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Review

Critical review of technologies for the on-site treatment of hospital wastewater: From conventional to combined advanced processes

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ABSTRACT

This review aims to assess different technologies for the on-site treatment of hospital wastewater (HWW) to remove pharmaceutical compounds (PhCs) as sustances of emerging concern at a bench, pilot, and full scales from 2014 to 2020. Moreover, a rough characterisation of hospital effluents is presented. The main detected PhCs are antibiotics and psychiatric drugs, with concentrations up to 1.1 mg/L. On the one hand, regarding the presented technologies, membrane bioreactors (MBRs) are a good alternative for treating HWW with PhCs removal values higher than 80% in removing analgesics, anti-inflammatories, cardiovascular drugs, and some antibiotics. Moreover, this system has been scaled up to the pilot plant scale. However, some target compounds are still present in the treated effluent, such as psychiatric and contrast media drugs and recalcitrant antibiotics (erythromycin and sulfamethoxazole). On the other hand, ozonation effectively removes antibiotics found in the HWW (>93%), and some studies are carried out at the pilot plant scale. Even though, some families, such as the X-ray contrast media, are recalcitrant to ozone. Other advanced oxidation processes (AOPs), such as Fenton-like or UV treatments, seem very effective for removing pharmaceuticals, Antibiotic Resistance Bacteria (ARBs) and Antibiotic Resistance Genes (ARGs). However, they are not implanted at pilot plant or full scale as they usually consider extra reactants such as ozone, iron, or UV-light, making the scale-up of the processes a challenging task to treat high-loading wastewater. Thus, several examples of biological wastewater treatment methods combined with AOPs have been proposed as the better strategy to treat HWW with high removal of PhCs (generally over 98%) and ARGs/ARBs (below the detection limit) and lower spending on reactants. However, it still requires further development and optimisation of the integrated processes.

1. Introduction

Hospital wastewater (HWW) is one of the primary sources of pharmaceutical compounds (PhCs) in the environment, with significant contributions to wastewater loads. Generally, HWW discharges to Wastewater Treatment Plants (WWTP), and they are co-treated with urban wastewater (UWW). HWW is co-treated with urban wastewater in most countries, although the main physico-chemical parameters of HWW are higher than those found for UWW, as shown in Table 1 (El-Ogri et al., 2016; Nasri et al., 2017; Oliveira et al., 2018). The concentration ranges measured in HWW for total organic matter, chlorides and nitrites, and heavy metals are significantly higher than those found in UWW. The higher values recorded for gadolinium, mercury, and platinum have been attributed to specific drugs, mainly contrast media, diagnostic agents, disinfectants, diuretic agents, and antineoplastics.

Due to significant water consumption per bed (higher dilution of the hospital effluent) and the presence of disinfectants and antibiotics in HWW (Carraro et al., 2016), faecal contamination (faecal and total

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Table 1
Main chemical features of hospital influents.

PARAMETER	RANGE OF CONCENTRATIONS	REFERENCE
GENERAL CHARACTERISATION		
Conductivity, μS/cm	300–3682	Boillot et al. (2008); El-Ogri et al. (2016); Oliveira et al. (2018); Verlicchi et al., 2012a; Wiest et al. (2018)
PH	6–9	Kosma et al. (2010); Majumder et al. (2020)
Redox potential, mV	850–950	Boillot et al. (2008); Oliveira et al. (2018); Verlicchi et al., 2010a
Fat and oil, mg/L	50–210	Oliveira et al. (2018); Verlicchi et al., 2010a
Chloride, mg/L	31–18509	El-Ogri et al. (2016); Emmanuel et al. (2004); Verlicchi et al., 2012a
Total N, mg N/L	19–320	Boillot et al. (2008); Oliveira et al. (2018); Wiest et al. (2018) Luja-Mondragón et al., 2019; Top et al. (2020); Vo et al., 2019a
NH_4^+, mg NH_4^+/L	10–70	McArdell et al. (2011); Verlicchi et al., 2012a; Wen et al. (2004); Wiest et al. (2018)
Nitrite, mg NO_2^-/L	0.06–4.46	El-Ogri et al. (2016); McArdell et al. (2011)
Nitrate, mg NO_3^-/L	0.3–8.6	Majumder et al. (2020); McArdell et al. (2011); Nasri et al. (2017)
Phosphate, mg P-PO_4/L	2–31	Boillot et al. (2008); El-Ogri et al. (2016); Verlicchi et al., 2012a; Verlicchi et al., 2010a; Wiest et al. (2018)
Phosphorous, mg/L	2.1–23	El-Ogri et al. (2016); Wiest et al. (2018); Vo et al., 2019a
Sulfate, mg SO_4^{2-}/L	20–2370	El-Ogri et al. (2016)
Suspended solids, mg/L	27–3260	El-Ogri et al. (2016); Oliveira et al. (2018); Wiest et al. (2018); Vo et al., 2019a
COD (Chemical Oxygen Demand), mg/L	39–7764	Boillot et al. (2008); El-Ogri et al. (2016); Oliveira et al. (2018)
Dissolved COD, mg/L	380–700	McArdell et al. (2011)
DOC (Dissolver Organic Carbon), mg/L	6–1663	Nasri et al. (2017); Wiest et al. (2018)
TOC (Total Organic Carbon), mg/L	31–565	Beier et al. (2012); Nasri et al. (2017); Wiest et al. (2018)
BOD_5 (Biological Oxygen Demand), mg/L	<4–2575	Da Costa Machado et al. (2017); de Oliveira Schwaickhardt et al. (2017); El-Ogri et al. (2016)
BOD_5/COD (biodegradability index)	0.1–0.8	Da Costa Machado et al. (2017); El-Ogri et al. (2016); Nasri et al. (2017)
AOX (Adsorbable Organic Halides), μg/L	1.1–15.2	de Oliveira Schwaickhardt et al. (2017); Nasri et al. (2017); Wiest et al. (2018); Top et al. (2020)
Turbidity (NTU)	100–480	Nasri et al. (2017)
Total Phenols (mg/L)	0.1–78	Da Costa MacHado et al. (2017); Khan et al., 2020a; Top et al. (2020)
EC_{50} (*Daphnia*), TU	9.8–117	Emmanuel et al. (2004); Machado et al. (2007)
Total surfactants, mg/L	0.26–34	Top et al. (2020); Verlicchi et al. (2010b); Wiest et al. (2018)
Total disinfectants, mg/L	2–200	Kümmerer (2001); Verlicchi et al., 2012a
Heavy metals		
Gd, μg/L	<1–300	de Oliveira Schwaickhardt et al. (2017)
Hg, μg/L	0.3–37	de Oliveira Schwaickhardt et al. (2017); Luja-Mondragón et al., 2019; Nasri et al. (2017)
Pt, μg/L	0.01–289	de Oliveira Schwaickhardt et al. (2017)
Ag, μg/L	150–437·10^3	Oliveira et al. (2018)
As, μg/L	0.8–17	de Oliveira Schwaickhardt et al. (2017); Luja-Mondragón et al., 2019
Cu, μg/L	27–4010	de Oliveira Schwaickhardt et al. (2017); El-Ogri et al. (2016); Nasri et al. (2017)
Ni, μg/L	7–670	de Oliveira Schwaickhardt et al. (2017); Luja-Mondragón et al., 2019
Pb, μg/L	0–1050	de Oliveira Schwaickhardt et al. (2017); El-Ogri et al. (2016); Nasri et al. (2017)
Zn, μg/L	70–4880	de Oliveira Schwaickhardt et al. (2017); Nasri et al. (2017)
Fe, μg/L	361–4830	El-Ogri et al. (2016); Nasri et al. (2017)
Cd, μg/L	10–70	El-Ogri et al. (2016)
Cr, μg/L	390–630	Luja-Mondragón et al., 2019; Nasri et al. (2017)
Co, μg/L	0.13–0.26	Nasri et al. (2017)
Mn, μg/L	25–55	Nasri et al. (2017)
Microorganisms		
E. coli, MPN/100 mL	10^3–7.7·10^7	de Oliveira Schwaickhardt et al. (2017); El-Ogri et al. (2016)
Enterococci, MPN/100 mL	10^3–10^6	de Oliveira Schwaickhardt et al. (2017)
Faecal coliform, MPN/100 mL	10^3–7.7·10^7	de Oliveira Schwaickhardt et al. (2017); El-Ogri et al. (2016)
Total coliform, MPN/100 mL	2.5·10^3–10^7	de Oliveira Schwaickhardt et al. (2017); Wyasu, 2019
Spore sulfite-reducing anaerobes, CFU/100 mL	3.1·10^6	El-Ogri et al. (2016)
Norovirus, genomic copies/L	2.4·10^6	de Oliveira Schwaickhardt et al. (2017)
Adenovirus, genomic copies/L	2.8·10^6	de Oliveira Schwaickhardt et al. (2017)
Rotavirus	1.9·10^6	de Oliveira Schwaickhardt et al. (2017)
Hepatitis A virus	10^4	de Oliveira Schwaickhardt et al. (2017)
Pseudomonas aeruginosa, CFU/100 mL	5.3·10^6	El-Ogri et al. (2016)
Staphylococcus aureus, CFU/100 mL	7.5·10^5	El-Ogri et al. (2016)
Salmonella & *Vibrio*, CFU/100 mL	PRESENCE	El-Ogri et al. (2016)
SARS-CoV-2	500-18700 genome copies/L	Saba et al. (2021)

