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Review

Role of Design and Operational Factors in the Removal of Pharmaceuticals by Constructed Wetlands

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Abstract: This study evaluates the role of design, operational, and physicochemical parameters of constructed wetlands (CWs) in the removal of pharmaceuticals (PhCs). The correlation analysis demonstrates that the performance of CWs is governed by several design and operational factors (area, depth, hydraulic loading rate, organic loading rate, and hydraulic retention time), and physicochemical parameters (dissolved oxygen, temperature, and pH); the removal efficiency of about 50% of the examined PhCs showed a significant correlation with two or more factors. Plants contributed significantly in the removal of some of the PhCs by direct uptake and by enhancing the process of aerobic biodegradation. The use of substrate material of high adsorption capacity, rich in organic matter, and with high surface area enhanced the removal of PhCs by adsorption/sorption processes, which are the major removal mechanisms of some PhCs (codeine, clarithromycin, erythromycin, ofloxacin, oxytetracycline, carbamazepine, and atenolol) in CWs. Although the removal of almost all of the studied PhCs showed seasonal differences, statistical significance was established in the removal of naproxen, salicylic acid, caffeine, and sulfadiazine. The effective PhCs removal requires the integrated design of CWs ensuring the occurrence of biodegradation along with other processes, as well as enabling optimal values of design and operational factors, and physicochemical parameters.

Keywords: constructed wetlands; design and operational parameters; pharmaceuticals; physicochemical parameters; removal efficiency; removal mechanisms; wastewater

1. Introduction

Constructed wetlands (CWs) are cost-effective and nature-based wastewater treatment technologies that were extensively investigated for the removal of organic matter and nutrients (nitrogen and phosphorus) (e.g., References [1–5]), as well as pharmaceuticals (PhCs) from wastewater [6–12]. Li et al. [8] conducted a review on the role of design parameters, including physical configuration, hydraulic mode, and vegetation species, in the removal of PhCs. Consistent with that, Gorito et al. [11] summarized the removal processes and the influence of design and operation parameters on the removal of four PhCs by CWs (azithromycin, clarithromycin, diclofenac, and erythromycin), which are on the priority list of the European Union (EU). Carvalho et al. [7] provided comprehensive insight into the potential of CWs for phytoremediation. Analogous to that, Ekperusi et al. [12] only considered the role of plants (duckweed, *Lemna minor*) in the removal of PhCs.

Moreover, several individual studies examined the effect of plants in CWs by considering the removal of PhCs in planted and unplanted CWs as noted in Table 1. The role of a support matrix in the removal of PhCs was explored by several authors, by using a substrate material of high adsorption capacity, rich in organic surfaces, and with high surface area (Table 1). The role of operational factors (hydraulic loading rate (HLR) and hydraulic retention time (HRT)) and physicochemical

parameters (pH, temperature, and dissolved oxygen (DO)) was explored by some researchers (Table 1). The role of temperature was explored by considering the effect of seasonality (summer/winter) on the removal of PhCs by several studies (Table 1). However, detailed statistical analysis is lacking, for example, a meta-analysis of available studies to establish significant correlation among PhC removal and governing factors. Nevertheless, the correlation of design and operational factors, and physicochemical parameters with the removal of PhCs was done within individual studies (also a limited number) but not between studies, as well as only for the removal of a limited number of PhCs. For instance, in the case of operational factors, correlation analysis was conducted only on the role of HRT, by few studies such as Zhang et al. [13] and Matamoros and Salvadó [14]. Similarly, in the case of physicochemical parameters, correlation analysis to investigate their impact was conducted by Hijosa-Valsero et al. [15,16], Chen et al. [17], Matamoros et al. [18], and Vymazal et al. [19].

Table 1. The design, operational, and physicochemical parameters of studied constructed wetlands (CWs) and corresponding references.

Design, Operational, and Physicochemical Parameters	References
Operational Factors	
Hydraulic loading rate (HLR)	Matamoros et al. [20]; Zhang et al. [21]; Dan et al. [22]; Ávila et al. [23]; Sharif et al. [24]
Hydraulic retention time (HRT)	Conkle et al. [25]; Matamoros et al. [26]; Zhang et al. [13,27]; Matamoros and Salvadó [14]; Dordio and Carvalho [28]; Verlicchi et al. [29]; Herrera-Cárdenas et al. [30]; Auvinen et al. [31]; Vymazal et al. [19]; Salcedo et al. [32]
Physicochemical Parameters	
pH	Hijosa-Valsero et al. [16]; Carvalho et al. [33]; Zhang et al. [34]
Temperature	Hijosa-Valsero et al. [16]; Ávila et al. [35]; Dan et al. [22]; Verlicchi et al. [29]; Matamoros et al. [36]; Vymazal et al. [19]; Nuel et al. [37]; Zhang et al. [34]
Dissolved oxygen (DO)	Ávila et al. [35,38]; Chen et al. [17]; Auvinen et al. [31,39]; Kahl et al. [40]; Li et al. [41,42]; Vymazal et al. [19]; Zhang et al. [34]; Nivala et al. [43]
Planted and Unplanted CWs	Dordio et al. [44]; Hijosa-Valsero et al. [15,16,45,46]; Xian et al. [47]; Zhang et al. [13,27]; Reyes-Contreras et al. [48]; Carvalho et al. [33]; Dan et al. [22]; Dordio and Carvalho [28]; Carranza-Diaz et al. [49]; Macci et al. [50]; Li et al. [41,51]; He et al. [52]; Salcedo et al. [32]; Zhang et al. [34]; Button et al. [53]
Role of Support Matrix	Dordio et al. [44]; Dan et al. [22]; Dordio and Carvalho [28]; Ávila et al. [38]; Chen et al. [54]; Auvinen et al. [31]; Huang et al. [55]; Salcedo et al. [32]; Park et al. [56]; Nivala et al. [43]
Effect of Seasonality (Summer/Winter)	Matamoros et al. [26,36]; Dordio et al. [44]; Hijosa-Valsero et al. [15,16]; Reyes-Contreras et al. [48]; Dan et al. [22]; Liu et al. [57]; Rühmland et al. [58]; Zhang et al. [34]

Therefore, the main objectives of this study are (1) to critically evaluate and summarize the available evidence on major PhCs removal processes in CWs, (2) to examine the role of design and operational factors of CWs in PhCs removal, (3) to analyze the impact of physicochemical parameters of CWs on PhCs removal, (4) to evaluate the role of plants and a support matrix of CWs in PhCs

removal, and (5) to investigate the temporal variations in the performance of CWs for PhCs removal due to seasonal effects.

2. Methods

The research papers, review papers, and books were obtained from various sources, such as Scopus, Google Scholar, and individual journal websites, related to the performance of different types of CWs for the removal of different categories of PhCs. The snowball sampling method yielded over 100 journal articles, which were screened for the purpose of this research. Then, based on 65 peer-reviewed journal publications, a database was compiled containing information of 253 CWs with case studies from 19 countries (Tables S1–S4, Supplementary Materials). Although the removal of a wide range of PhCs (over 100) was investigated by these studies, sufficient data are not available in most of the cases. Therefore, this database contains influent and effluent concentrations, removal efficiencies, and removal rates of selected 26 PhCs grouped into eight categories according to their therapeutic classes (Table S5, Supplementary Materials).

Additionally, the information on the physicochemical properties of the selected PhCs was gathered from various sources (e.g., journal papers, reports, and websites) for molecular formula/structure/weight, water solubility, dissociation constant (pKa), organic carbon sorption coefficient (Log Koc), octanol–water partition coefficient (Log Kow), and distribution coefficient (Log Dow) (Table S6, Supplementary Materials). The design and operational factors, as well as physicochemical parameters such as treatment scale and type, wastewater type, depth, area, HLR, organic loading rate (OLR), HRT, experiment duration, system age, filter media composition, pH, temperature, effluent DO, and oxidation–reduction potential (ORP), of four types of CWs (free water surface CW (FWSCW), horizontal flow CW (HFCW), vertical flow CW (VFCW), and hybrid CW (HCW)) were considered to examine their role in the removal of PhCs. Some of these parameters are summarized in Table 2, and details are provided in Tables S1–S4 (Supplementary Materials). Where needed, the population equivalent (PE) was calculated based on the common relationship, where 1 PE = 60 g of biochemical oxygen demand (BOD)·day^{-1}. BOD values were approximated using the ratio of chemical oxygen demand (COD) and BOD (COD/BOD = 2) in the studies where BOD was not reported.

Table 2. Summary of selected design, operational, and physicochemical parameters of the studied four types of CWs.

Design, Operational, and Physicochemical Parameters	FWSCW	HFCW	VFCW	HCW
Number of CWs	47	110	48	37
Number of studies	17	32	17	20
Scale of application	Lab, pilot, full	Lab, pilot, full	Lab, pilot	Lab, pilot, full
Type of treatment	Primary, secondary, tertiary	Primary, secondary, tertiary	Primary, secondary, tertiary	Secondary, tertiary
Depth (m)	0.7 ± 0.8	0.6 ± 0.2	0.7 ± 0.2	1.0 ± 0.7
Area (m^2·PE^{-1})	10 ± 8	7.7 ± 5.3	4.3 ± 3.8	9.2 ± 6.2
HLR (m^3·m^{-2}·day^{-1})	0.1 ± 0.1	0.4 ± 1.0	0.2 ± 0.1	0.1 ± 0.2
OLR (g COD·m^{-2}·day^{-1})	17 ± 25	25 ± 28	62 ± 102	21 ± 30
HRT (days)	5.4 ± 7.1	4. 3 ± 4.7	5.7 ± 5.1	8 ± 14
pH	7.1 ± 0.6	7.5 ± 0.6	7.2 ± 0.4	7.4 ± 0.4
Temperature (°C)	16 ± 7	17 ± 7	19 ± 8	14 ± 6
Effluent DO (mg·L^{-1})	1.3 ± 2.2	1.8 ± 2.0	3.4 ± 3.0	2.4 ± 2.5

Notes: Free water surface CW (FWSCW); Horizontal flow CW (HFCW); Vertical flow CW (VFCW); Hybrid CW (HCW); Population equivalent (PE); Hydraulic loading rate (HLR); Organic loading rate (OLR); Chemical oxygen demand (COD); Hydraulic retention time (HRT); Dissolved oxygen (DO).

Firstly, a detailed analysis of the examined PhCs was conducted based on studied literature including the designed database, which focused on therapeutic classes, types of PhCs, and identification of the mechanisms responsible for their removal (Table 3). Secondly, statistical analysis was conducted to estimate the mean and standard deviation of the selected studied variables. Pearson correlation was estimated to examine the influence of selected design and operational factors (depth, area, HLR, HRT, and OLR) and physicochemical parameters (pH, temperature, and effluent DO) on the performance of CWs for PhC removal. The statistical comparison between planted and unplanted CWs, as well as in summer and winter seasons, for the removal of PhCs was done with a *z*-test for comparison of means.

Table 3. Removal mechanisms of selected 26 pharmaceuticals (PhCs) in CWs.

