ciprofloxacin	124.4	8602.3	8.1	81.6	1034.8	<5
	Ofloxacin	36.2	2893.6	<5	9.5	365.5	<5
	Erythromycin	<5	<5	1923.3	<5	<5	523.5
	Enrofloxacin	<5	<5	<5	<5	<5	<5
	Flumequine	87.4	11,657.8	325.9	212.6	9010.6	199.5
	Lincomycin	825.6	<5	12.3	321.4	7.4	97.5
	Carbamazepine	20,903.6	1092.5	375.6	8998.6	605.8	29.1
	Diclofenac	251.9	2331.6	671.4	41.2	2147.6	313.3

Note: System 1.1, 2.1, and 3.1 represent TFCWs filled with sand, raw zeolite, and modified zeolite, respectively. System 1.2, 2.2, and 3.2 represent HSSFCWs filled with raw zeolite. The mark of <5 represents below the detection limits.

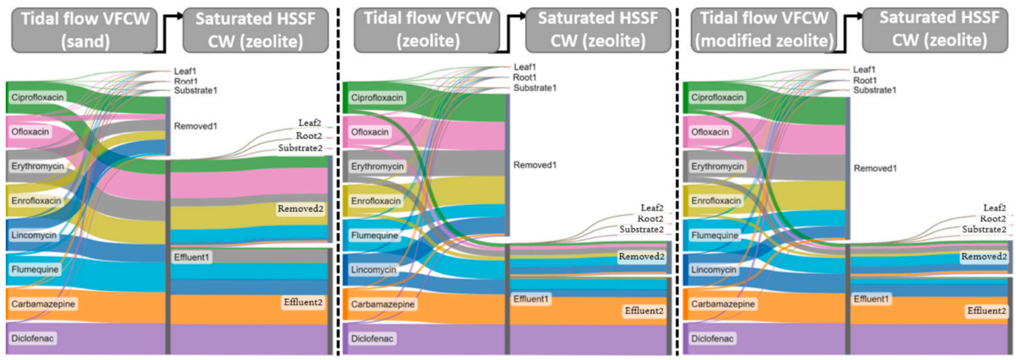

Fig. 4. Sankey diagram of the mass distribution for pharmaceutical compounds at three hybrid CWs.

and no specific requirements. Previous studies reported that the log removal of total coliform and *E. coli* for activated sludge systems ranged from 1 to 2 (Barrios-Hernández et al., 2020). With primary sedimentation and sand filters, the values can reach 3–4 log removal (Ottoson et al., 2006). In this study, the total coliform and *E. coli* concentrations in the wetland influent (effluent of the existing activated sludge systems) were 1.6×10^5 and 2.2×10^2 MPN/100 mL, respectively, which exceed the Jordanian water reuse regulation. Previous studies with similar wetland system setups, configured with vertical flow and HSSFCWs, showed 3.02–3.89 and 4.71 log removals for total coliform and *E. coli* during domestic wastewater treatment (García et al., 2013; Tunçsiper et al., 2012). In the case of pharmaceutical wastewater treatment in this study, slightly lower removals were observed, with final effluent concentrations of 540, 1300, and 1300 MPN/100 mL for total coliform (1.09–2.47 log removal) and 4, 4.5, and <1.8 MPN/100 mL for *E. coli* (1.89–>2.09 log removal) in the three hybrid systems, respectively. In compliance with statutory requirements, the treated effluent from all systems met the highest standards for irrigation reuse through nature-based treatment processes rather than relying on costly disinfection systems.

3.4.2. Key factors for systems design and operations

Principal component analysis (PCA) was conducted to discern the interrelationships between nutrient removal, the fate of eight pharmaceutical compounds, and treatment performance across each CW (Fig. 5). TFCWs filled with raw zeolite (system 2.1) and modified zeolite (system 3.1) located in the upper part of the coordinate (Fig. 5a), showed significant positive correlations with the removal of pollutants, including organics, nutrients, and pharmaceuticals. Compared with those systems, the TFCW filled with normal sand (system 1.1) demonstrated less efficacy in pollutant removal, indicating the desirability of zeolite application to augment system performance. For the second stage HSSFCWs, all three systems (1.2, 2.2, and 3.2) were located in the right part of the coordinate. Although system 2.2 and 3.2 exhibited better positive correlations with pharmaceuticals removal, which may be due to lower compound loading from superior first-stage treatment in TFCWs. Both first stage TFCWs and second stage HSSFCWs exhibited positive correlations with pharmaceutical removal, with TFCWs excelling in the removal of organics and nutrients. Thus, the hybrid CWs approach is a desirable option for pharmaceutical wastewater treatment, but the necessity of TFCWs can be evaluated if conventional pollutants are not the targets.

Considering the monitoring of total coliform and *E. coli* only at initial and final effluent stages, these parameters were included in the PCA analysis to gauge overall system performance (Fig. 5b). Systems 2 and 3 consistently demonstrated superior positive collaboration with the removal of all pollutants compared to System 1. Notably, System 3, incorporating modified zeolite in the first-stage TFCWs, showed better performance compared to system 2. Balancing treatment efficacy (Fig. 3) against potential additional costs associated with zeolite modification, it is recommended to employ raw zeolite in the proposed hybrid CWs for pharmaceutical wastewater treatment. It should be emphasised that if the selected zeolite is contaminated with other pollutants, such as heavy metals, these attached pollutants may leach out and cause deterioration of the effluent. Therefore, it is necessary to assess the composition of the zeolite sources prior to their application as wetland media.