coliforms) has been detected higher in UWW than in HWW (Emmanuel et al., 2004). The higher concentrations of copper and iron are attributed to the erosion of drainage pipes (El-Ogri et al., 2016). Also, HWW has a higher concentration of pathogenic viruses such as norovirus, adenovirus, rotavirus, hepatitis A virus, and enterovirus (Oliveira et al., 2018). In addition, the SARS-CoV-2 virus has been detected in HWW & UWW during the last two years (Saba et al., 2021).

A great variety of PhCs present in HWW result from medical (diagnosis, radiology, inpatients care, laboratory, research, or operation emergencies) and non-medical (toilets, kitchens, or laundry) hospital activities (Carraro et al., 2016; Chonova et al., 2016). The type, number, and concentration of PhCs in HWW can change depending on the hospital characteristics: wards, units, bed numbers, hospital age and number of patients (Al Aukidy et al., 2018; Verlicchi et al., 2012b). Moreover, it is essential to consider that the composition could change with time and seasonally (Diaz, 2003). PhCs in aqueous environmental matrices can cause undesirable effects in aquatic ecosystems (Ankley et al., 2007), although their concentration is very low, in the range of ng/L to μg/L. Consequently, those emerging compounds cause serious concern in the water policymakers/water management community and the scientific community.

Despite the exponential growth of this research field since the late 1990s, the European Union proposed only eight pharmaceuticals in the latest Decision 2020/1161 establishing a new Watch List (European Commission, 2020) (Amoxicillin Ciprofloxacin, Sulfamethoxazole, Trimethoprim, Venlafaxine and O-desmethylvenlafaxine). Switzerland, Iran and China are the only countries with relevant legislation regarding the WWTP discharge limits in terms of emerging pollutants. In Iran and China, the legislation is based on control requirements and environmental standards for treating HWWs. However, Switzerland proposes a list of twelve emerging pollutants that should be removed at least 80% in their WWTPs by 2040. Among them, there are priority compounds on the EU observation lists, including citalopram or metoprolol (Rizzo et al., 2019). Regardless, all unregulated PhCs are candidates for future regulation (Verlicchi et al., 2010a).

The PhCs identified in HWW are from different therapeutic classes such as antibiotics, psychiatric and cardiovascular drugs, lipid regulators, antidiabetics, analgesics, anti-inflammatories, contrast media, hormones, and antiviral/anthelmintics (Azuma et al., 2019; Le Corre et al., 2012; Verlicchi et al., 2012b). Fig. 1 and Table SM-1 show the concentration ranges for the major PhCs detected in hospital wastewater effluents, indicating their concentration range.

The antibiotic compounds are the most commonly PhCs used in modern medicine that quickly reach the aquatic environment (Kümmerer, 2009; Watkinson et al., 2009). Moreover, the increased concentration of antibiotics in the aquatic environment could develop antibiotic-resistance bacteria (ARBs) and antibiotic-resistant genes (ARGs), which may transfer to human pathogens (Kümmerer, 2009; Martinez, 2009; Wright, 2010). Non-target environmental organisms are inevitably exposed, occasioning a potential risk of ecosystem disruption (Carbajo et al., 2015; Isidori et al., 2005).

Anticancer or antineoplastic drugs have increased in the last decades, and these compounds have been detected in wastewater and surface water. They have cytotoxic, genotoxic, mutagenic, carcinogenic, and teratogenic effects, seriously affecting wildlife and human health (Kümmerer et al., 2016; Negreira et al., 2014).

Halogenated organic compounds are also present in HWW. They are not biodegradable and are poorly eliminated in the biological treatment of the WWTP (Kovalova et al., 2012), reaching the surface water and introduced into the food chain. The primary source of halogenated organic compounds is some disinfectants like chlorophenols and iodinated X-ray contrast media (Ternes and Hirsch, 2000).

Most pharmaceuticals in hospital effluents present maximum concentrations below 10 μg/L. However, higher concentrations are typically identified for specific PhCs (e.g., paracetamol, cyclophosphamide, amoxicillin, iomeprol, iopromide), reaching concentrations within the low mg/L (Verlicchi et al., 2012a).

Another critical point to consider is the ecotoxicity of HWW. HWW has been proved to be much more toxic than UWW, as indicated by recent ecotoxicity studies testing the mobility of *Daphnia magna*, the growth of *Pseudokirchneriella subcapitata* and the reproduction rate of *Brachionus calyciflorus* (Laquaz et al., 2018). Ecotoxicity tests performed with a mixture of PhCs on aquatic organisms showed that the toxicity was amplified, sometimes by over five orders of magnitude, especially when several of the PhCs present have synergistic behavior compared to isolated compounds (Flaherty & Dodson, 2005).

Antibiotics are effective against pathogenic bacteria (Roose-Amsaleg and Laverman, 2016). Some of them, such as sulfamethoxazole,