Therapeutic Class/Pharmaceutical	Possible Removal Mechanism	References	Most Dominant Removal Mechanism *
Analgesic/Anti-Inflammatory			
Diclofenac	Biodegradation (anaerobic)	Ávila et al. [38,59]; Hijosa-Valsero et al. [60]; Chen et al. [17]; Kahl et al. [40]; He et al. [52]; Zhang et al. [34]; Nivala et al. [43]	Photodegradation; biodegradation (aerobic) **
	Biodegradation (aerobic)	Hijosa-Valsero et al. [15,16,60]; Ávila et al. [35,38]; Kahl et al. [40]	
	Photodegradation	Matamoros et al. [26]; Matamoros and Salvadó [14]; Ávila et al. [23,61]; Rühmland et al. [58]; Chen et al. [17]; Francini et al. [62]; Zhang et al. [34]	
	Plant uptake	Hijosa-Valsero et al. [15]; Zhang et al. [13,63]	
Ibuprofen	Biodegradation (aerobic)	Matamoros et al. [20,64]; Hijosa-Valsero et al. [15,65]; Ávila et al. [23,35,38,59,61]; Matamoros and Salvadó [14]; Li et al. [8]; Zhu and Chen [66]; Chen et al. [17]; Vymazal et al. [19]; Březinova et al. [67]; Zhang et al. [34]; Nivala et al. [43]	Biodegradation (aerobic)
	Sorption	Dordio et al. [44]; Dordio and Carvalho [28]	
	Adsorption	Auvinen et al. [31]	
	Photodegradation	Reyes-Contreras et al. [48]; Zhang et al. [10]	
	Plant uptake	Hijosa-Valsero et al. [15]; Li et al. [51]	
Ketoprofen	Biodegradation	Hijosa-Valsero et al. [15]; Zhang et al. [27]; Chen et al. [17]; Francini et al. [62]; Zhang et al. [34]	Photodegradation
	Photodegradation	Matamoros et al. [26]; Matamoros and Salvadó [14]; Reyes-Contreras et al. [48]; Francini et al. [62]; Zhang et al. [34]	
Naproxen	Biodegradation (aerobic)	Matamoros et al. [20,68]; Hijosa-Valsero et al. [15]; Matamoros and Salvadó [14]; Zhang et al. [21]; Chen et al. [17]; He et al. [52]; Zhang et al. [34]; Nivala et al. [43]	Biodegradation (aerobic) **; photodegradation
	Biodegradation (anaerobic)	Matamoros et al. [68]; Ávila et al. [59]; Li et al. [8]; He et al. [52]; Nivala et al. [43]	
	Photodegradation	Matamoros et al. [26]; Reyes-Contreras et al. [48]; Hijosa-Valsero et al. [46]; Zhang et al. [34]	
	Plant uptake	Hijosa-Valsero et al. [15]; Zhang et al. [69]; He et al. [52]	
Salicylic acid	Biodegradation	Hijosa-Valsero et al. [15,16]; Reyes-Contreras et al. [48]; Zhang et al. [27]	Biodegradation (aerobic) **
	Plant uptake	Hijosa-Valsero et al. [46]	
Analgesic			
Acetaminophen	Biodegradation (aerobic)	Ávila et al. [35,61]; Koottatep et al. [70]; Li et al. [42]; Vystavna et al. [71]	Biodegradation (aerobic) **
	Biodegradation (anaerobic)	Chen et al. [17]	
	Photodegradation	Ávila et al. [61]; Li et al. [42]	
	Adsorption	Ávila et al. [61]; Koottatep et al. [70]	
	Sorption	Chen et al. [17]	
	Plant uptake	Li et al. [42]	
Codeine	Biodegradation (aerobic)	Rühmland et al. [58]; Petrie et al. [72]	Sorption; biodegradation (aerobic)
	Sorption	Petrie et al. [72]	
Tramadol	Biological transformation	Rühmland et al. [58]; Chen et al. [17]; Petrie et al. [72]	Biological transformation
Antibiotic			
Clarithromycin	Biodegradation	Hijosa-Valsero et al. [45]; Berglund et al. [73]	Photodegradation; sorption
	Sorption	Hijosa-Valsero et al. [45]; Berglund et al. [73]	
	Photodegradation	Hijosa-Valsero et al. [45]; Berglund et al. [73]	

Table 3. *Cont.*

Therapeutic Class/Pharmaceutical	Possible Removal Mechanism	References	Most Dominant Removal Mechanism *
Antibiotic			
Erythromycin	Biodegradation (aerobic)	Rühmland et al. [58]; Chen et al. [54]	Biodegradation (aerobic); adsorption
	Adsorption	Chen et al. [54]	
	Plant uptake	Hijosa-Valsero et al. [45]	
Lincomycin	Biodegradation	Chen et al. [54]	Biodegradation (aerobic) **
	Sorption	Chen et al. [54]	
Ofloxacin	Adsorption	Chen et al. [54]	Biodegradation (anaerobic) **; adsorption
	Biodegradation	Chen et al. [54]; Yan et al. [74]	
Oxytetracycline	Adsorption	Dordio and Carvalho [28]; Berglund et al. [73]; Huang et al. [55]	Adsorption; plant uptake
	Plant uptake	Dordio and Carvalho [28]; Huang et al. [55]	
	Biodegradation (aerobic)	Dordio and Carvalho [28]; Huang et al. [55]	
Sulfadiazine	Biodegradation	Xian et al. [47]	Biodegradation (anaerobic) **
	Fermentation	Dan et al. [22]	
Sulfamethazine	Adsorption	Liu et al. [57]; Chen et al. [54]; Choi et al. [75]	Biodegradation (aerobic) **; plant uptake
	Biodegradation	Xian et al. [47]; Liu et al. [57]; Chen et al. [54]; Choi et al. [75]	
	Fermentation	Dan et al. [22]	
	Plant uptake	Xian et al. [47]	
Sulfamethoxazole	Adsorption	Choi et al. [75]; Liang et al. [76]	Biodegradation (aerobic; anaerobic) **
	Sorption	Zhu and Chen [66]	
	Biodegradation (aerobic)	Conkle et al. [25]; Choi et al. [75]; Sgroi et al. [77]; Button et al. [53]	
	Biodegradation (anaerobic)	Hijosa-Valsero et al. [45]; Dan et al. [22]; Rühmland et al. [58]; Liang et al. [76]; Sgroi et al. [77]	
	Photodegradation	Hijosa-Valsero et al. [45]	
	Plant uptake	Xian et al. [47]; Hijosa-Valsero et al. [45]	
Sulfapyridine	Biodegradation (aerobic)	Conkle et al. [25]	Biodegradation (anaerobic) **
	Biodegradation (anaerobic)	Dan et al. [22]	
Trimethoprim	Biodegradation (aerobic)	Hijosa-Valsero et al. [45]; Rühmland et al. [58]	Biodegradation (anaerobic) **
	Biodegradation (anaerobic)	Dan et al. [22]	
Monensin	Biodegradation	Chen et al. [54]	Biodegradation (aerobic) **
Stimulants/Psychoactive Drugs			
Caffeine	Biodegradation (aerobic)	Matamoros and Bayona [78]; Hijosa-Valsero et al. [60]; Zhang et al. [10]; Chen et al. [17]; Li et al. [42]; Vymazal et al. [19]; Vystavna et al. [71]; He et al. [52]	Biodegradation (aerobic) **; plant uptake
	Biodegradation (anaerobic)	Hijosa-Valsero et al. [15]; Carranza-Diaz et al. [49]; He et al. [52]	
	Adsorption onto carbon-rich surfaces of the gravel bed	Matamoros and Bayona [78]; Dettenmaier et al. [79]; Wang et al. [80]; Li et al. [42]	
	Plant uptake	Hijosa-Valsero et al. [15]; Zhang et al. [81]; Zhu and Chen [66]; Chen et al. [17]; Li et al. [42]; Petrie et al. [72]	
Psychiatric drugs			
Carbamazepine	Adsorption onto the available organic surfaces	Matamoros et al. [64,82]; Hijosa-Valsero et al. [16]; Carranza-Diaz et al. [49]; Sharif et al. [24]; Vystavna et al. [71]; Park et al. [56]	Adsorption; Sorption; plant uptake
	Sorption	Dordio et al. [44]; Dordio and Carvalho [28]; Park et al. [56]	
	Biodegradation (aerobic)	Hijosa-Valsero et al. [15]	
	Reductive transformation	Kahl et al. [40]; Nivala et al. [43]	
	Plant uptake	Hijosa-Valsero et al. [15,46]; Macci et al. [50]; Yan et al. [74]; Petrie et al. [72]; He et al. [52]	
Venlafaxine	Precipitation	Breitholtz et al. [83]; Vystavna et al. [71]	Plant uptake; precipitation
	Biological transformation	Rühmland et al. [58]; Petrie et al. [72]	
	Plant uptake	Petrie et al. [72]	
Beta blockers			
Atenolol	Biodegradation (aerobic)	Conkle et al. [25]; Rühmland et al. [58]	Sorption
	Biodegradation (anaerobic)	Chen et al. [17]	
	Adsorption	Auvinen et al. [31]; Park et al. [56]	
	Sorption	Petrie et al. [72]; Park et al. [56]	
	Photodegradation	Salgado et al. [84]	
	Plant uptake	Francini et al. [62]	
Metoprolol	Biodegradation (aerobic)	Conkle et al. [25]; Rühmland et al. [58]; Chen et al. [17]; He et al. [52]	Biodegradation (aerobic)

Table 3. *Cont.*

Therapeutic Class/Pharmaceutical	Possible Removal Mechanism	References	Most Dominant Removal Mechanism *
Lipid regulators			
Gemfibrozil	Biodegradation (aerobic)	Conkle et al. [25]; Yi et al. [85]; Zhang et al. [34]	Biodegradation (aerobic)
Diuretics			
Furosemide	Hydrolysis	Chen et al. [17]; Vymazal et al. [19]	Hydrolysis; biodegradation (aerobic) **
	Photolysis	Chen et al. [17]	

Note: Authors' own insight based on physicochemical properties, removal mechanisms, and limited evidence in the literature (*); authors' own insight based on physicochemical properties and removal mechanisms (**).

3. Results and Discussion

3.1. Removal Mechanisms in CWs for PhCs Removal

The available evidence in the literature and physicochemical properties of PhCs indicate that specific processes are involved in the removal of certain types of PhCs in CWs (Table 3 and Table S6, Supplementary Materials). The complex physical, chemical, and biological processes such as photodegradation, volatilization, adsorption/sorption, plant uptake and accumulation, and biodegradation (aerobic and anaerobic) may occur simultaneously depending on the design of a CW [10,11].

3.2. Role of Design and Operational Factors of CWs in the Removal of PhCs

The Pearson correlation analysis was conducted to assess the role of selected design and operational factors such as depth, area, HLR, OLR, and HRT in the removal of PhCs. It is evident from the correlation statistics presented in Table 4 that these parameters play an important role in the wetland performance, albeit with different degrees of influence.

Table 4. Pearson correlation statistics among the studied factors and the removal efficiency of 26 selected PhCs.

Parameter	Depth	Area	HLR	OLR	HRT	Temp	pH	Eff. DO
Ibuprofen	**0.326**	−0.115	−0.150	0.111	0.099	0.062	−0.121	**0.541**
Naproxen	0.199	−0.002	**−0.251**	0.055	0.140	**0.350**	−0.169	**0.348**
Diclofenac	**0.451**	**−0.279**	−0.191	−0.018	**0.313**	**0.316**	0.179	**0.562**
Ketoprofen	**0.320**	**−0.249**	0.053	−0.134	**0.293**	**0.308**	**0.438**	**0.465**
Salicylic acid	−0.044	**0.567**	**−0.394**	**−0.518**	0.119	**0.676**	0.134	**0.297**
Acetaminophen	0.123	0.238	−0.386	0.243	−0.127	−0.201	−0.436	0.051
Codeine	0.833	0.632	−0.260	**−0.986**	0.072	−0.097	−0.802	−0.215
Tramadol	0.231	−0.132	−0.487	−0.224	−0.116	0.135	−0.787	−0.413
Sulfadiazine	**−0.641**	−0.309	−0.042	0.230	NA	**0.833**	0.056	NA
Sulfamethoxazole	0.057	0.003	−0.278	−0.164	0.179	0.010	0.037	0.018
Clarithromycin	0.018	0.107	0.268	−0.624	**0.544**	−0.577	0.955	0.528
Erythromycin	−0.050	**0.628**	**−0.601**	**−0.592**	0.412	−0.149	**0.554**	−0.445
Lincomycin	0.000	**0.609**	−0.408	**−0.600**	−0.508	**−0.546**	**0.576**	**−0.526**
Trimethoprim	−0.114	0.261	**−0.353**	**−0.347**	−0.324	0.143	−0.254	**−0.891**
Oxytetracycline	−0.068	**−0.995**	**−0.779**	NA	0.372	NA	−0.520	NA
Ofloxacin	0.053	−0.353	0.167	0.467	**−0.713**	NA	**0.784**	0.506
Sulfamethazine	**−0.385**	−0.006	−0.112	−0.194	**0.634**	−0.246	**0.413**	0.333
Sulfapyridine	**0.599**	0.318	−0.213	−0.272	NA	−0.304	0.080	NA
Monensin	NA	0.280	−0.296	−0.296	NA	−0.128	−0.022	0.172
Carbamazepine	0.181	−0.211	−0.144	0.030	0.209	0.247	0.070	−0.094
Venlafaxine	1.000	−0.307	**−0.708**	0.697	−0.523	0.403	−0.792	0.362
Caffeine	0.158	0.147	−0.154	0.038	0.095	**0.465**	−0.002	0.187
Furosemide	0.005	0.582	−0.720	−0.661	0.622	NA	NA	NA
Atenolol	0.227	−0.169	0.008	**0.734**	0.398	0.166	−0.971	−0.577
Metoprolol	0.180	−0.122	−0.405	0.602	0.100	−0.365	0.478	0.025
Gemfibrozil	**0.561**	0.207	−0.247	**−0.650**	**0.711**	0.248	**−0.913**	**0.576**

Note: Bold values indicate significant correlation between the parameters at a 95% confidence level; hydraulic loading rate (HLR); organic loading rate (OLR); hydraulic retention time (HRT); temperature (Temp); effluent (Eff); dissolved oxygen (DO); NA: not available.