3.4.3. Future research needs and assurance

A global survey indicates that nearly 10 million people could die each year due to antimicrobial resistance (AMR) if the situation is left

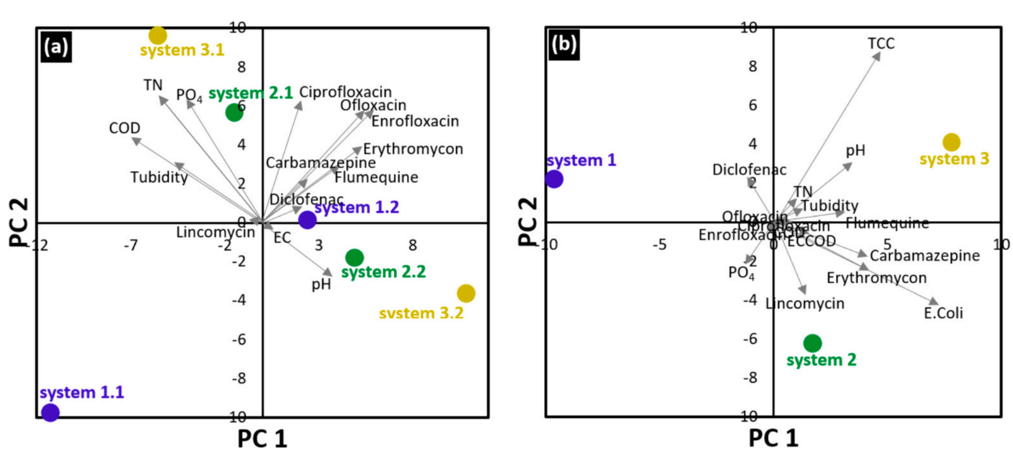

Fig. 5. Principal component analysis (PCA) of the treatment performance patterns in each constructed wetland (CW) system (a) and the overall performance of three hybrid CWs (b). The original data used for the factors (arrows in the figure) were the value differences between influent and effluent (removal efficiencies).

unchanged, and wastewater is the key source of AMR. Along with the biodegradation of antibiotics in CWs, there is a potential for the proliferation and accumulation of AMR (Bai et al., 2022), posing latent risks to human health when treated water is repurposed for irrigation. Therefore, it is essential to assess the fate and dynamics of AMR within nature-based solutions while treating pharmaceutical wastewater to proactively ensure the safety of the treated wastewater for subsequent reuse. Additionally, as evidenced by prior studies, certain by-products emerging from pharmaceutical degradation exhibit higher toxicity compared to their parent compounds (Matamoros et al., 2008; Pan et al., 2021), indicating the necessity for thorough monitoring and toxicity assessments. Nevertheless, regulations play a crucial role in guiding industries and practitioners in the application and monitoring of treatment systems. Challenges arise as pharmaceutical compounds, AMR, and by-products often do not align with regulatory priorities, or the costs associated with their comprehensive monitoring are extremely high. This highlights the need for collaborative efforts involving researchers, practitioners, and policymakers. Such holistic partnerships are essential in promoting the deployment of advanced technologies and aligning practices with evolving environmental sustainability goals.

4. Conclusions

This study demonstrated that the investigated hybrid CWs with the innovation of tidal flow operation and the use of local Jordanian zeolite could effectively treat real pharmaceutical industry wastewater. The final effluent met the highest standards for treated wastewater for irrigation reuse in terms of water quality and pathogen levels. The hybrid CWs were effective in removing a range of pharmaceutical compounds, with superior performance observed in zeolite-filled systems compared to sand-filled CWs. The enhancement of the treatment via additional modification of zeolite was found to be less significant. The biodegradation of the compounds through microbial-mediated processes and within plant tissues was identified as the key removal pathway, rather than direct plant uptake and substrate adsorption. Future research should focus on assessing antimicrobial resistance (AMR) dynamics within CWs, monitoring by-products, and fostering collaborations with policymakers to promote environmental sustainability.

CRediT authorship contribution statement

Othman Al-Mashaqbeh: Writing – original draft, Project administration, Methodology, Funding acquisition. **Layal Alsalhi:** Writing – original draft, Investigation, Data curation. **Lana Salaymeh:** Investigation. **Gabriela Dotro:** Writing – review & editing, Funding acquisition. **Tao Lyu:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data available within the article and its supplementary materials.

Acknowledgment

This work was supported by two consecutive Transforming Systems through Partnership (TSP) projects sponsored by the UK Royal Academy of Engineering (TSP2021\100376 and TSP-2324-6\136). The project titles are "Development of a nature-based solution for pharmaceutical wastewater treatment in Jordan" and "Reassuring the Safety of Treated Pharmaceutical Industrial Wastewater for Reuse in Jordan using Innovative Nature-based Solutions".

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.173634.

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