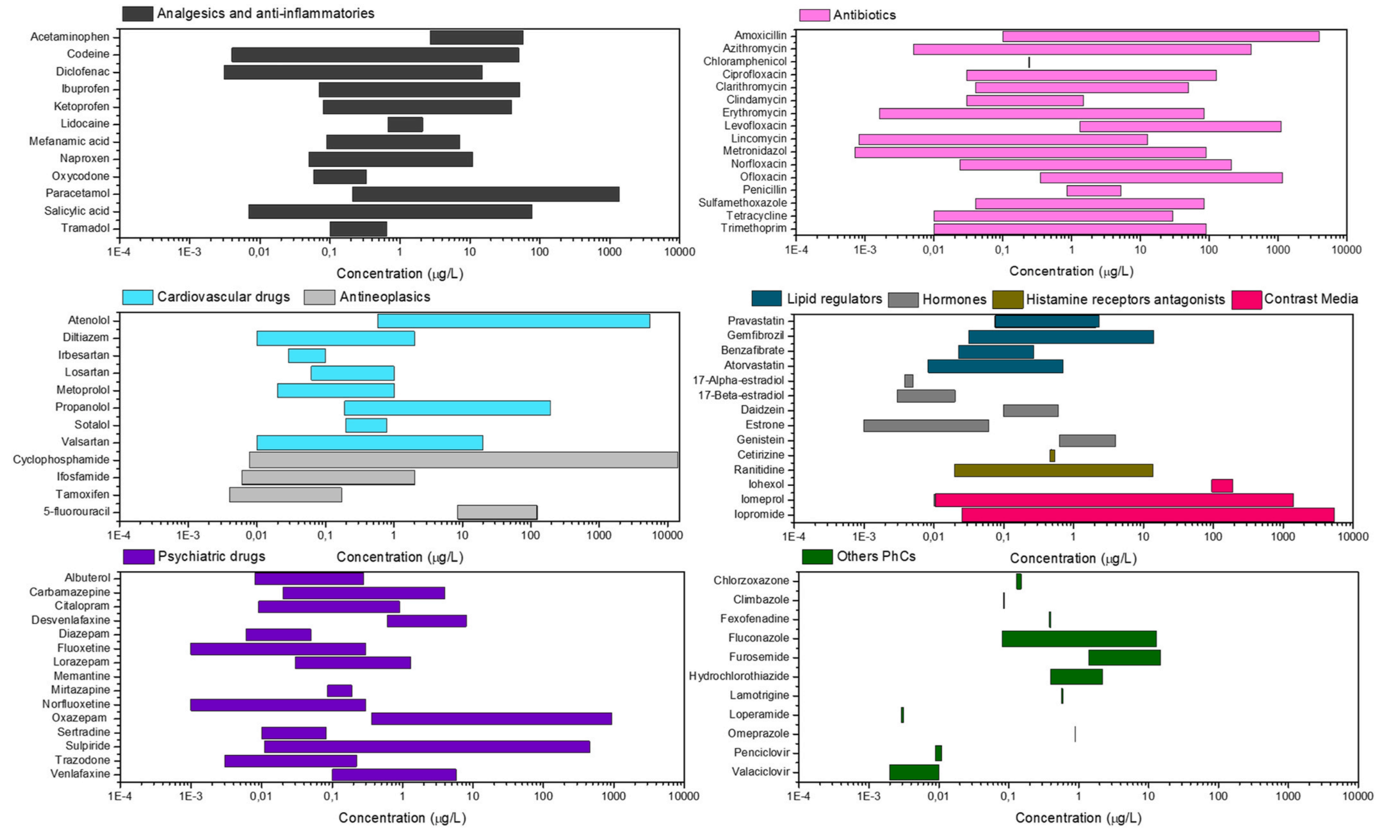

Fig. 1. The concentration range of pharmaceutical compounds detected in HWW.

ciprofloxacin, gentamicin, trimethoprim, and vancomycin (Schmidt et al., 2012), affect the nitrifying bacteria that play an important role in ecological balance and nutrient cycles in aquatic ecosystems. However, amoxicillin and ceftriaxone have shown no significant risk for fish and *Daphnia* (Pirsaheb et al., 2020). Some antibiotics are less persistent, such as trimethoprim, which is potentially toxic only to macrophytes, harmful to algae and not toxic for all the other aquatic groups (Kolar et al., 2014). The anti-inflammatory agents and the lipid regulators are toxic to an extensive range of organisms, from algae and cyanophytes to invertebrates (Huang et al., 2011). However, they are non-toxic to the freshwater fish *Lepomis macrochirus* (bluegill sunfish) (Halling-Sørensen et al., 1998). The anticonvulsant carbamazepine is classified as a harmful compound, being reported as producing a very moderate toxicity (at 74–138 mg/L) to daphnids, zebrafish *Danio rerio* and amphibians (Fent et al., 2006; Ferrari et al., 2003), and induces oxidative stress in the freshwater cnidarian *Hydra attenuata* (at a threshold value of 7.1 μg/L) (Vernouillet et al., 2010). The β -blockers adversely impact the survival, growth, and reproduction of secondary consumers such as *Hyalella azteca, Daphnia magna, Daphnia lumholtzi*, and *Ceriodaphnia dubia* (Cleuvers, 2005; Huggett et al., 2002). Antineoplastics are the least investigated in their toxicity to organisms (Lienert et al., 2007). Additionally, cytostatic compounds, which enter the environment in small quantities, are designed to act on DNA to prevent the growth and division of tumour cells via interference with the genetic material. Hence, they are likely to produce genotoxicity.

In most countries, HWW is discharged into the urban sewer without pre-treatment and co-treated with UWW in the conventional wastewater treatment plants (WWTP) (Carraro et al., 2016). The concentrations and spectrum of pharmaceuticals in HWW are higher than in UWW (Chonova et al., 2016). Conventional WWTPs are highly efficient in reducing suspended solids, organic matter, and nutrients concentration. Though, it drops treating HWW with PhCs (Carballa et al., 2004; Castiglioni et al., 2006; Gros et al., 2007; Jelić et al., 2012; Rosal et al., 2008, 2010; Santos et al., 2013).

The PhCs removal shows considerable variability (Diaz, 2003), is compound-specific, and depends on the applied treatment and its parameters. Thus, a dedicated treatment for HWWs should always be the best solution, avoiding the emission of PhCs into the environment and spreading pathogens from its discharge to the municipal wastewater system.

This study aims to present and discuss a deep characterisation and progress of the treatments of PhCs in HWW. In the last years, most studies focused on the degradation of PhCs were carried out in synthetic HWW instead of real effluents. Even though the results obtained were essential to get preliminary information on the feasibility of the tested processes. However, the complexity of hospital wastewater effluents makes necessary to intensify the research with actual water matrices. Many review papers have been recently published regarding the occurrence and fate of micropollutants and their potential treatment in HWW (Khan et al., 2021; Khan et al., 2020a; Lutterbeck et al., 2020; Majumder et al., 2020; Papageorgiou et al., 2019). Most of these studies are based on removing PhCs through conventional techniques (Khan et al., 2020a), but only a few have treated the removal of PhCs using advanced technologies. In this work, several processes are evaluated, from classical ones to more original approaches such as hybrid processes, from bench scale to pilot plants and even the latest full-scale plants currently existing.

2. Technologies for hospital wastewater treatment

This central point of the review is dedicated to evaluate the newest treatments proposed in the literature for the on-site treatment of HWW. This study is based on 51 publications regarding 76 studies on treating hospital effluents at different scales (lab, pilot and full-scale), where physicochemical, biological, and advanced oxidation for wastewater treatment have been applied. They were carried out in 20 other countries worldwide between **2014 and 2020**. Table 2 reports the main characteristics of the essential studies included in this review, indicating the type of treatment, scale, country, aim and principal parameters. As it can be seen, HWW has been treated by different processes. Fig. 2a shows the number of articles focused on the selected technologies for HWW treatment presented in this review: physico-chemical, biological and combined processes. Although physico-chemical treatment is used before its co-treatment with urban wastewater at domestic wastewater treatment plants, these treatments are not very frequent. Biological wastewater treatment processes, divided into four different technologies (constructed wetlands, conventional activated sludge (CAS), membrane bioreactors (MBR) and fungal treatment), are frequently proposed as an alternative for the HWW treatment, being the 24% of the studies presented in this area due to the lowest cost as an extrapolation of UWW treatment. Nevertheless, due to the refractory nature of the organic compounds in the HWW, Advanced Oxidation Processes (AOPs) and their combinations (28 and 39%) are the leading studied technologies to reduce the PhCs in the hospital streams. In this sense, combined technologies (physico-chemical and biological) have also been proposed to increase the efficiency of the treatment.

Fig. 2b shows the evolution of the studies over the different years. As can be seen, sole AOPs processes for HWW have lost interest during the last years, being replaced by their combination with other technologies.

Regarding the scale, as it is shown in Fig. 3, most treatments are still at low Technology Readiness Levels (TRLs), but some (16%) are studied on a pilot plant scale. The latter are based on biological wastewater treatments and their combinations, and only a few are centered on AOPs due to the associated high costs.

2.1. Physico-chemical treatments

Physico-chemical treatments, such as chemical coagulation, sedimentation, electrocoagulation, or adsorption, may constitute a single stage in the wastewater treatment process of HWW and an additional treatment during pre-treatment steps to improve the biodegradation of the wastewater in the secondary treatment, usually biological processes. However, only a few studies were carried out based on the use of physico-chemical processes for HWW, and all of them were at a bench scale.