3.2.1. Depth

The depth showed a positive correlation with the removal efficiency of 18 out of 26 studied PhCs, along with a significant positive correlation with the removal efficiency of ibuprofen, diclofenac, ketoprofen, sulfapyridine, and gemfibrozil (Table 4), which represents an enhancement in their removal upon increasing the depth of the system. The removal of PhCs by biodegradation was confirmed by their similar removal at all water depths, as well as in the dark control, during an in situ degradation experiment [58]. The positive correlation with depth can be explained by the fact that one of the major removal pathways is biodegradation (aerobic and anaerobic) in the case of ibuprofen, diclofenac, ketoprofen, sulfapyridine, and gemfibrozil (Table 3). On the other hand, although the major removal mechanism is also biodegradation in the case of sulfadiazine and sulfamethazine (Table 3), the removal efficiency of these PhCs demonstrates significant negative correlation with the depth of the system. It is noteworthy that the removal of PhCs in CWs might not only relate to one design parameter; all the parameters might directly or indirectly impact their removal.

3.2.2. Area

Area exhibited a significant correlation with the removal efficiency of six PhCs (diclofenac, ketoprofen, salicylic acid, erythromycin, lincomycin, and oxytetracycline). The significant positive correlation with the removal efficiency of salicylic acid, erythromycin, and lincomycin (Table 4), indicates that the high footprint facilitates the performance enhancement. Although the large land area increases the cost of operation, a subsequent longer HRT improves the removal of PhCs (e.g., References [30,31]), since the removal mechanisms of PhCs including adsorption/sorption onto the surfaces of the media and the rates of plant uptake are slow [72]. Similarly, anaerobic biodegradation is slower than aerobic biodegradation; thus, longer HRT is needed to achieve the same removal efficiency [31]. Analogous to that, longer HRT promotes the photodegradation reactions involved in the removal of some PhCs in FWSCWs [26]. For instance, Herrera-Cárdenas et al. [30] achieved the enhanced removal efficiency of caffeine with an increase in HRT from three to five days (50% and 89%, respectively) in an HFCW (Table S2, Supplementary Materials). The positive correlation of the removal efficiency of caffeine with area (although not significant) (Table 4) indicates the contribution of anaerobic biodegradation, sorption onto organic surfaces, and plant uptake to its removal in CWs (Table 3). Several studies considered that one of the removal pathways is adsorption/sorption in the case of erythromycin and lincomycin (Table 3). Similarly, plant uptake is attributed to salicylic acid and erythromycin (Table 3). Although the major removal mechanisms are photodegradation and anaerobic biodegradation in the case of diclofenac and ketoprofen (Table 3), and adsorption/sorption in the case of oxytetracycline (Table 3), the removal efficiency of these PhCs exhibits significant negative correlation with land area, which indicates the impact of other design and operational parameters on their removal. For instance, the improvement in the removal efficiency with an increase in HRT from two to four days was observed by Zhang et al. for diclofenac (49% and 55%, respectively) [13] and by Zhang et al. for ketoprofen (91% and 96%, respectively) [27]. Similarly, Dordio and Carvalho [28] reported the improvement in the removal efficiency of oxytetracycline (89% and 99%, respectively) with an increase in HRT from three to nine days.

3.2.3. HLR

HLR showed a significant negative correlation with the removal efficiency of six PhCs (naproxen, salicylic acid, erythromycin, trimethoprim, oxytetracycline, and venlafaxine), as well as a negative correlation with the removal efficiency of 22 out of 26 studied PhCs (Table 4), which indicates a decline in the performance of CWs with increasing HLR (e.g., References [22–24]). The significant negative correlation of trimethoprim with HLR is evident by the reduction in its removal efficiency at an HLR of 0.5 $m^3 \cdot m^{-2} \cdot day^{-1}$ (57%) compared with HLRs of 0.25 and 0.125 $m^3 \cdot m^{-2} \cdot day^{-1}$ (87% and 95%, respectively) in HFCWs [22] (Table S2, Supplementary Materials). Furthermore, the negative

correlation of the removal efficiency of ibuprofen and diclofenac with HLR (although not significant) is explicit by the reduction in their removal efficiencies at an HLR of 0.18 $m^3 \cdot m^{-2} \cdot day^{-1}$ (82% in both cases) compared with an HLR of 0.06 $m^3 \cdot m^{-2} \cdot day^{-1}$ (90% and 92%, respectively) in HCWs [23] (Table S4, Supplementary Materials). Although the removal efficiency of carbamazepine was very low in an FWSCW (12%) at an HLR of 0.03 $m^3 \cdot m^{-2} \cdot day^{-1}$, it was further decreased by increasing the HLR to 0.06 $m^3 \cdot m^{-2} \cdot day^{-1}$ (4.0%) [24] (Table S1, Supplementary Materials). A higher HLR represents a high number of pulses per day, which lowers the oxygen transfer capacity; moreover, in the case of hydrophobic compounds, their adsorption onto particulate matter decreases due to lower contact time [23]. Thus, the removal of those PhCs by aerobic biodegradation and by the adsorption onto particles is affected if the system is operated at high HLR for a longer period of time. Several studies attributed the removal of naproxen, salicylic acid, erythromycin, and trimethoprim to aerobic biodegradation (Table 3). The major removal mechanism in the case of oxytetracycline was adsorption onto the substrate, along with aerobic biodegradation (Table 3).

3.2.4. OLR

OLR showed a significant correlation with the removal efficiency of seven PhCs (salicylic acid, codeine, erythromycin, lincomycin, trimethoprim, atenolol, and gemfibrozil). The significant negative correlation of OLR with the removal efficiency of salicylic acid, codeine, erythromycin, lincomycin, trimethoprim, and gemfibrozil (Table 4) highlights the influence of wastewater strength, yielding higher performance for low-strength wastewater and vice versa. The HLR of systems and the OLR are positively correlated with each other. The amount of organic matter going into the wetlands increases the microbial activity, which promotes the degradation of pollutants at a certain HLR. However, the further increase in HLR reduces the HRT and, consequently, the short contact time with the microbes leading to lower treatment performance of the system. Additionally, a high HLR promotes microbial overproduction and plant growth, which might reduce the porosity of the CWs [22]. Zhang et al. [27] established that, in HFCWs, PhC removal rate was linearly proportional to the influent mass loading rate at different HRTs (two days and six days). The removal of these PhCs is attributed to aerobic biodegradation in the case of salicylic acid, codeine, erythromycin, lincomycin, trimethoprim, and gemfibrozil (Table 3). Several studies ascribed the removal to adsorption/sorption in the case of codeine, erythromycin, and lincomycin (Table 3). The negative correlation (although non-significant) of the removal efficiency of diclofenac with OLR (Table 4) is consistent with the findings of Matamoros et al. [18]. Its removal efficiency was decreased from 24% to 14% upon increasing OLR from 14 to 38 g $COD \cdot m^{-2} \cdot day^{-1}$. Nevertheless, the removal efficiency of ketoprofen exhibited a negative correlation with OLR (Table 4), as Matamoros et al. [18] reported the improvements in its removal in HFCW and the corresponding removal efficiency were 13% and 32%, respectively (Table S2, Supplementary Materials). On the other hand, the significant positive correlation of the removal efficiency of atenolol with OLR indicates that its removal is favored by several other pathways including anaerobic biodegradation, plant uptake, and photodegradation (Table 3). Similarly, the positive correlation with the removal efficiency of naproxen, ibuprofen, and carbamazepine (although non-significant) can be explained by the enhanced removal of these PhCs in an HFCW upon increasing OLR from 14 g $COD \cdot m^{-2} \cdot day^{-1}$ (58%, 16%, and 12%, respectively) to 38 g $COD \cdot m^{-2} \cdot day^{-1}$ (74%, 39%, and 28%, respectively) [18] (Table S2, Supplementary Materials).

3.2.5. HRT

HRT showed a significant correlation with the removal efficiency of six PhCs (diclofenac, ketoprofen, clarithromycin, ofloxacin, sulfamethazine, and gemfibrozil). The significant positive correlation with the removal efficiency of diclofenac, ketoprofen, clarithromycin, sulfamethazine, and gemfibrozil (Table 4) indicates that longer contact time improves the removal of PhCs (e.g., References [28,30,31]). The removal of PhCs in CWs involves different mechanisms including adsorption onto the substrate media, sorption onto carbon-rich surfaces, plant uptake, anaerobic

biodegradation, and photodegradation, which are slow processes [26,31,72], thus requiring longer HRT for their completion. For instance, adsorption/sorption is one of the main removal mechanisms in the case of clarithromycin and sulfamethazine (Table 3). Similarly, plant uptake is one of the removal pathways in the case of diclofenac and sulfamethazine (Table 3). Several studies attributed the removal to anaerobic biodegradation in the case of diclofenac and ketoprofen (Table 3). The major contribution in the removal of some PhCs is ascribed to photodegradation such as diclofenac, ketoprofen, and clarithromycin (Table 3). The significant positive correlation with diclofenac is in agreement with the observations of Vystavna et al. [71]. They reported higher removal efficiency of diclofenac with an increase in HRT from 10 to 13 days (39% and 94%, respectively) (Table S4, Supplementary Materials). However, some studies did not observe significant differences for the removal efficiency of PhCs at different HRTs [13,27]. It can also be seen in Table 4 that the removal efficiency of different categories of PhCs is not significantly correlated with HRT. Nevertheless, HRT is an important parameter for the empirical design and operation of CWs. A smaller land area is required with a shorter HRT, which consequently lowers the capital and operational cost [13,27,30]. Herrera-Cárdenas et al. [30] reported the enhanced removal efficiency of caffeine at an HRT of five days (96%); however, with a shorter HRT of three days, although more than 50% of removal efficiency is achieved, the removal should be sufficient to significantly decrease the toxicity of the effluent.

3.3. Role of Physicochemical Parameters of CWs in the Removal of PhCs

The Pearson correlation analysis was done to observe the role of the selected physicochemical parameters of CWs such as pH, temperature, and effluent DO in the removal of PhCs. It is evident from the correlation statistics presented in Table 4 that these parameters play an important role in the wetland performance, albeit with different degrees of influence.

3.3.1. pH

The pH of the influent wastewater can be considered an important parameter because it controls several biotic processes [15,28]. The optimal pH values are reported to be near-neutral for plant development, as well as for nitrification and heterotrophic microbial activities, in CWs [15,28,86]. In the case of the ionizable compounds, the extent of their removal depends on their degree of ionization, which is controlled by the pH in the system [28], and the presence of plants influences the performance of CWs by regulating the pH (~7.5) [33]. The high effluent pH of the CW affects the adsorption behavior [31], since pH affects the dissociation of PhCs and their subsequent attachment to soil/sediment via ion exchange [87]. However, the pH value showed a significant positive correlation with the removal efficiency of five of the studied PhCs (ketoprofen, erythromycin, lincomycin, ofloxacin, and sulfamethazine) and a significant negative correlation with the removal efficiency of gemfibrozil (Table 4). Some studies attributed the removal to aerobic biodegradation in the case of erythromycin, lincomycin, and sulfamethazine, as well as the removal of sulfamethazine by plant uptake (Table 3), since the pH of the system is positively correlated with DO and, consequently, with the removal of PhCs under aerobic conditions. Although the removal of gemfibrozil is attributed to aerobic biodegradation (Table 3), its removal efficiency showed a significant negative correlation with pH. The significant positive correlation with the removal efficiency of ofloxacin is due to the fact that one of its major removal mechanisms is adsorption (Table 3).

3.3.2. Temperature

Temperature showed a significant positive correlation with the removal efficiency of six of the studied PhCs (naproxen, diclofenac, ketoprofen, salicylic acid, sulfadiazine, and caffeine) and a significant negative correlation with the removal efficiency of lincomycin (Table 4). Truu et al. [86] reported that high temperature promotes the endothermic hydrolysis reaction and improves biodegradation processes. Most of the PhCs are hydrolytically stable with a long half-life under typical environmental conditions [88]; thus, microbial degradation is the most probable pathway for their

removal in CWs, and it is enhanced at warm temperature (15–25 °C) [15], especially in the case of nitrifying and proteolytic bacteria [15,86]. The removal of PhCs showed a positive correlation with temperature, which is attributed to biodegradation in the case of naproxen, diclofenac, ketoprofen, salicylic acid, sulfadiazine, and caffeine (Table 3). Similarly, the warm temperature also enhances plant growth, as well as the activity of rooted plants [36] and, accordingly, the removal of PhCs by plant uptake [15,46,50,72,74]. This can be explained by the higher removal of naproxen, diclofenac, ketoprofen, salicylic acid, sulfadiazine, and caffeine at high temperature (in summer) compared with low temperature (in winter) (Figure 2a,b and Tables S9 and S10, Supplementary Materials). On the other hand, the abiotic processes like adsorption are also temperature-dependent. This is an exothermic process and favored by low temperature. The negative correlation of temperature with the removal efficiency of lincomycin can be explained by the fact that one of its main removal mechanisms is sorption (Table 3).

3.3.3. Effluent DO

Effluent DO is among the most significant parameters, as indicated by its significant correlation with the removal efficiency of eight PhCs (ibuprofen, naproxen, diclofenac, ketoprofen, salicylic acid, lincomycin, trimethoprim, and gemfibrozil). The significant positive correlation with the removal efficiency of ibuprofen, naproxen, diclofenac, ketoprofen, salicylic acid, and gemfibrozil (Table 4) represents the importance of DO in the removal processes of these PhCs. These observations are consistent with previous studies. For instance, the removal of ibuprofen, naproxen, diclofenac, ketoprofen, salicylic acid, and gemfibrozil is ascribed to aerobic biodegradation (Table 3). Ávila et al. [38] attributed the improvement in the removal efficiency of ibuprofen (> 99%) in an aerated (AA) VFCW compared with non-aerated (NA) VFCW (95%) to the elevated level of DO in an AA-VFCW compared with an NA-VFCW (5.2 and 3.4 $mg{\cdot}L^{-1}$, respectively) (Table S3, Supplementary Materials). The significant negative correlation with the removal efficiency of lincomycin and trimethoprim indicates that the removal of these PhCs is hindered under oxic conditions. These observations are in agreement with previous studies. For instance, Chen et al. [54] attributed the removal of lincomycin to anaerobic biodegradation, and Dan et al. [22] observed the removal of trimethoprim at lower ORP (−258 mV to −192 mV), attributed to anaerobic biodegradation. Consistent with that, Ávila et al. [38] observed the better removal efficiency of diclofenac in an NA-VFCW compared with an AA-VFCW (65% and 58%, respectively) (Table S3, Supplementary Materials).

3.4. Role of Plants and Support Matrix of CWs in the Removal of PhCs

The role of plants and a support matrix of CWs in the removal of PhCs is comprehensively discussed based on the information available in the studies considered in this review.

3.4.1. Role of Plants

It was suggested that biotic pathways (microbial and plant uptake) are the most probable degradation routes for some PhCs (e.g., References [32,34,42,62,72,89]). In addition to direct uptake, the indirect positive effects of plant presence such as degradation by enzymatic exudates, as well as release of oxygen and root exudates (such as carbohydrates and amino acids) by the plant roots in the rhizosphere, which can provide organic carbon and a nutrient source for microorganisms, supports them in aerobically degrading and consequently enhancing the overall bioavailability of PhCs (e.g., References [32,37,52,90,91]). This might be the reason of the enhanced removal efficiency in planted CWs compared with unplanted CWs. The use of plants like *Phragmites australis*, *Typha* spp., *Typha angustifolia*, and *Typha latifolia*, which are reported for the treatment of PhCs in CWs, indicates the important influence of plant species on the removal of PhCs [8,62,72]. For instance, the vegetal uptake of naproxen and carbamazepine was recognized in CWs for *Typha* spp. [44,46], *Cyperus alternifolius* [74], and *Phragmites australis* [50,52,72], in addition to diclofenac uptake by *Typha angustifolia* [13] and *Phragmites australis* [52]. For instance, Macci et al. [50] reported the higher removal efficiency of

carbamazepine (61%) in a planted VFCW (*Phragmites australis*) compared with the unplanted system (8.3%). However, Wang et al. [92] calculated its translocation factor (zero or below 1.0) from roots to the shoots of the plant, which indicates rhizofiltration as one of the sources of its remediation. He et al. [52] observed almost twice the removal efficiency of naproxen in a planted HFCW (*Phragmites australis*) compared with an unplanted system (97 ± 3% and 50%, respectively), and Zhang et al. [13] revealed the higher removal efficiency of diclofenac (55%) in a planted HFCW compared with an unplanted system (41%). Similarly, the concentration of salicylic acid was higher in plants (*Phragmites australis* and *Typha angustifolia*) due to the uptake by roots compared with adsorption [46].

Li et al. [42] reported that *Spirodela polyrhiza* contributed to the removal of acetaminophen. For instance, the removal efficiency of acetaminophen in systems with and without plants was 98% and 84%, respectively. In an HFCW, the removal of erythromycin (63%) was only achieved in the planted system (*Phragmites australis*), which indicates that its removal is favored by the presence of plants [45]. Xian et al. [47] observed that, in an FWSCW, planted systems showed higher removal efficiency of sulfamethoxazole (92%) compared with unplanted systems (73%). Similarly, Dordio and Carvalho [28] observed that, in a VFCW, the removal efficiency of oxytetracycline was higher (97%) in planted systems (*Phragmites australis*) compared with unplanted systems (89%). Zhang et al. [81] affirmed that direct uptake, accumulation, and translocation of caffeine in plant tissues (*Scirpus validus*) can be very important mechanisms for the phytoremediation of caffeine. Almost all of the caffeine (>99%) was removed, and direct plant assimilation accounted for more than 60% of caffeine elimination from nutrient solutions. Similarly, the detection of ibuprofen in the leaves of *Typha angustifolia* with an even distribution in the lamina and sheath tissues reveals the phytoextraction process of ibuprofen. Ibuprofen is taken up by the roots of *Typha angustifolia*, and then translocates from the roots to the leaves before accumulating in leaf tissues. For instance, root uptake of ibuprofen was partially transformed to carboxyibuprofen, 2-hydroxyibuprofen, and 1-hydroxyibuprofen in the sheath (1375, 236, and 302 $ng \cdot g^{-1}$, respectively) and in the lamina (1051, 694, and 179 $ng \cdot g^{-1}$, respectively). The accumulation of transformation products (TPs) of ibuprofen in the leaves of *Typha angustifolia* is evidence of the phytotransformation of ibuprofen in plant tissues [51]. In addition to that, He et al. [52] noted the phytotransformation of TPs of ibuprofen. They reported the presence of hydroxyibuprofen and glucopyranosyloxy-hydroxyibuprofen (GT-hydroxy-IBP) in root and rhizome tissues, and hydroxyibuprofen in stem and leaf tissues, which indicated the conversion of hydroxyibuprofen to GT-hydroxy-IBP in the plant tissues. The findings of Wang et al. [92] suggested that rhizofiltration is one of the sources of its remediation based on its estimated translocation factor (zero or below 1.0).

Some studies designated the effect of different plant species on the removal of certain PhCs in CWs. For instance, Francini et al. [62] observed the higher removal efficiency of atenolol (76%) in a VFCW planted with *Phragmites australis* compared with a VFCW planted with *Salix matsudana* (52%). Salcedo et al. [32] investigated the effect of different plant species on the removal of caffeine and reported its highest removal efficiency in an HFCW planted with *Phragmites australis* compared with HFCWs planted with *Typha latifolia* and *Cyperus papyrus*. The corresponding removal efficiency was 96 ± 1%, 90 ± 5%, and 82 ± 12%, which was much higher compared with the unplanted system (64 ± 13%). In contrast, He et al. [52] reported the complete removal (100%) of caffeine in a planted HFCW (*Phragmites australis*) and an unplanted HFCW, which is consistent with the findings of Wang et al. [92]. They calculated its translocation factor (zero or below 1.0) from roots to the shoots of the plant, which suggests that rhizofiltration is one of the sources of its removal.

The effect of plants in CWs was also examined by considering the removal efficiency of PhCs in planted and unplanted CWs (Table 1). Statistical comparison was not carried out for a few PhCs, as sufficient data were not available in those cases (clarithromycin, erythromycin, lincomycin, oxytetracycline, and metoprolol) (Tables S7 and S8, Supplementary Materials).

The removal efficiency of diclofenac, ibuprofen, naproxen, salicylic acid, caffeine, carbamazepine, gemfibrozil, and sulfamethoxazole was higher in the planted CWs compared with unplanted CWs

(Figure 1a,b). However, the results of the *z*-test for comparison of means for statistical significance or non-significance of observed differences in planted and unplanted CWs (Table S8, Supplementary Materials) in the removal efficiency of 13 PhCs indicated non-significant differences in the removal efficiency of 12 PhCs. Only the removal efficiency of ibuprofen was significantly higher in planted CWs compared with unplanted CWs (Figure 1a), which is consistent with the studies of He et al. [52] and Zhang et al. [34]. For instance, He et al. [52] reported its significantly higher removal efficiency in planted CWs compared with unplanted CWs (97 ± 5% and 40%, respectively). The non-significant results are also in agreement with the studies, which indicated that planted systems are more efficient when they are young. When systems get older, some disturbing processes like clogging or shading might lead to non-significant differences in the treatment performance of planted and unplanted CWs [48]. For instance, the removal efficiency of carbamazepine and salicylic acid was not significantly different in planted (*Typha angustifolia*) and unplanted HFCWs [13,27,48]. The removal efficiency of carbamazepine in planted and unplanted HFCWs was 30% and 29%, respectively [13] and the removal efficiency of salicylic acid was 88% in planted and unplanted HFCWs [27]. Some studies revealed that the presence of plants is not important for the removal of antibiotics such as sulfonamides and trimethoprim [22,45,53]. For instance, Dan et al. [22] found non-significant differences in the removal efficiency of sulfapyridine in planted and unplanted HFCWs (83% and 87%, respectively). Button et al. [53] observed the similar and complete removal (100%) of sulfamethoxazole in planted (*Phalaris arundinacea*) and unplanted VFCWs. However, Hijosa-Valsero et al. [45] observed that unplanted systems, being more directly insolated and highly populated by microscopic algae, obtained significantly better removal efficiency of trimethoprim (96%) compared with planted systems (84%).