Sponza and Alicanoglu (2018) studied the adsorption of macropollutants and ofloxacin from a HWW using a graphene oxide (GO)-magnetite composite as an adsorbent. Ofloxacin and Chemical Oxygen Demand (COD) adsorption yields increased to 39% and 60%, respectively, for a Nano-GO/M concentration of 5 g/L at 21 °C and pH value of 7.8. Moreover, Van Doorslaer et al. (2015), investigated the adsorption of moxifloxacin (MOX) from a hospital effluent on titanium dioxide. The adsorption of the antibiotic on the adsorbent was enhanced by a factor of 1.6 in the presence of organic constituents like humic, fulvic acids and bovine serum albumin, which might be explained by the formation of TiO_2–organic matter complexes. By contrast, the addition of chloride anions and inorganic carbon had a detrimental effect on the adsorption of moxifloxacin, decreasing by a factor of 3.

Moreover, the removal of ciprofloxacin from HWW by electrocoagulation processes has been studied (Ahmadzadeh et al., 2017). A high ciprofloxacin removal efficiency was obtained (89%), associated with electrode and energy consumptions of 66.8 g/m^3 and 0.613 kWh/m^3, respectively.

In a study focused on the adsorption treatment of the PhCs contained in a HWW on several carbon materials, Álvarez-Torrellas et al., 2017 found that PhCs were efficiently removed from the effluent by all the tested adsorbents, detecting, after the adsorption treatment, only two compounds at very low concentrations (atenolol, 5.50 ng/L, and trazodone, 5.55 ng/L), from 59 different pharmaceutical compounds measured in the raw effluent.

Nonfodji et al. (2020), used a coagulant involving Moringa oleifera seeds and polyaluminum chloride composite to treat HWW. The

Table 2
List of studies included in the review with a brief description of aims and main studied parameters.

Reference	Country	Technology	Scale	Aims of the work	Studied Parameters
del Álamo et al. (2020)	Spain	Fenton	BENCH SCALE	Evaluation of the operating conditions of a heterogeneous Fenton process using a HWW fortified with carbamazepine. The efficiency of the process was assessed for the removal of 18 PhCs contained in the HWW.	18 PhCs from different categories
El Morabet et al. (2020)	India	Submerged Membrane Bioreactor (SMBR) Extended Aeration (EA)	BENCH SCALE	Evaluation of the performance of SMBR and EA processes, coupled with Tubesettler.	Biological Oxygen Demand (BOD_5), Chemical Oxygen Demand (COD), Mixed Liquour Suspended Solids (MLSS), NO_3^-
Khan et al. (2020b)	Saudi Arabia, India Iran Ukraine	Coupling 7 different biological treatments O_3 O_3/H_2O_2	BENCH SCALE	Compare the efficiency of O_3 and O_3/H_2O_2 with seven existing biological treatment methods for macroscopic characterisation, microbial activity, and high-risk pharmaceuticals from hospital effluents.	Diclofenac, Ibuprofen, Carbamazepine, Diazepam, Erythromycin, Ofloxacin, Furosemide, Simvastatin
Khan et al. (2020c)	India	Constructed Wetlands	PILOT SCALE	Removal of organic matter and nutrients from HWW	COD, Total Suspended Solids (TSS), BOD_5, phosphate, pH, alkalinity, nitrate
Mahdavi et al. (2020)	Iran	Coagulation, flocculation, sedimentation and ultrafiltration	BENCH SCALE	Combination of several processes to improve HWW quality for its reusability assessment.	Turbidity, colour, COD, and Total Organic Carbon (TOC)
Nonfodji et al. (2020)	Republic of Benin	Coagulation	BENCH SCALE	Coagulation process of organic matter and pathogenic bacteria in hospital wastewater	Turbidity, COD, aromaticity, *E. coli*, *V. cholerae*, *P. aeruginosa*
Shokoohi et al. (2020)	Iran	Conventional Activated Sludge (CAS) Earthworm-based vermifilter	FULL SCALE PILOT PLANT	Removal of antibiotics in a hospital effluent through a pilot-scale vermifilter and a CAS system.	Trimethoprim, ofloxacin, ciprofloxacin, sulfamethoxazole, tetracycline and metronidazole
Esfandyari et al. (2019)	Iran	Electrocoagulation	BENCH SCALE	Treatment of HWW by electrocoagulation using aluminium and iron electrodes	Cefazolin, COD, and turbidity
Konstas et al. (2019)	Greece	Photocatalysis	BENCH SCALE	Comparison of the photocatalytic performance of different heterogeneous catalysts to degrade PhCs in the secondary wastewater effluent from the University Hospital of Ioannina city.	19 PhCs from different categories
Moussavi et al. (2019)	Iran	Biological + VUV/H_2O_2 Biological + CUV/H_2O_2	BENCH SCALE	Performance of VUV/H_2O_2 and UVC/H_2O_2 for the disinfection and post-treatment of biologically treated wastewater.	TOC, detergents, *E. coli*
Ouarda et al. (2019)	Canada	EAOP	BENCH SCALE	Elimination of PhCs present in HWW by an advanced electrochemical oxidation process.	12 PhCs from different categories
Serna-Galvis et al. (2019)	Colombia	Biological + Sonochemical	BENCH SCALE	Propose a strategy for improving sono-degradation of the pollutants after the biological process by adding ferrous ions and UVC.	15 PhCs from different categories
Rodrigues-Silva et al. (2019)	Brazil	UASB + O_3+	BENCH SCALE	Remove the residual antimicrobial activity from HWW and biologically treated wastewater	Norfloxacin, Ciprofloxacin, Ofloxacin
Tang et al. (2019)	Denmark	MBBR + O_3	PILOT PLANT SCALE	Study the effect of ozone dosage on PhCs removal in the effluent of a pilot MBBR.	20 PhCs from different categories
Vo et al. (2019b)	–	Constructed Vertical Wetland	PILOT PLANT SCALE	Remove a high-dose of acetaminophen-contaminated HWW by peroxidase enzymes.	COD, Total Kjedahl Nitrogen (TKN), Total Phosphorous (TP). Acetaminophen
Vo et al., 2019a	Vietnam	Sponge MBR + O_3	BENCH SCALE	Removal of the antibiotics from HWW by combining sponge-MBR with ozonation	Trimethoprim, norfloxacin, erythromycin, ofloxacin, ciprofloxacin and sulfamethoxazole.
Ahmadzadeh and Dolatabadi (2018)	Iran	Electro Fenton	BENCH SCALE	Removal of acetaminophen in an HWW using an electro-Fenton treatment.	Acetaminophen.
Ooi et al. (2018)	Denmark	MBBR	PILOT PLANT	A pilot plant involving six moving bed biofilm reactors in series was built to join in BOD removal, nitrification, and denitrification, as well as pre-polishing COD for ozonation.	Ac. sulfadiazine, ibuprofen, iomeprol, sulfadiazine, sulfamethoxazole, trimethoprim.
Souza et al. (2018)	Brazil	O_3 O_3/UV O_3/Fe^{2+} O_3/Fe^{2+}/UV	BENCH SCALE	Determine the degradation of PhCs after-treatment of the HWWs by ozone.	Degradation of 82 PhCs, toxicity and mineralisation efficiency.
Sponza and Alicanoglu (2018)	Turkey	Adsorption Photocatalysis	BENCH SCALE	Adsorption and photocatalytic treatment using a nanoparticle graphene oxide magnetite composite.	BOD_5, COD, TSS, TKN, total phosphorus. Ofloxacin
Wiest et al. (2018)	France	CAS	FULL SCALE	Comparison of hospital and urban effluents treatment by CAS for 2 years.	TSS, COD, BOD_5, and NH_4^+ and 13 PhCs from different categories
de Oliveira Schwaickhardt et al. (2017)	Brazil	$UVC/UVV/O_3$	BENCH SCALE	Study seven different configurations combine UVC and UVV photoreactors based on removing the load parameters, detoxification, and life cycle assessment.	Conventional Parameters: COD, BOD, $N–NH_4^+$, TKN, TP, ecotoxicity and Life Cycle Assessment (LCA)
Álvarez-Torrellas et al., 2017	Spain	Adsorption	BENCH SCALE	Adsorption of different PhCs on several carbon materials as adsorbents.	Ciprofloxacin, carbamazepine, TOC, TN, $CO_2^{3-}$and aromaticity
Domenjoud et al. (2017)	France	CAS + O_3	PILOT PLANT SCALE	Integrate ozonation within a conventional activated sludge process.	15 PhCs from different categories