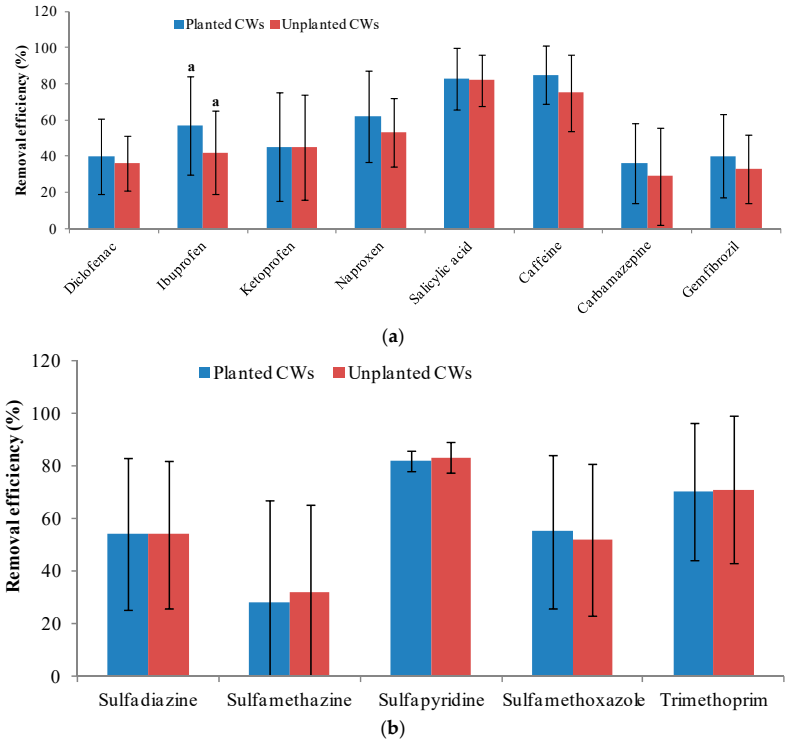


Figure 1. The removal efficiency (mean and standard deviation) of pharmaceuticals (PhCs) in planted and unplanted constructed wetlands (CWs). Note: (**a**) For ibuprofen, "**a**" shows the significant difference in the removal efficiency in planted and unplanted CWs at $\alpha = 0.05$ ($p < 0.05$). (**b**) The removal efficiency of studied PhCs in planted and unplanted CWs was not significantly different at $\alpha = 0.05$ ($p < 0.05$). The number of observations for studied PhCs in planted and unplanted CWs is given in Table S7 (Supplementary Materials). Negative values in the case of standard deviation were capped at zero to improve the readability of the graph. Actual values (e.g., below zero) can be found in Table S7 (Supplementary Materials).

3.4.2. Role of Support Matrix

Chen et al. [54] studied the removal of antibiotics (erythromycin, lincomycin, monensin, ofloxacin, and sulfamethazine) in HFCWs using different substrate materials (oyster shell, zeolite, medical stone, and ceramic); among them, zeolite as a substrate was the best choice for the treatment of target compounds in domestic wastewater. This indicated that adsorption and/or sorption as a removal mechanism could contribute to eliminating PhCs. For instance, they observed the contribution of adsorption (35%) to the total removal efficiency of erythromycin (82%), when zeolite was used as a substrate material. Similarly, ofloxacin was completely removed (100%) in an HFCW, and 24% of it was removed by adsorption onto zeolite. Huang et al. [55] reported that the removal of oxytetracyline was affected by substrate type. The brick particle-based media showed higher removal capacities compared with oyster shell, which can be attributed to the larger porosity and average micropore size, and the high percentage of crystalline iron oxide (32%) in brick particle. However, the removal efficiency in both types of VFCWs was almost similar (97% and 94%, respectively). Analogous to that, Dan et al. [22] revealed that the vesuvianite CWs had the best removal of sulfadiazine, sulfapyridine, and sulfamethoxazole compared with gravel CWs and zeolite CWs. For instance, the removal efficiency of sulfadiazine by the vesuvianite VFCW, gravel VFCW, and zeolite VFCW was 27%, 21%, and 13%, respectively, in winter, considering that adsorption is the dominant removal pathway at low temperature. Although the removal of sulfonamides was considered to be difficult through adsorption onto the substrate media, the relatively better removal in vesuvianite CWs may be due to the larger porosity of vesuvianite, which means a longer HRT and, thus, pollutants have more time for reaction in vesuvianite CWs. In addition to that, vesuvianite has a large specific surface area, which is particularly suitable for the growth of microorganisms and the formation of biofilms that promotes the degradation processes. This can be explained by the improvement in the removal efficiency of sulfadiazine in summer by the vesuvianite VFCW compared to the gravel VFCW and zeolite VFCW (67%, 60% and 55%, respectively) when microbial degradation is the most probable pathway for the removal of PhCs.

Ávila et al. [38] found that the unsaturated sand-based VFCW performed substantially better than the unsaturated gravel-based VFCW for the removal of PhCs. This is due to the reason that sand media provided a larger available surface area for microbial growth and higher oxygen to promote the elimination of substances that are mainly removed via aerobic biodegradation pathways. For instance, the removal efficiency of ibuprofen in the gravel-based VFCW was 95%, but almost complete removal was achieved in sand-based VFCW (99.7%). Similarly, the beneficial effect of a sand filter was observed for the removal of caffeine, ibuprofen, naproxen, and diclofenac. The removal efficiency of caffeine, ibuprofen, naproxen, and diclofenac was 96%, 95%, 90%, and 53%, respectively, in the gravel-based VFCW; however, comparatively better removal of these PhCs was achieved in a subsequent sand-based VFCW with the corresponding removal efficiency of 99%, 99%, 98%, and 77% [43]. Salcedo et al. [32] observed the moderate removal of caffeine in an unplanted HFCW using different substrate materials (volcanic gravel and river gravel). The corresponding removal efficiency of caffeine was 65 ± 11% and 62 ± 14%, respectively.

Some studies investigated that, in HFCWs and VFCWs, the adsorption of PhCs onto light expanded clay aggregates (LECA) is the major removal pathway (>50% removal efficiency within 6 h), although, on a larger timescale, plants also contributed significantly for the overall performance of the system [28,44]. For instance, Dordio et al. [44] reported that carbamazepine was extensively sorbed by the LECA matrix, which is explicit by the almost similar removal efficiency in planted and unplanted HFCWs in winter (88% and 87%, respectively) when adsorption is the dominant removal pathway. The removal of ibuprofen was attributed to the combination of sorption and biodegradation because of its comparatively higher removal efficiency in planted HFCWs than with unplanted HFCWs, even in winter (82% and 74%, respectively). However, it was highly removed in unplanted systems, which indicates the higher adsorption capacity of LECA. Auvinen et al. [31] also reported that the use of LECA as a substrate material contributed to the adsorption of atenolol and carbamazepine efficiently, which facilitated achieving the higher removal efficiency of both PhCs (98% and 94%, respectively).

Park et al. [56] investigated the sorption of PhCs by soil organic matter (SOM) by electrostatic interactions; SOM is located on the surface of soil and/or sediment and exhibits a negative charge because of the functional groups present (i.e., carboxylic and phenolic groups). Thus, the electrostatic interaction of SOM with positively charged PhCs provides one of the major removal mechanisms (adsorption and/or sorption) in CWs. The estimated removal efficiency of carbamazepine and atenolol in the SOM sorption experiment was 40% and 60%, respectively, after 6 h of HRT and their removal efficiency in CWs was 50%. Although, in CWs, higher removal is expected compared with lab-scale sorption experiments due to the occurrence of all the removal mechanisms such as photodegradation, biodegradation, plant uptake, adsorption, and/or sorption, the results were similar at both scales. This indicates the implication of desorption of PhCs in CWs.

3.5. Effect of Seasonality on the Removal of PhCs

Several studies reported the variation in removal of PhCs in summer and winter, due to the difference in external temperature, which directly affects water temperature and oxygen solubility [40,43] and plays a major role in the removal processes of PhCs in CWs such as biodegradation, plant uptake, and adsorption/sorption processes. Several studies reported that microbial degradation is the most probable pathway for the removal of PhCs in CWs, and it is enhanced at warm temperature in summer (15–25 °C) [13,15,17,22,34,36,37,48], especially in the case of nitrifying and proteolytic bacteria [15,86]. Some studies reported that, in summer, a more active vegetative stage of plants also contributes to this variability (e.g., References [13,36,48]). Transpiration rate is a key variable that determines the rate of PhC plant uptake, which is higher in summer [16,93]. Furthermore, the higher solar irradiation in summer increases the photodegradation rate (e.g., References [34,37,58]). On the other hand, abiotic processes like adsorption are also temperature-dependent but exothermic processes and, thus, favored by low temperature (in winter) [48]. The temperature of the studied CW effluents in summer and winter was 22 ± 7 and 8.6 ± 3.5 °C, respectively, and the corresponding effluent DO was 1.4 ± 1.5 and 1.1 ± 1.6 mg·L^{-1} (Tables S1–S4, Supplementary Materials).

The removal efficiency of 22 PhCs during summer and winter periods is presented in Table S9 (Supplementary Materials). Statistical comparison was carried out for a few PhCs, as sufficient data were not available in other cases (acetaminophen, codeine, tramadol, clarithromycin, erythromycin, venlafaxine, atenolol, metoprolol, and furosemide). The results of the *z*-test for comparison of means for statistical significance or non-significance of observed differences during summer and winter (Table S10, Supplementary Materials) in the removal efficiency of 13 PhCs are discussed below and are substantiated by Figure 2a,b. The removal efficiency of naproxen, salicylic acid, caffeine, and sulfadiazine showed statistically significant seasonal differences (Figure 2a,b and Tables S9 and S10, Supplementary Materials). The significantly higher removal efficiency of naproxen in summer (62 ± 19%) compared with winter (44 ± 14%) (Figure 2a and Tables S9 and S10, Supplementary Materials) could be due to the main contribution of aerobic biodegradation and photodegradation in its removal (Table 3). The removal in winter indicates that anaerobic biodegradation is also responsible for the removal of naproxen (Table 3). Nevertheless, Matamoros et al. [68] reported that the degradation of naproxen was similar under aerobic and anaerobic conditions. Similarly, the significantly higher removal efficiency of salicylic acid and caffeine in summer (89 ± 6% and 83 ± 19%, respectively) compared with winter (63 ± 18% and 53 ± 25%, respectively) (Figure 2a and Tables S9 and S10, Supplementary Materials) indicates the improvement in their main removal mechanisms in summer, which are aerobic biodegradation and plant uptake (Table 3). Analogous to that, the removal efficiency of sulfadiazine exhibited significant seasonal differences (Figure 2b and Table S10, Supplementary Materials). Its removal efficiency was more than twice in summer (66 ± 9%) compared with winter (28 ± 16%) (Table S9), which was attributed to enhanced biodegradation in CWs at warm temperature [22].

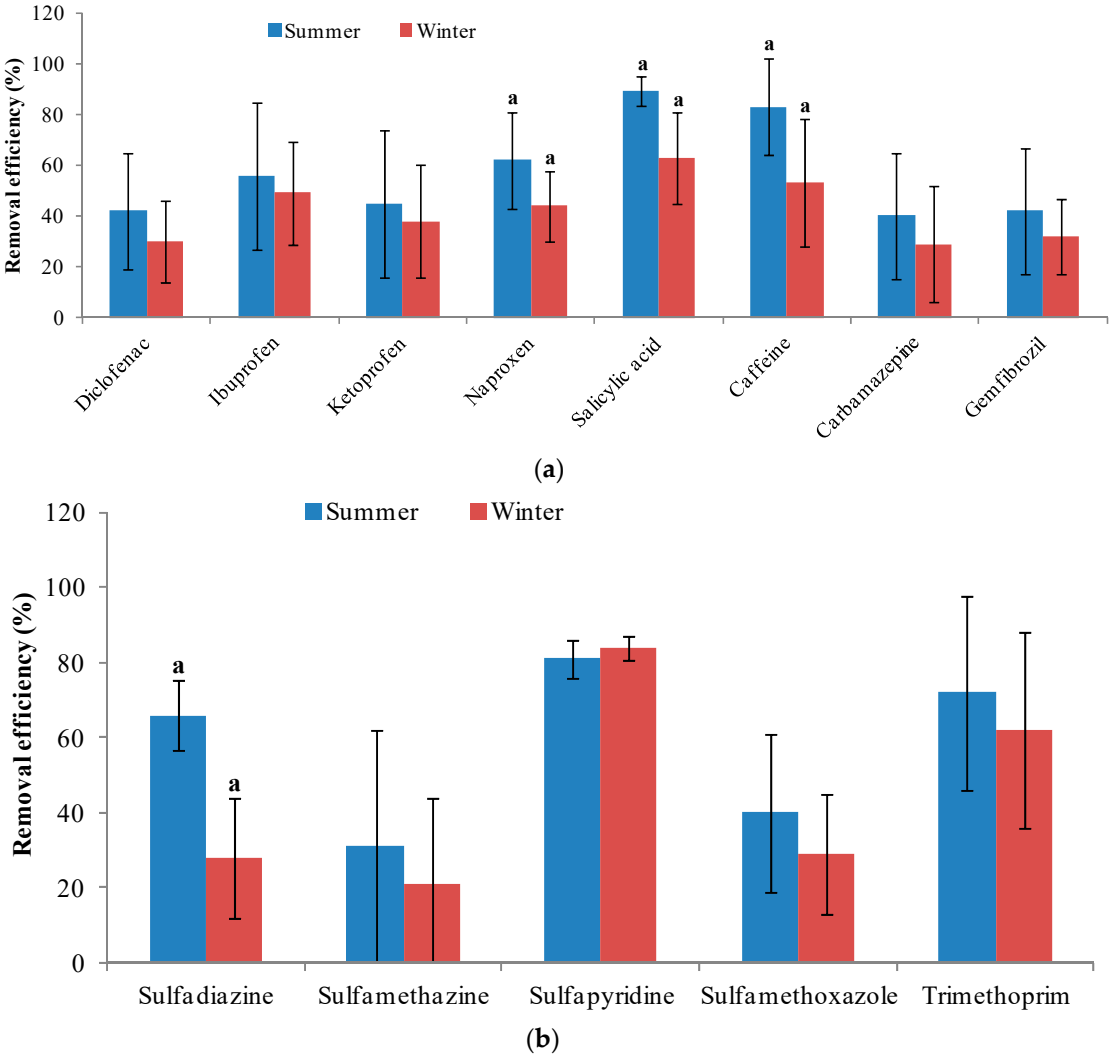


Figure 2. The removal efficiency (mean and standard deviation) of PhCs with different types of CWs in different seasons. Note: (**a**) For naproxen, salicylic acid, and caffeine "**a**" shows the significant difference in the removal efficiency during summer and winter at $\alpha = 0.05$ ($p < 0.05$). (**b**) For sulfadiazine, "**a**" shows the significant difference in the removal efficiency during summer and winter at $\alpha = 0.05$ ($p < 0.05$). The number of observations of studied PhCs for seasonal effect is given in Table S9 (Supplementary Materials). Negative values in the case of standard deviation were capped at zero to improve the readability of the graph. Actual values (e.g., below zero) can be found in Table S9 (Supplementary Materials).

On the other hand, although diclofenac, ibuprofen, ketoprofen, carbamazepine, gemfibrozil, sulfamethazine, sulfamethoxazole, and trimethoprim were removed comparatively better in summer than in winter (Figure 2a,b and Table S9, Supplementary Materials), the removal efficiency of these PhCs did not exhibit significant seasonal differences (Table S10, Supplementary Materials). Several studies ascribed the removal of these PhCs to aerobic and/or anaerobic biodegradation, plant uptake, and photodegradation, as well as adsorption onto and/or sorption by organic surfaces (Table 3). Nevertheless, the non-significant seasonal differences in the removal efficiency of PhCs might be due to the higher influent concentrations of some PhCs in winter (Table S9, Supplementary Materials), which increased their removal, since PhCs follow first-order removal kinetics. Similarly, the high presence of root biomass from plants might enhance the rhizosphere sorption and plant uptake of PhCs when biodegradation is inhibited in winter [17]. These processes are not as temperature-sensitive as biodegradation, and they might be the dominant removal pathways of PhCs in winter [17,40,43].

4. Conclusions

CWs were extensively investigated for the treatment of wastewater for the removal of PhCs. This paper presents a comprehensive and critical review of the literature and a statistical analysis of available data from peer-reviewed studies. Pearson correlation was estimated to examine the influence of selected design and operational factors (area, depth, HLR, HRT, and OLR), and physicochemical parameters (effluent DO, temperature, and pH) on the performance of CWs for the removal of PhCs. The role of plants and a support matrix in the removal of PhCs was comprehensively reviewed from the studies reported in this review. Finally, the impact of seasonality (summer and winter) on the removal of PhCs was critically evaluated. The following specific conclusions can be inferred from this research:

1. Area, depth, HLR, HRT, and OLR play an important role, although with variable influence, in wetland performance for the removal of PhCs. Depth and OLR showed a significant correlation with the removal efficiency of seven of the studied PhCs, whereas the other three factors, area, HLR, and HRT, were significantly correlated with the removal efficiency of six of the studied PhCs. However, the correlation was not significant with the removal efficiency of the same PhCs, which indicates that the removal of PhCs in CWs might not only relate to one design and operational parameter; all the parameters might directly or indirectly impact their removal. For instance, the removal efficiency of some PhCs showed a significant correlation with three factors such as diclofenac and ketoprofen (depth, area, and HRT), salicylic acid and erythromycin (area, HLR, and OLR), and gemfibrozil (depth, OLR, and HRT). The removal efficiency of some PhCs showed a significant correlation with two of the studied factors such as sulfamethazine (depth and HRT), lincomycin (area and OLR), trimethoprim (HLR and OLR), and oxytetracycline (area and HLR).
2. Effluent DO, temperature, and pH play an important role in the removal of PhCs but to different extents. The correlation of these parameters was not significant with the removal efficiency of the same PhCs, which indicates the direct or indirect effect of all the physicochemical parameters on their removal. The significant correlation of effluent DO and temperature with the removal efficiency of most of the studied PhCs (eight and seven, respectively) represents the importance of DO and temperature for the enhancement of microbial processes, which contribute more in their removal. For instance, the removal efficiency of naproxen, diclofenac, ketoprofen, salicylic acid, and lincomycin showed a significant correlation with temperature and effluent DO. The pH can be considered an important parameter because it controls several biotic processes such as plant development, nitrification, and heterotrophic production, as well as abiotic processes such as the attachment of ionizable PhCs to soil/sediment via ion exchange. In CWs, the presence of plants influences the performance by regulating the pH (~7.5), which is the optimal value of pH to control these processes. Nevertheless, the pH directly showed a significant correlation with the removal efficiency of six of the studied PhCs (ketoprofen, erythromycin, lincomycin, ofloxacin, sulfamethazine, and gemfibrozil), which are mainly removed by aerobic biodegradation (erythromycin, lincomycin, sulfamethazine, and gemfibrozil), anaerobic biodegradation (ketoprofen and ofloxacin), adsorption (erythromycin and ofloxacin), and plant uptake (sulfamethazine).
3. Plants contribute significantly to the removal of some PhCs by direct uptake (oxytetracycline, sulfamethazine, caffeine, carbamazepine, and venlafaxine). In addition to direct uptake, the other positive effects of plants such as degradation by enzymatic exudates, as well as release of root exudates (such as carbohydrates and amino acids) and oxygen by the plant roots in the rhizosphere, are suitable for aerobic biodegradation, which also enhances the removal efficiency of PhCs in planted CWs compared with unplanted CWs. Aerobic biodegradation was demonstrated as one of the major removal mechanisms of most of the PhCs (15 out of 26).
4. The use of substrate material of high adsorption capacity and rich in organic matter enhances the removal efficiency of PhCs by adsorption onto the substrate and sorption by organic surfaces, as these are the major removal mechanisms of most of the examined PhCs (codeine, clarithromycin,

erythromycin, ofloxacin, oxytetracycline, carbamazepine, and atenolol) in CWs owing to their physicochemical properties. Additionally, the use of substrate media that could provide a larger available surface area for microbial growth and higher oxygen to promote the elimination of PhCs, which are mainly removed via aerobic biodegradation pathways, is suggested for the enhanced removal of a variety of PhCs by CWs.

5. The removal efficiency of PhCs in CWs was comparatively higher in summer compared with winter due to the difference in external temperature, which directly affects water temperature and oxygen solubility, while playing a major role in the removal processes of PhCs such as biodegradation, plant uptake, and photodegradation at warm temperature, and adsorption/sorption processes at low temperature. Although the removal efficiency of almost all of the studied PhCs showed seasonal differences, statistical significance was established in the removal of naproxen, salicylic acid, caffeine, and sulfadiazine. These PhCs are removed better in summer compared with winter, since the major processes contributing to their removal such as biodegradation (naproxen, salicylic acid, caffeine, and sulfadiazine), plant uptake (caffeine), and photodegradation (naproxen) are enhanced in summer.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4441/11/11/2356/s1: Table S1. The performance of FWSCWs for pharmaceuticals removal; Table S2. The performance of HFCWs for pharmaceuticals removal; Table S3. The performance of VFCWs for pharmaceuticals removal; Table S4. The performance of HCWs for pharmaceuticals removal; Table S5. The studied 26 pharmaceuticals categorized according to their therapeutic classes; Table S6. Physicochemical properties of selected 26 pharmaceuticals; Table S7. Statistics (mean and standard deviation) of pharmaceuticals in planted and unplanted CWs; Table S8. The results (p-values) of the z-test for comparison of means for the removal of pharmaceuticals in planted and unplanted CWs; Table S9. Statistics (mean and standard deviation) of pharmaceuticals in different seasons; Table S10. The results (p-values) of the z-test for comparison of means for the removal of pharmaceuticals in different seasons.

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References

1. Kadlec, R.H.; Wallace, S.D. *Treatment Wetlands*, 2nd ed.; CRC Press: Boca Raton, FL, USA, 2009.
2. Vymazal, J. The use of hybrid constructed wetlands for wastewater treatment with special attention to nitrogen removal: A review of a recent development. *Water Res.* **2013**, *47*, 4795–4811. [CrossRef] [PubMed]
3. Ilyas, H.; Masih, I. The performance of the intensified constructed wetlands for organic matter and nitrogen removal: A review. *J. Environ. Manag.* **2017**, *198*, 372–383. [CrossRef] [PubMed]
4. Ilyas, H.; Masih, I. Intensification of constructed wetlands for land area reduction: A review. *Environ. Sci. Pollut. Res.* **2017**, *24*, 12081–12091. [CrossRef] [PubMed]
5. Ilyas, H.; Masih, I. The effects of different aeration strategies on the performance of constructed wetlands for phosphorus removal. *Environ. Sci. Pollut. Res.* **2018**, *25*, 5318–5335. [CrossRef]
6. Imfeld, G.; Braeckevelt, M.; Kuschk, P.; Richnow, H.H. Monitoring and assessing processes of organic chemicals removal in constructed wetlands, a review. *Chemosphere* **2009**, *74*, 349–362. [CrossRef]
7. Carvalho, P.N.; Basto, M.C.P.; Almeida, C.M.R.; Brix, H. A review of plant–pharmaceutical interactions: From uptake and effects in crop plants to phytoremediation in constructed wetlands. *Environ. Sci. Pollut. Res.* **2014**, *21*, 11729–11763. [CrossRef]
8. Li, Y.; Zhu, G.; Ng, W.J.; Tan, S.K. A review on removing pharmaceutical contaminants from wastewater by constructed wetlands: Design, performance and mechanism. *Sci. Total Environ.* **2014**, *468–469*, 908–932. [CrossRef]