(*continued on next page*)

Table 2 (*continued*)

Reference	Country	Technology	Scale	Aims of the work	Studied Parameters
García-Muñoz et al. (2017)	Spain	Photo-Fenton	BENCH SCALE	Application of the photoassisted-Fenton process for potential on-site treatment of HWW.	COD, TOC, total coliforms, sulfadimethoxine.
Giannakis et al., 2017	Colombia	Photo-Fenton	BENCH SCALE	Application of photo-Fenton for the removal of PhCs and the inactivation of pathogen microorganisms.	Iohexol, venlafaxine, and *Saccharomyces cerevisiae*
Hrenovic et al. (2017)	Croatia	Physico-chemical treatment/biological treatment	FULL SCALE	Study of bacterial resistance to β-lactam antibiotics (Carbapenems-CRBP)	Conventional Parameters: COD, BOD, $N{-}NH_4^+$, TKN, TP, Carbapenem-resistant bacteria, Intestinal enterococci, Total heterotrophic bacteria.
Mir-Tutusaus et al. (2017)	Spain	Fungal reactor	BENCH SCALE	Treatment of a lengthy operation of non-spiked, non-sterile wastewater in a continuous fungal fluidised bed bioreactor coupled to a coagulation-flocculation pretreatment for 56 days.	PhCs from different categories, and bacterial and fungal communities
Nguyen et al. (2017)	Viet Nam	Membrane Bioreactor (MBR)	BENCH SCALE	Treatment of an HWW for antibiotics removal in a MBR using hollow fiber and flat sheet membrane systems.	COD, TKN, NH_4+ –N, NO_2^- –N, NO_3^--N, TP, antibiotics
Sponza and Güney (2017)	Turkey	Photocatalysis Photolysis	BENCH SCALE	Degradation of 2,3,4,5,6-pentabromotoluene, 2,3,4,5,6-pentabromoethyl benzene, triclosan and gemfibrozil using cerium (IV) oxide and titanium (IV) oxide nanoparticles.	COD Gemfibrozil, Triclosan 2,3,4,5,6-pentabromotoluene, y 2,3,4,5,6-pentabromoethyl benzene
Al Qarni et al. (2016)	Saudi Arabia	CAS	FULL SCALE	Investigation of the occurrence and fate of selected P at on-site hospital wastewater treatment plants (HWWTPs) operating under high ambient temperature conditions.	COD, NH_4^+-N, NO_2^-−N, NO_3^-−N, antibiotics, analgesics, β-blockers, anaesthetics, anticonvulsants, cytostatic antineoplastics, lipid regulators, and caffeine.
Anjana Anand et al., 2016	India	Photo-Fenton	BENCH SCALE	Optimisation of the fluidised bed solar photo-Fenton to reduce the COD and improve biodegradability.	COD, TSS, biodegradability
Chiarello et al. (2016)	–	MBR	BENCH SCALE	Removal by MBR of four widespread PhCs (metformin, paracetamol, tetracycline, and enalapril) in HWW.	CODs, Total COD, NH_4^+-N, Alkalinity, Suspended solids, pH and temperature.
Chonova et al., 2016	France	CAS	PILOT PLANT SCALE	CAS system performed parallel on HWW and UWW.	TSS, COD, NO_3^-, NO_2^-; NH_4^+; PO_4^{3-}, conductivity, anti-inflammatory PhCs from different categories
Ferre-Aracil et al. (2016)	Spain	O_3 O_3/H_2O_2	PILOT PLANT SCALE	Application of ozone with hydrogen peroxide to abate some antineoplastic products present in HWW.	Irinotecan, ifosfamide, cyclophosphamide, capecitabine
Lucas et al. (2016)	Spain	Fungal	BENCH SCALE	Elimination of 81 PhCs using a fungal biological treatment (*Trametes versicolor*).	81 PhCs from different categories
Munoz et al. (2016)	Spain	Intensified Fenton	BENCH SCALE	Treatment of a real HWW by an intensified Fenton process at moderate temperatures	COD, TOC, phenols and toxicity.
Nguyen et al. (2016)	Viet Nam	MBR Sponge-MBR	BENCH SCALE	MBR and Sponge-MBR treatment of HWW at low flux conditions. Comparison of the treatment performance and fouling characteristics	COD, TKN, NH_4^+ –N, NO_2 ⁻-N, NO_3^-, TN, TP
Prasertkulsak et al. (2016)	Thailand	MBR	PILOT PLANT SCALE	Removal efficiencies, fate, removal mechanism and microbial community of PhCs in MBR operated under actual fluctuation of wastewater characteristics.	BOD, COD), TKN, NH_4^+-N, SS, MLSS. Triclosan and gemfibrozil.
Wigh et al. (2016)	France	CAS + O_3	BENCH SCALE	A mixture of urban and hospital effluents was evaluated for ecotoxicity with an advanced bioassay battery: biological + ozonation.	Toxicity and genotoxicity
Česen et al. (2015)	Slovene	UV, O_3 UV/O_3, UV/H_2O_2, O_3/H_2O_2 $UV/O_3/H_2O_2$.	BENCH SCALE	Removal of cyclophosphamide (CP) and Ifosfamide (IF) from HWW using biological treatment based on attached-growth biomass combined with abiotic treatment.	IF and CP removal
Casas et al. (2015)	Denmark	CAS MBBR	PILOT PLANT SCALE	Combination of suspended activated sludge and biofilm processes (hybrid biofilm and activated sludge system, Hybas™) for HWW treatment.	COD, NH_4^+-N, NO_2^--N and NO_3^--N
Ferrando-Climent et al., 2015	Spain	Fungal bioreactor	BENCH SCALE	Removal of 10 selected anticancer drugs	10 anticancer drugs
Mousaab et al. (2015)	France	CAS + UF BBR + UF	BENCH SCALE	Removal of PhCs by biological treatment coupled with membrane filtration. Evolution of membrane fouling.	COD, TSS, VSS, TN 21 PhCs from different categories
Somensi et al. (2015)	Brazil	O_3 O_3/US	BENCH SCALE	Compare the bacterial disinfection and DNA denaturation efficiency of ozonolysis and ozonolysis/sonolysis to treat HWW.	DNA denaturation efficiency is quantified by viable cell counts and agarose gel electrophoresis.
Van Doorslaer et al. (2015)	Belgium	Adsorption Photocatalysis	BENCH SCALE	Adsorption and photocatalytic degradation of Moxifloxacin (MOX) from different HWW	MOX
Arslan et al. (2014)	Turkey	O_3 O_3/US O_3/H_2O_2	BENCH SCALE	Determine the optimal experimental conditions to treat a HWW by ozonation process combining with O_3/UV and $O_3/UV/H_2O_2$.	COD and absorbance
Lin et al. (2014)	Taiwan	UV	BENCH SCALE	Photolysis of ketamine and ketamine's primary metabolite, norketamine. Phototransformation pathway and toxicity of the byproducts	Ketamine and Norketamine

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Table 2 (*continued*)

Reference	Country	Technology	Scale	Aims of the work	Studied Parameters
Lee et al. (2014)	Switzerland	MBR + O_3 MBR + O_3/H_2O_2	BENCH SCALE	Determination of the optimal ozone doses for PhCs elimination	25 PhCs from different categories
Wilde et al. (2014)	Brazil	O_3 Fe^{2+}/O_3	BENCH SCALE	Degradation of a mixture of β-blockers by O_3 and Fe^{2+}/O_3. Evaluate the effect of pH and $[Fe^{2+}]$. Determine the kinetics and pathway.	COD, ABS (254 nm) Atenolol, Metoprolol and Propranolol
Cruz-Morató et al. (2014)	Spain	Fungal bioreactor	BENCH SCALE	Degradation of a wide array of PhCs and endocrine disruptor compounds (EDCs) present in HWW under non-sterile conditions	51 PhCs & EDCs, COD, TOC, N–NH^{4+}, Conductivity, TSS, pH and toxicity assessment

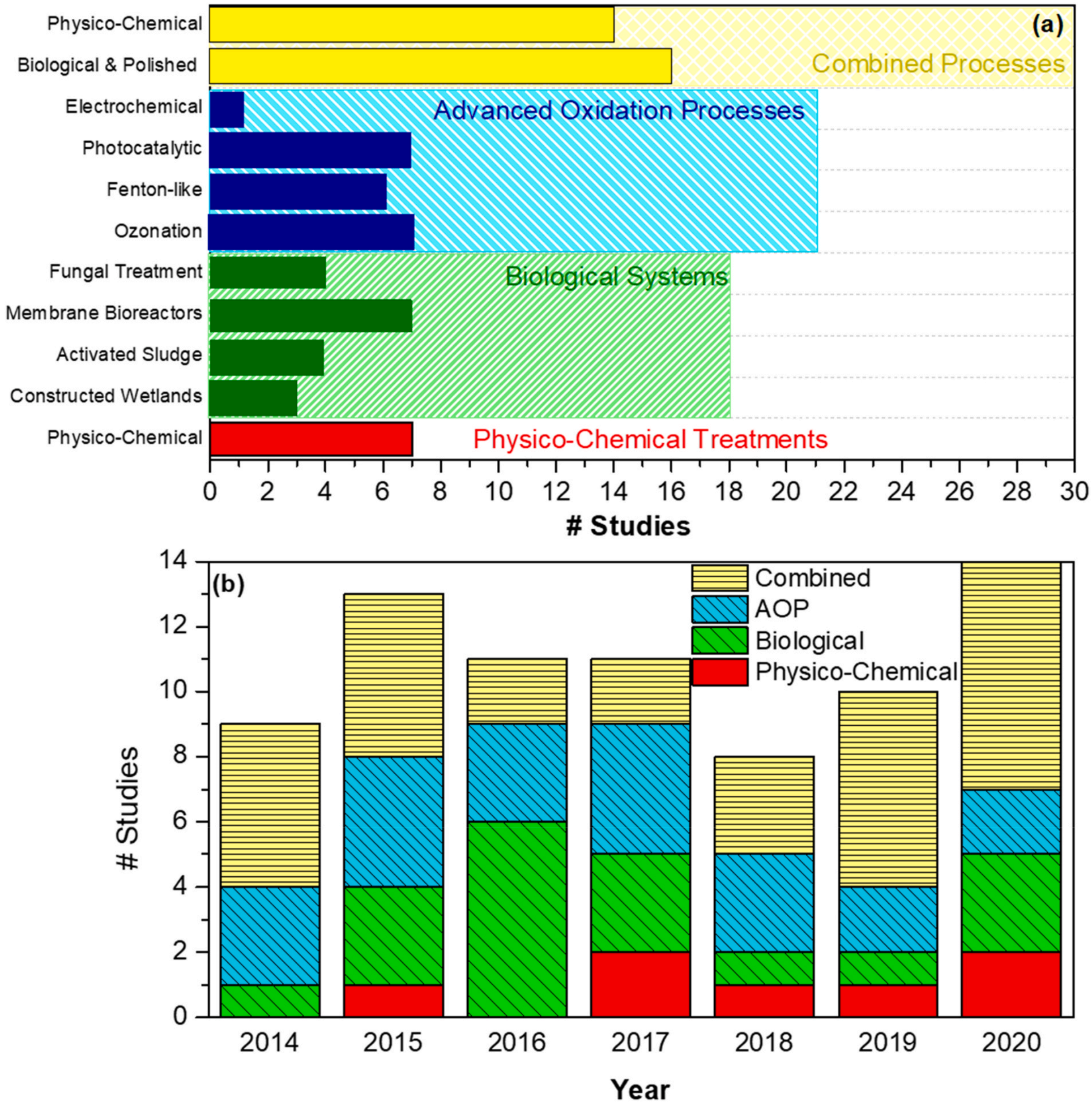

Fig. 2. Number of published studies between 2014 and 2020 concerning the treatment of HWW.

obtained removals, using 320 mg/L of this coagulant, were 64%, 38% and 16% for turbidity, COD and aromaticity, respectively. Moreover, high disinfection values were also achieved, 74% for *E. coli*, 76% for *V. cholerae,* and 90% for *P. aeruginosa*.

Esfandyari et al., (2019) studied an electrocoagulation process, based on aluminum and iron electrodes, for cefazolin removal in HWW. Authors observed that the highest removal efficiency of antibiotics, COD, and turbidity occurred at neutral pHs. Authors believe that those reductions may be attributed to the formation of aluminum hydroxide flocs through the combination of aluminum released from the surface of the electrode and the hydroxide ions present in the solution. The results do not show a good sign of removing PhCs or their residues with coagulation treatments. Thus, more research is required regarding adsorbent saturation and regeneration.

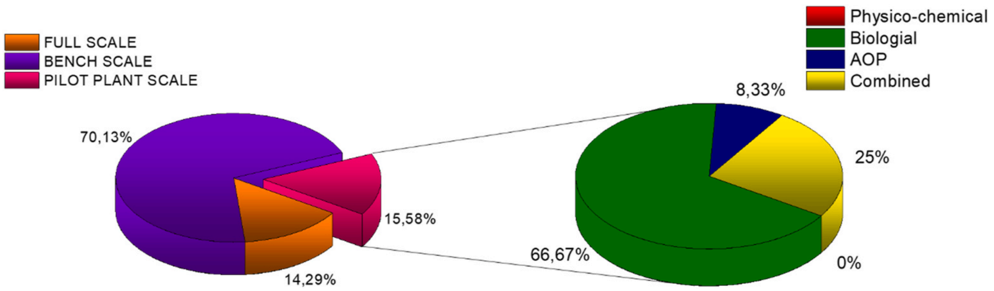

Fig. 3. Scales of the studies between 2014 and 2020 concerning the treatment of HWW.

2.2. *Biological systems*

2.2.1. *Constructed wetlands*

Only a few research studies deal with removing PhCs from hospital effluents using constructed wetlands (CW) (Auvinen et al., 2017; Vo et al., 2019b; Khan et al., 2020c). The first one (Auvinen et al., 2017) used an aerated pilot-scale sub-surface flow (SFF) constructed wetland (CW). The studied PhCs were atenolol (ATL), bisoprolol (BSP), carbamazepine (CBZ), diclofenac (DCF), and gabapentin (GBP). After the treatment, ATL and BSP were moderately degraded (>75 and 50%, respectively). Poor removal was observed for CBZ, DCF and GBP, obtaining 8, 35 and 37% (average), respectively. It was observed that ATL is biodegradable under aerobic and anoxic conditions, faster when oxygen is present. Also, the removal of BSP was more efficient in aerobic conditions. In this study, aeration was necessary to meet the discharge standards set for COD at the Hydraulic Retention Time (HRT) applied (0.5–2 d). The measured average concentrations of those pharmaceuticals after the treatment were (450, 350, 4570, 3340 and 1190 ng/L for ATL, BSP, CBZ, DCF and GBP, respectively.

Plants, such as Scirpus validus, generate peroxidase enzymes to relieve pollutants' stress. Vo et al. (2019b) developed a pilot-scale vertical flow constructed wetland to remove high-doses of acetaminophen (ACT) in HWW. They documented the correlation of peroxidase enzyme extruded by Scirpus validus and PhCs removal efficiency to propose a low-cost method to monitor pollutants removal. Results showed that the proposed system removed ACT to values lower than 10 μ/L. Moreover, the constructed wetland removed COD, Total Kejdahl Nitrogen (TKN) and Total Phosphorous (TP), meeting the wastewater discharged standards of Thailand and Vietnam. Furthermore, it could be demonstrated that ACT concentrations in CW effluents and enzymes *S. validus* exhibited a significant correlation that helped reduce the analytical cost of PhCs treatment, using several multivariate regression models.