9. Verlicchi, P.; Zambello, E. How efficient are constructed wetlands in removing pharmaceuticals from untreated and treated urban wastewaters? A review. *Sci. Total Environ.* **2014**, *470–471*, 1281–1306. [CrossRef]
10. Zhang, D.; Gersberg, R.M.; Ng, W.J.; Tan, S.K. Removal of pharmaceuticals and personal care products in aquatic plant-based systems: A review. *Environ. Pollut.* **2014**, *184*, 620–639. [CrossRef]
11. Gorito, A.M.; Ribeiro, A.R.; Almeida, C.M.R.; Silva, A.M.T. A review on the application of constructed wetlands for the removal of priority substances and contaminants of emerging concern listed in recently launched EU legislation. *Environ. Pollut.* **2017**, *227*, 428–443. [CrossRef]
12. Ekperusi, A.O.; Sikoki, F.D.; Nwachukwu, E.O. Application of common duckweed (*Lemna minor*) in phytoremediation of chemicals in the environment: State and future perspective. *Chemosphere* **2019**, *223*, 285–309. [CrossRef] [PubMed]
13. Zhang, D.Q.; Tan, S.K.; Gersberg, R.M.; Sadreddini, S.; Zhu, J.; Tuan, N.A. Removal of pharmaceutical compounds in tropical constructed wetlands. *Ecol. Eng.* **2011**, *37*, 460–464. [CrossRef]
14. Matamoros, V.; Salvadó, V. Evaluation of the seasonal performance of a water reclamation pond-constructed wetland system for removing emerging contaminants. *Chemosphere* **2012**, *86*, 111–117. [CrossRef] [PubMed]
15. Hijosa-Valsero, M.; Matamoros, V.; Sidrach-Cardona, R.; Martin-Villacorta, J.; Becares, E.; Bayona, J.M. Comprehensive assessment of the design configuration of constructed wetlands for the removal of pharmaceuticals and personal care products from urban wastewaters. *Water Res.* **2010**, *44*, 3669–3678. [CrossRef]
16. Hijosa-Valsero, M.; Matamoros, V.; Pedescoll, A.; Martín-Villacorta, J.; Bécares, E.; García, J.; Bayona, J.M. Evaluation of primary treatment and loading regimes in the removal of pharmaceuticals and personal care products from urban wastewaters by subsurface-flow constructed wetlands. *Int. J. Environ. Anal. Chem.* **2011**, *91*, 632–653. [CrossRef]
17. Chen, Y.; Vymazal, J.; Březinová, T.; Koželuh, M.; Kule, L.; Huang, J.; Chen, Z. Occurrence, removal and environmental risk assessment of pharmaceuticals and personal care products in rural wastewater treatment wetlands. *Sci. Total Environ.* **2016**, *566–567*, 1660–1669. [CrossRef]
18. Matamoros, V.; Rodríguez, Y.; Bayona, J.M. Mitigation of emerging contaminants by full-scale horizontal flow constructed wetlands fed with secondary treated wastewater. *Ecol. Eng.* **2017**, *99*, 222–227. [CrossRef]
19. Vymazal, J.; Březinová, T.D.; Koželuh, M.; Kule, L. Occurrence and removal of pharmaceuticals in four full-scale constructed wetlands in the Czech Republic-the first year of monitoring. *Ecol. Eng.* **2017**, *98*, 354–364. [CrossRef]
20. Matamoros, V.; Arias, C.; Brix, H.; Bayona, J.M. Removal of pharmaceuticals and personal care products (PPCPs) from urban wastewater in a pilot vertical flow constructed wetland and a sand filter. *Environ. Sci. Technol.* **2007**, *41*, 8171–8177. [CrossRef]
21. Zhang, D.Q.; Gersberg, R.M.; Zhu, J.; Hua, T.; Jinadasa, K.B.S.N.; Tan, S.K. Batch versus continuous feeding strategies for pharmaceutical removal by subsurface flow constructed wetland. *Environ. Pollut.* **2012**, *167*, 124–131. [CrossRef]
22. Dan, A.; Yang, Y.; Dai, Y.-N.; Chen, C.-X.; Wang, S.-Y.; Tao, R. Removal and factors influencing removal of sulfonamides and trimethoprim from domestic sewage in constructed wetlands. *Bioresour. Technol.* **2013**, *146*, 363–370. [CrossRef] [PubMed]
23. Ávila, C.; Matamoros, V.; Reyes-Contreras, C.; Piña, B.; Casado, M.; Mita, L.; Rivetti, C.; Barata, C.; García, J.; Bayona, J.M. Attenuation of emerging contaminants in a hybrid constructed wetland system under different hydraulic loading rates and their associated toxicological effects in wastewater. *Sci. Total Environ.* **2014**, *470–471*, 1272–1280. [CrossRef] [PubMed]
24. Sharif, F.; Westerhoff, P.; Herckes, P. Impact of hydraulic and carbon loading rates of constructed wetlands on contaminants of emerging concern (CECs) removal. *Environ. Pollut.* **2014**, *185*, 107–115. [CrossRef] [PubMed]
25. Conkle, J.; White, J.R.; Metcalfe, C.D. Reduction of pharmaceutically active compounds by a lagoon wetland wastewater treatment system in Southeast Louisiana. *Chemosphere* **2008**, *73*, 1741–1748. [CrossRef]
26. Matamoros, V.; García, J.; Bayona, J.M. Organic micropollutant removal in a full-scale surface flow constructed wetland fed with secondary effluent. *Water Res.* **2008**, *42*, 653–660. [CrossRef]
27. Zhang, D.Q.; Gersberg, R.M.; Hua, T.; Zhu, J.; Tuan, N.A.; Tan, S.K. Pharmaceutical removal in tropical subsurface flow constructed wetlands at varying hydraulic loading rates. *Chemosphere* **2012**, *87*, 273–277. [CrossRef]
28. Dordio, A.; Carvalho, A.J.P. Constructed wetlands with light expanded clay aggregates for agricultural wastewater treatment. *Sci. Total Environ.* **2013**, *463–464*, 454–461. [CrossRef]

29. Verlicchi, P.; Galletti, A.; Petrovic, M.; Barceló, D.; Al Aukidy, M.; Zambello, E. Removal of selected pharmaceuticals from domestic wastewater in an activated sludge system followed by a horizontal subsurface flow bed-analysis of their respective contributions. *Sci. Total Environ.* **2013**, *454–455*, 411–425. [CrossRef]
30. Herrera-Cárdenas, J.; Navarro, A.E.; Torres, E. Effects of porous media, macrophyte type and hydraulic retention time on the removal of organic load and micropollutants in constructed wetlands. *J. Environ. Sci. Health Part A* **2016**, *51*, 380–388. [CrossRef]
31. Auvinen, H.; Gebhardt, W.; Linnemann, V.; Laing, G.D.; Rousseau, D.P.L. Laboratory- and full-scale studies on the removal of pharmaceuticals in an aerated constructed wetland: Effects of aeration and hydraulic retention time on the removal efficiency and assessment of the aquatic risk. *Water Sci. Technol.* **2017**, *76*, 1457–1465. [CrossRef]
32. Salcedo, J.J.P.; Montes, G.H.E.; Frómeta, A.E.N.; Osorio, A.C.; Negrete, J.M. Removal of organic micropollutants from riverine waters using constructed wetlands: A mesocosms experiment. *Int. J. Appl. Eng. Res.* **2018**, *13*, 15740–15748.
33. Carvalho, P.N.; Araújo, J.L.; Mucha, A.P.; Basto, M.C.P.; Almeida, C.M.R. Potential of constructed wetlands microcosms for the removal of veterinary pharmaceuticals from livestock wastewater. *Bioresour. Technol.* **2013**, *134*, 412–416. [CrossRef]
34. Zhang, X.; Jing, R.; Feng, X.; Dai, Y.; Tao, R.; Vymazal, J.; Cai, N.; Yang, Y. Removal of acidic pharmaceuticals by small-scale constructed wetlands using different design configurations. *Sci. Total Environ.* **2018**, *639*, 640–647. [CrossRef] [PubMed]
35. Ávila, C.; Reyes, C.; Bayona, J.M.; García, J. Emerging organic contaminant removal depending on primary treatment and operational strategy in horizontal subsurface flow constructed wetlands: Influence of redox. *Water Res.* **2013**, *47*, 315–325. [CrossRef]
36. Matamoros, V.; Rodríguez, Y.; Albaigés, J. A comparative assessment of intensive and extensive wastewater treatment technologies for removing emerging contaminants in small communities. *Water Res.* **2016**, *88*, 777–785. [CrossRef]
37. Nuel, M.; Laurent, J.; Bois, P.; Heintz, D.; Wanko, A. Seasonal and ageing effect on the behaviour of 86 drugs in a full-scale surface treatment wetland: Removal efficiencies and distribution in plants and sediments. *Sci. Total Environ.* **2018**, *615*, 1099–1109. [CrossRef]
38. Ávila, C.; Nivala, J.; Olsson, L.; Kassa, K.; Headley, T.; Mueller, R.A.; Bayona, J.M.; García, J. Emerging organic contaminants in vertical subsurface flow constructed wetlands: Influence of media size, loading frequency and use of active aeration. *Sci. Total Environ.* **2014**, *494–495*, 211–217. [CrossRef]
39. Auvinen, H.; Havran, I.; Hubau, L.; Vanseveren, L.; Gebhardt, W.; Linnemann, V.; Oirschot, D.V.; Laing, G.D.; Rousseau, D.P.L. Removal of pharmaceuticals by a pilot aerated sub-surface flow constructed wetland treating municipal and hospital wastewater. *Ecol. Eng.* **2017**, *100*, 157–164. [CrossRef]
40. Kahl, S.; Nivala, J.; Afferden, M.V.; Müller, R.A.; Reemtsma, T. Effect of design and operational conditions on the performance of subsurface flow treatment wetlands: Emerging organic contaminants as indicators. *Water Res.* **2017**, *125*, 490–500. [CrossRef]
41. Li, Y.; Wu, B.; Zhu, G.; Liu, Y.; Ng, W.J.; Appan, A.; Tan, S.K. High-throughput pyrosequencing analysis of bacteria relevant to cometabolic and metabolic degradation of ibuprofen in horizontal subsurface flow constructed wetlands. *Sci. Total Environ.* **2016**, *562*, 604–613. [CrossRef]
42. Li, J.; Zhou, Q.; Campos, L.C. Removal of selected emerging PPCP compounds using greater duckweed (*Spirodela polyrhiza*) based lab-scale free water constructed wetland. *Water Res.* **2017**, *126*, 252–261. [CrossRef] [PubMed]
43. Nivala, J.; Kahl, S.; Boog, J.; Afferden, M.; Reemtsma, T.; Müller, R.A. Dynamics of emerging organic contaminant removal in conventional and intensified subsurface flow treatment wetlands. *Sci. Total Environ.* **2019**, *649*, 1144–1156. [CrossRef] [PubMed]
44. Dordio, A.V.; Carvalho, A.J.P.; Teixeira, D.M.; Dias, C.B.; Pinto, A.P. Removal of pharmaceuticals in microcosm constructed wetlands using Typha Spp. and LECA. *Bioresour. Technol.* **2010**, *101*, 886–892. [CrossRef] [PubMed]
45. Hijosa-Valsero, M.; Fink, G.; Schlüsener, M.P.; Sidrach-Cardona, R.; Martín-Villacorta, J.; Ternes, T.; Bécares, E. Removal of antibiotics from urban wastewater by constructed wetland optimization. *Chemosphere* **2011**, *83*, 713–719. [CrossRef] [PubMed]