Khan et al. (2020c) evaluated a pilot-scale horizontal surface flow constructed wetland (HSFCW) coupled with a Tube settler installed in New Delhi, India, at pilot scale. The system was tested for 3 months and treated 10 m^3/day to evaluate the removal of pollutants from HWW. The HSFCW achieved removal efficiencies of more than 90% for COD, TSS and BOD_5. However, neither constructed wetlands nor tube setters removed nitrates, which may be due to the predominance of aerobic conditions.

Although constructed wetlands have zero energy consumption, they require a larger surface area than conventional purification systems, and some PhCs are refractory to this treatment.

2.2.2. *Conventional activated sludge*

Conventional activated sludge (CAS) treatments have been traditionally designed to remove biodegradable organic matter and nutrients (nitrogen and phosphorus) from UWW through the action of microorganisms. The most classic version of CAS consists of a sequence of anaerobic-anoxic-aerobic reactors followed by a secondary settler, although different configurations are acceptable. Several reviews have analysed the efficient removal of PhCs discharged together with UWW in a Wastewater Treatment Plant (WWTP) (Majumder et al., 2020; Verlicchi et al., 2012a; Wang and Wang, 2016).

The emergent concern about whether HWW should be treated as domestic discharges has increased the number of studies focused on treating HWW as specific discharge using CAS systems. However, these systems are scarce regarding PhCs removal. Table SM-2 collects data on the concentration or removal percentage of global characterisation parameters measured in some influents and effluents of several Hospital Wastewater Treatment Plants (HWWTPs), which have treatment plants based on CAS systems, most of them at full scale, mainly in China, India, Iran, and Vietnam (Al Aukidy et al., 2018).

In some cases, the HWWTPs did not present enough efficiency to achieve the imposed standards. Such is the case of the full-scale HWWTP that treats the HWW originated from CHAL hospital, situated in Contamine sur Arve, France. The HWW is pumped to Bellecombe WWTP via a separate sewer system to conventional primary treatment (grit chamber and screen bar). It is oxidised in a CAS process with sequential aerobic and anoxic conditions, then disinfected by a chlorination step, and finally discharged into the Arve River (Wiest et al., 2018). The study revealed high concentrations of organic carbon, paracetamol, ketoprofen, antibiotic and gadolinium in HWW. Diclofenac and propranolol were efficiently removed, with 77% and 87% values, respectively. However, the treatment was not able to remove carbamazepine. Excluding the latter, the overall PhC removal efficiency was 74%. The higher PhC removal, especially for diclofenac and ketoprofen, is due to the higher HRT (Wiest et al., 2018).

Figure SM-1 represents the PhCs concentration for the influents and effluents of three HWWTPs working with CAS systems located in the Centre Hospitalier Alpes Lèman in France (Chonova et al., 2016) at a pilot plant scale, in Riyadh in Saudi Arabia (Al Qarni et al., 2016) at full scale, and in the Atiyeh Hospital in Iran (Shokoohi et al., 2020) at full scale, treating flow rates between 150 and 800 m^3/day. Although there is a high variability of PhCs concentrations among the different influents, all studies reported high removal values for paracetamol and ibuprofen. In contrast, compounds such as carbamazepine, albendazole or crotamiton showed resistance to degradation. Specifically, Chonova et al., 2016 reported high removal for all the studied PhCs (10) except for carbamazepine. Al Qarni et al. (2016) obtained removal efficiencies for most PhCs (12) higher than 90%. Atenolol, carbamazepine, and clarithromycin were removed with removal values higher than 86%. As a rule, the degradation of PhCs by a CAS system in the HWWTPs followed the same tendency that in WWTPs. It is worth mentioning the case of atenolol, which showed a high removal in hospital wastewater treatments versus the exhibited in the WWTPs or the case of diclofenac, which is characterised by their high persistence in both effluents from WWTPs and HWWTPs (Kosma et al., 2010). However, it exhibited a high removal when the wastewater was pre-treated by chemical flocculation (Sim et al., 2013). Thus, in this case a combined treatment could be a solution.

2.2.3. *Membrane bioreactors*

Membrane bioreactors (MBR) enable improving the quality of effluents with high organic matter and nutrient removal efficiencies. Disinfection can be milder or even unnecessary, as they also considerably reduce the number of solids discharged, and pathogens (Melin et al., 2006). Though, the widespread application of MBRs is limited by membrane fouling, increasing the operational and investment costs (Alsalhy et al., 2018; Remy et al., 2010; Sipma et al., 2010).

HWW, which contains many microbial pathogens and viruses, could be an important application area for MBR systems. MBR could reduce chlorine addition to values lower than 1.0 mg/L and shorten contact time, positively affecting microorganism inactivation (Liu et al., 2010). Because of the complete retention of biosolids in the MBR, these systems allow high mixed liquor suspended solids (MLSS) concentrations (12–15 g MLSS/L), high sludge retention time (SRT) (20 d^{-1}) and low sludge loading rates (0.1 g COD/g VSS d) (Witzig et al., 2002; Yoon et al., 2004).

Adsorption and biodegradation were responsible for removing PhCs in MBR, being the adsorption mechanism dominant when log (K_{ow}) values are greater than 3.2 (Wijekoon et al., 2013). The removal of PhCs in the MBR system is also affected by the sludge age, concentration, composition of wastewater, operating temperature, pH, and conductivity. Moreover, the existence of anoxic and anaerobic compartments could also affect (Luo et al., 2014).

More than 50 plants have been built in China for the full-scale treatment of HWW, with capacities ranging from 20 to 2000 m^3/d (Liu et al., 2010). In pilot-scale experiments, Casas et al. (2015) found that the removal of many PhCs could be effectively achieved using a moving bed biofilm reactor (MBBR) with high elimination rates (> 80%) for ibuprofen and propranolol in batch experiments. However, the removal decreased (< 20%) for some PhCs such as sulfamethoxazole, venlafaxine, iopromide and tramadol (Casas et al., 2015). Table SM-3 shows recent results of PhCs removal from HWW in several MBR systems.

Chiarello et al. (2016) stated that MBR systems represent a new generation of processes that have outperformed conventional treatment for HWW showing better effluent quality. Thus, a bench-scale MBR was effective for enalapril (94.3%), tetracycline (99.4%), and paracetamol (98.8%) removal. Also, the polar compound metformin was less effectively removed (35.4%).

Prasertkulsak et al. (2016) operated a pilot-scale MBR at a short HRT of 3 h to treat HWW. The results revealed the importance of the adsorption of the colloidal particles on supernatant sludge for the PhCs removal and subsequently removed by membrane filtration. However, biodegradation during short HRT was also significant for some compounds. DGGE (Denaturing Gradient Gel Electrophoresis) profile revealed the development of pharmaceutical degrading microorganisms in MBR. To finish, Nguyen et al. (2017), efficiently operated a hollow fiber and flat sheet sponge MBR at 10–20 L/h flux treating HWW. High removal values of norfloxacin, ciprofloxacin, ofloxacin, tetracycline and trimethoprim were observed, whereas, in this case, erythromycin was slowly removed.

Khan et al. (2020b) studied the pre-treatment of seven different HWW treatment technologies (fluidised aerobic bed reactor, extended aeration, submerged aerated fixed films reactor, eco-bio reactor, CW, and MBR. MBR and CW effectively removed conventional chemical and biological parameters. However, MBR also exhibited 100% elimination of ibuprofen, carbamazepine, and furosemide.