46. Hijosa-Valsero, M.; Reyes-Contreras, C.; Domínguez, C.; Bécares, E.; Bayona, J.M. Behaviour of pharmaceuticals and personal care products in constructed wetland compartments: Influent, effluent, pore water, substrate and plant roots. *Chemosphere* **2016**, *145*, 508–517. [CrossRef]
47. Xian, Q.; Hu, L.; Chen, H.; Chang, Z.; Zou, H. Removal of nutrients and veterinary antibiotics from swine wastewater by a constructed macrophyte floating bed system. *J. Environ. Manag.* **2010**, *91*, 2657–2661. [CrossRef]
48. Reyes-Contreras, C.; Hijosa-Valsero, M.; Sidrach-Cardona, R.; Bayona, J.M.; Bécares, E. Temporal evolution in PPCP removal from urban wastewater by constructed wetlands of different configuration: A medium-term study. *Chemosphere* **2012**, *88*, 161–167. [CrossRef]
49. Carranza-Diaz, O.; Schultze-Nobre, L.; Moeder, M.; Nivala, J.; Kuschk, P.; Koeser, H. Removal of selected organic micropollutants in planted and unplanted pilot-scale horizontal flow constructed wetlands under conditions of high organic load. *Ecol. Eng.* **2014**, *71*, 234–245. [CrossRef]
50. Macci, C.; Peruzzi, E.; Doni, S.; Iannelli, R.; Masciandaro, G. Ornamental plants for micro-pollutant removal in wetland systems. *Environ. Sci. Pollut. Res.* **2015**, *22*, 2406–2415. [CrossRef]
51. Li, Y.; Zhang, J.; Zhu, G.; Liu, Y.; Wu, B.; Ng, W.J.; Appan, A.; Tan, S.K. Phytoextraction, phytotransformation and rhizodegradation of ibuprofen associated with *Typha angustifolia* in a horizontal subsurface flow constructed wetland. *Water Res.* **2016**, *102*, 294–304. [CrossRef]
52. He, Y.; Sutton, N.B.; Lei, Y.; Rijnaarts, H.H.M.; Langenhoff, A.A.M. Fate and distribution of pharmaceutically active compounds in mesocosm constructed wetlands. *J. Hazard. Mater.* **2018**, *357*, 198–206. [CrossRef] [PubMed]
53. Button, M.; Cosway, K.; Sui, J.; Weber, K. Impacts and fate of triclosan and sulfamethoxazole in intensified re-circulating vertical flow constructed wetlands. *Sci. Total Environ.* **2019**, *649*, 1017–1028. [CrossRef] [PubMed]
54. Chen, J.; Wei, X.-D.; Liu, Y.-S.; Ying, G.-G.; Liu, S.-S.; He, L.-Y.; Su, H.-C.; Hu, L.-X.; Chen, F.-R.; Yang, Y.-Q. Removal of antibiotics and antibiotic resistance genes from domestic sewage by constructed wetlands: Optimization of wetland substrates and hydraulic loading. *Sci. Total Environ.* **2016**, *565*, 240–248. [CrossRef]
55. Huang, X.; Zheng, J.; Liu, C.; Liu, L.; Liu, Y.; Fan, H. Removal of antibiotics and resistance genes from swine wastewater using vertical flow constructed wetlands: Effect of hydraulic flow direction and substrate type. *Chem. Eng. J.* **2017**, *308*, 692–699. [CrossRef]
56. Park, J.; Cho, K.H.; Lee, E.; Lee, S.; Cho, J. Sorption of pharmaceuticals to soil organic matter in a constructed wetland by electrostatic interaction. *Sci. Total Environ.* **2018**, *635*, 1345–1350. [CrossRef]
57. Liu, L.; Liu, Y.-H.; Wang, Z.; Liu, C.-X.; Huang, X.; Zhu, G.-F. Behavior of tetracycline and sulfamethazine with corresponding resistance genes from swine wastewater in pilot-scale constructed wetlands. *J. Hazard. Mater.* **2014**, *278*, 304–310. [CrossRef]
58. Rühmland, S.; Wick, A.; Ternes, T.A.; Barjenbruch, M. Fate of pharmaceuticals in a subsurface flow constructed wetland and two ponds. *Ecol. Eng.* **2015**, *80*, 125–139. [CrossRef]
59. Ávila, C.; Pedescoll, A.; Matamoros, V.; Bayona, J.M.; García, J. Capacity of a horizontal subsurface flow constructed wetland system for the removal of emerging pollutants: An injection experiment. *Chemosphere* **2010**, *81*, 1137–1142. [CrossRef]
60. Hijosa-Valsero, M.; Matamoros, V.; Martin-Villacorta, J.; Becares, E.; Bayona, J.M. Assessment of full-scale natural systems for the removal of PPCPs from wastewater in small communities. *Water Res.* **2010**, *44*, 1429–1439. [CrossRef]
61. Ávila, C.; Bayona, J.M.; Martín, I.; Salas, J.J.; García, J. Emerging organic contaminant removal in a full-scale hybrid constructed wetland system for wastewater treatment and reuse. *Ecol. Eng.* **2015**, *80*, 108–116. [CrossRef]
62. Francini, A.; Mariotti, L.; Gregorio, S.D.; Sebastiani, L.; Andreucci, A. Removal of micro-pollutants from urban wastewater by constructed wetlands with *Phragmites australis* and *Salix matsudana*. *Environ. Sci. Pollut. Res.* **2018**, *25*, 36474–36484. [CrossRef] [PubMed]
63. Zhang, D.Q.; Hua, T.; Gersberg, R.M.; Zhu, J.; Ng, W.J.; Tan, S.K. Fate of diclofenac in wetland mesocosms planted with Scirpus validus. *Ecol. Eng.* **2012**, *49*, 59–64. [CrossRef]
64. Matamoros, V.; Caselles-Osorio, A.; García, J.; Bayona, J.M. Behaviour of pharmaceutical products and biodegradation intermediates in horizontal subsurface flow constructed wetland. A microcosm experiment. *Sci. Total Environ.* **2008**, *394*, 171–176. [CrossRef] [PubMed]
65. Hijosa-Valsero, M.; Sidrach-Cardona, R.; Martín-Villacorta, J.; Valsero-Blanco, M.C.; Bayona, J.M.; Bécares, E. Statistical modelling of organic matter and emerging pollutants removal in constructed wetlands. *Bioresour. Technol.* **2011**, *102*, 4981–4988. [CrossRef]

66. Zhu, S.; Chen, H. The fate and risk of selected pharmaceutical and personal care products in wastewater treatment plants and a pilot-scale multistage constructed wetland system. *Environ. Sci. Pollut. Res.* **2014**, *21*, 1466–1479. [CrossRef]
67. Březinova, T.D.; Vymazal, J.; Koželuh, M.; Kule, L. Occurrence and removal of ibuprofen and its metabolites in full-scale constructed wetlands treating municipal wastewater. *Ecol. Eng.* **2018**, *120*, 1–5. [CrossRef]
68. Matamoros, V.; Hijosa, M.; Bayona, J.M. Assessment of the pharmaceutical active compounds removal in wastewater treatment systems at enantiomeric level. Ibuprofen and naproxen. *Chemosphere* **2009**, *75*, 200–205. [CrossRef]
69. Zhang, D.Q.; Gersberg, R.M.; Hua, T.; Zhu, J.F.; Goyal, M.K.; Ng, W.J.; Tan, S.K. Fate of pharmaceutical compounds in hydroponic mesocosms planted with Scirpus validus. *Environ. Pollut.* **2013**, *181*, 98–106. [CrossRef]
70. Koottatep, T.; Phong, V.H.N.; Chapagain, S.K.; Panuvatvanich, A.; Polprasert, C.; Ahn, K.-H. Potential of laterite soil coupling fenton reaction in Acetaminophen (ACT) removal in constructed wetlands. *Water Air Soil Pollut.* **2017**, *228*, 283. [CrossRef]
71. Vystavna, Y.; Frkova, Z.; Marchand, L.; Vergeles, Y.; Stolberg, F. Removal efficiency of pharmaceuticals in a full scale constructed wetland in East Ukraine. *Ecol. Eng.* **2017**, *108*, 50–58. [CrossRef]
72. Petrie, B.; Rood, S.; Smith, B.D.; Proctor, K.; Youdan, J.; Barden, R.; Kasprzyk-Hordern, B. Biotic phase micropollutant distribution in horizontal sub-surface flow constructed wetlands. *Sci. Total Environ.* **2018**, *630*, 648–657. [CrossRef] [PubMed]
73. Berglund, B.; Khan, G.A.; Weisner, S.E.B.; Ehde, P.M.; Fick, J.; Lindgren, P.-E. Efficient removal of antibiotics in surface-flow constructed wetlands, with no observed impact on antibiotic resistance genes. *Sci. Total Environ.* **2014**, *476–477*, 29–37. [CrossRef] [PubMed]
74. Yan, Q.; Feng, G.; Gao, X.; Sun, C.; Guo, J.-S.; Zhu, Z. Removal of pharmaceutically active compounds (PhACs) and toxicological response of Cyperus alternifolius exposed to PhACs in microcosm constructed wetlands. *J. Hazard. Mater.* **2016**, *301*, 566–575. [CrossRef]
75. Choi, Y.-J.; Kim, L.-H.; Zoh, K.-D. Removal characteristics and mechanism of antibiotics using constructed wetlands. *Ecol. Eng.* **2016**, *91*, 85–92. [CrossRef]
76. Liang, Y.; Zhu, H.; Bañuelos, G.; Shutes, B.; Yan, B.; Cheng, X. Removal of sulfamethoxazole from salt-laden wastewater in constructed wetlands affected by plant species, salinity levels and co-existing contaminants. *Chem. Eng. J.* **2018**, *341*, 462–470. [CrossRef]
77. Sgroi, M.; Pelissari, C.; Roccaro, P.; Sezerino, P.H.; García, J.; Vagliasindi, F.G.A.; Ávila, C. Removal of organic carbon, nitrogen, emerging contaminants and fluorescing organic matter in different constructed wetland configurations. *Chem. Eng. J.* **2018**, *332*, 619–627. [CrossRef]
78. Matamoros, V.; Bayona, J.M. Elimination of pharmaceuticals and personal care products in subsurface flow constructed wetlands. *Environ. Sci. Technol.* **2006**, *40*, 5811–5816. [CrossRef]
79. Dettenmaier, E.M.; Doucette, W.J.; Bugbee, B. Chemical hydrophobicity and uptake by plant roots. *Environ. Sci. Technol.* **2009**, *43*, 324–329. [CrossRef]
80. Wang, C.; Zheng, S.-S.; Wang, P.-F.; Qian, J. Effects of vegetations on the removal of contaminants in aquatic environments: A review. *J. Hydrodyn. B* **2014**, *26*, 497–511. [CrossRef]
81. Zhang, D.Q.; Hua, T.; Gersberg, R.M.; Zhu, J.; Ng, W.J.; Tan, S.K. Fate of caffeine in mesocosms wetland planted with *Scirpus validus*. *Chemosphere* **2013**, *90*, 1568–1572. [CrossRef]
82. Matamoros, V.; García, J.; Bayona, J.M. Behavior of selected pharmaceuticals in subsurface flow constructed wetlands: A pilot-scale study. *Environ. Sci. Technol.* **2005**, *39*, 5449–5454. [CrossRef] [PubMed]
83. Breitholtz, M.; Näslund, M.; Stråe, D.; Borg, H.; Grabic, R.; Fick, J. An evaluation of free water surface wetlands as tertiary sewage water treatment of micro-pollutants. *Ecotoxicol. Environ. Saf.* **2012**, *78*, 63–71. [CrossRef] [PubMed]
84. Salgado, R.; Pereira, V.J.; Carvalho, G.; Soeiro, R.; Gaffney, V.; Almeida, C. Photodegradation kinetics and transformation products of ketoprofen, diclofenac and atenolol in pure water and treated wastewater. *J. Hazard. Mater.* **2013**, *244*, 516–527. [CrossRef]
85. Yi, X.; Tran, N.H.; Yin, T.; He, Y.; Gin, K.Y.-H. Removal of selected PPCPs, EDCs, and antibiotic resistance genes in landfill leachate by a full-scale constructed wetlands system. *Water Res.* **2017**, *121*, 46–60. [CrossRef] [PubMed]

86. Truu, M.; Juhanson, J.; Truu, J. Microbial biomass, activity and community composition in constructed wetlands. *Sci. Total Environ.* **2009**, *407*, 3958–3971. [CrossRef] [PubMed]
87. Lorphensri, O.; Intravijit, J.; Sabatini, D.A.; Kibbey, T.C.G.; Osathaphan, K.; Saiwan, C. Sorption of Acetaminophen, 17α-ethynylestradiol, nalidixic acid, and norfloxacin to silica, alumina, and a hydrophobic medium. *Water Res.* **2006**, *40*, 1481–1491. [CrossRef] [PubMed]
88. Bialk-Bielinska, A.; Stolte, S.; Matzke, M.; Fabianska, A.; Maszkowska, J.; Kolodziejska, M.; Liberek, B.; Stepnowski, P.; Kumirska, J. Hydrolysis of sulphonamides in aqueous solutions. *J. Hazard. Mater.* **2012**, *221*, 264–274. [CrossRef] [PubMed]
89. Zhang, D.Q.; Luo, J.; Lee, Z.M.P.; Maspolim, Y.; Gersberg, R.M.; Liu, Y.; Tan, S.K.; Ng, W.J. Characterization of bacterial communities in wetland mesocosms receiving pharmaceutical-enriched wastewater. *Ecol. Eng.* **2016**, *90*, 215–224. [CrossRef]
90. Brimecombe, M.J.; Leij, F.A.A.M.; Lynch, J.M. Rhizodeposition and microbial populations. In *The Rhizosphere: Biogeochemistry and Organic Substrates at the Soil-Plant Interface*; Pinton, R., Varanini, Z., Nannipieri, P., Eds.; Marcel Dekker: New York, NY, USA, 2001; pp. 74–98.
91. Matamoros, V.; Nguyen, L.X.; Arias, C.A.; Salvadó, V.; Brix, H. Evaluation of aquatic plants for removing polar microcontaminants: A microcosm experiment. *Chemosphere* **2012**, *88*, 1257–1264. [CrossRef]
92. Wang, Y.; Yin, T.; Kelly, B.C.; Gin, K.Y.-H. Bioaccumulation behaviour of pharmaceuticals and personal care products in a constructed wetland. *Chemosphere* **2019**, *222*, 275–285. [CrossRef]
93. Pilon-Smits, E. Phytoremediation. *Ann. Rev. Plant Biol.* **2005**, *56*, 15–39. [CrossRef] [PubMed]



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