In conclusion, some PhCs can be removed with high efficiency, while others were poorly degraded in MBR systems. For example, antibiotics (ofloxacin, tetracycline, trimethoprim or norfloxacin), anti-inflammatory compounds (ibuprofen), analgesics (paracetamol), and cardiovascular PhCs (propanolol) were removed around 80–95%. In general terms, removing pharmaceuticals in MBR follows the following order: analgesics and anti-inflammatories > cardiovascular drugs > antibiotics > psychiatric drugs > contrast media.

2.2.4. *Fungal bioreactors*

Fungal bioreactors have been proposed as an attractive alternative for the on-site treatment of PhCs from hospital effluents due to the capacity of white-rot fungi (WRF), particularly *Trametes versicolor*, to degrade a wide range of emerging pollutants. The efficiency of the fungus *Trametes versicolor* immobilised on rotating biological contactors was demonstrated by treating UWWs contaminated with PhCs (Cruz del Álamo et al., 2020). The presence of advanced bio-oxidation promoters, a lignin-derived mediator and metal complexes with redox activity enhanced the performance of fungal biological wastewater treatment for the removal of PhCs, by combining the secretion of intra- and extra-cellular enzymes responsible for the degradation of organic molecules and the production of oxidising hydroxyl radicals driven by quinone-like redox cycles. Besides the advantages of this type of biological system, only a few research projects are focused on removing PhCs from hospital effluents by fungal reactors. Table SM-4 shows the recent studies of pharmaceuticals removal from hospital wastewater by fungal biological systems.

Cruz-Morató et al. (2014) studied the performance of a batch fluidised bed bioreactor using *Trametes versicolor* pellets under sterile and non-sterile conditions for the treatment of HWW with 99 detected PhCs and endocrine disruptor compounds (EDCs) at different HRT (30 min, 5 h, 1, 2, 5 and 8 days). The overall removal of PhCs was similar in both, the sterile and non-sterile, conditions. These results indicated that sterility is not mandatory for the removal of PhCs, as the non-sterile experiments showed that 46 out of the 51 detected PhCs were highly removed in 8 days. Analgesics were wholly removed after the treatment in 24 h. Then, all the measured antibiotics, detected at concentrations between 0.08 and 32 μg/L, were removed over 77% except for azithromycin (partially removed 26%). Also, psychiatric drugs were removed by over 80%. Caffeine was partially removed ca. 38%, while other EDCs were removed from 75 to 100%. Iopromide showed one of the highest concentrations in the studied hospital wastewater (at a concentration of 419 μg/L) and was only partially removed (34%) in the non-sterile treatment. The other PhCs detected in the HWW were removed from 50% to 100%. Moreover, the Microtox test showed a reduction in wastewater toxicity after the treatment.

Ferrando-Climent et al., 2015 studied the elimination of antineoplastic PhCs using a 10-L fluidised bed bioreactor inoculated with *Trametes versicolor* to evaluate the removal of 10 selected antineoplastic drugs present in HWW. All the tested anticancer drugs were removed entirely from the wastewater after 8 days of the batch experiment, except for ifosfamide and tamoxifen. Further individual degradation experiments were performed for cyclophosphamide, ifosfamide and tamoxifen to identify the generated by-products. Two metabolites (tamoxifen hydroxylated positional isomers) were identified as derived from the biodegradation of the parent compound.

On the other hand, Mir-Tutusaus et al. (2017) treated actual, non-sterile wastewater in a continuous fungal fluidised bed bioreactor after a coagulation-flocculation pre-treatment for an extended period of operation (56 days). This pre-treatment removed the solids concentration and the COD of the actual wastewater from 633 to 215 mg/L, and 1012 mg/L to 300 mg/L, respectively. The main aim of the research was the PhCs removal and its relation to microbial community evolution. 81 PhCs were analysed, and 46 were detected. Fungal treatment consistently removed the most detected PhCs, including recalcitrant ones such as psychiatric drugs and the antibiotic sulfamethoxazole. Only 34 compounds were detected after the treatment. The most common families detected were analgesics, anti-inflammatories, and β-blockers, as well as metabolites of carbamazepine and lipid regulators. The treated effluent did not show any toxicity; therefore, the treatment may have removed all the potentially toxic metabolites. Moreover, *T. versicolor* in pelleted morphology was maintained in the bioreactor for two months with an HRT of 3 d. However, partial renovation of the biomass was required to maintain the fungus activity.

Biological wastewater treatment based on fungal strains using

Trametes versicolor has shown remarkable results with removal values higher than 75% for analgesics, antibiotics (except azithromycin), psychiatric drugs, antineoplastics (except for fosfamide and tamoxifen) and endocrine disruptors. However, it is required to scale up the process and verify its robustness and efficiency.

2.3. Advanced oxidation processes (AOPs)

2.3.1. Ozonisation

Ozone is a powerful oxidant and disinfecting agent making it suitable for different wastewater treatment applications. It has been used worldwide for over a century in drinking water treatment plants to disinfect and remove organic and inorganic matter in raw water. Its usage is continuously increasing as a tertiary treatment for polishing effluents (Chiang et al., 2003; Xu et al., 2002) due to the more stringent discharge legislation, and reclaimed water reuse quality criteria (Czekalski et al., 2016). However, this treatment is also used for the removal of PhCs that suppose environmental and public health concerns (Paraskeva and Graham, 2002; Rosal et al., 2010), and to avoid the dissemination of antimicrobial-resistant bacteria (ARB) and antimicrobial-resistant genes (ARG) (Alexander et al., 2016; Czekalski et al., 2016). As previously mentioned, these pollutants are found in high concentrations in HWW (Carraro et al., 2016; Verlicchi et al., 2015), and the ozonisation process is an alternative to the on-site treatment.

The efficiency of ozonisation for pharmaceutical removal in HWW depends not only on pharmaceutical chemical structure but also on the wastewater matrix properties like alkalinity or pH (Hansen et al., 2016; Yu-Chen Lin et al., 2015). Ozonisation is strongly affected by dissolved organic compounds (DOC) in the wastewater matrix because this organic matter competes for the dissolved ozone or hydroxyl radicals with the PhCs, diminishing the available oxidant concentration (Hansen et al., 2016; Lyko and Nafo, 2013). The final objective is the total mineralisation of the PhCs (neither of the organic matter) and the suppression of the biological activity responsible for their concern or toxicity (Paraskeva and Graham, 2002). The required ozone dose to achieve this goal is mainly determined by the presence of DOC, whose concentration is in the range of mg/L, and not by the concentration of the PhCs, whose concentration is in the range of ng/L (micropollutant). Typical doses applied in wastewater treatment ranged from 0.8 to 1.5 g O_3 per g DOC (Alexander et al., 2016; Verlicchi et al., 2015). The high DOC concentration in a raw HWW, up to 500 mg/L (Carraro et al., 2016; Paola Verlicchi et al., 2010; Verlicchi et al., 2015), would make economically non–viable the direct ozonation of the wastewater and commonly ozonation is studied as a polishing step after biological process where the DOC concentration was around 6–8 mg/L (Hansen et al., 2016; Kovalova et al., 2013; Nielsen et al., 2013).

Ozone presents high efficiencies for micropollutant removal. PhCs removal is usually higher than 90% working with typical doses of ca. 1 g O_3 per g DOC (Antoniou et al., 2013). Nevertheless, there are important exceptions that should be considered. For example, iodinated X-ray contrast media group compounds (iomeprol, iopamidol, iopromide, diatrizoate) or antifungal fluconazole (compounds with high content in a halogenated compound or other aromatic deactivating groups) are recalcitrant to ozone, with efficiencies lower than 60% (Lee et al., 2014; Ternes et al., 2003). Some authors suggest that this lack of reactivity with ozone could be due to the lack of aromatic moieties (Verlicchi et al., 2015). It is important to note that these compounds are found in high concentrations in HWW and are poorly degraded in the biological processes (Kovalova et al., 2013; Nielsen et al., 2013). Thus, new alternatives must be studied.

Working with the ozone doses above-mentioned, many of the antibiotics found in HWW like ciprofloxacin, ofloxacin, norfloxacin, sulfamethoxazole or erythromycin were easily eliminated with removal values higher than 93%, reaching concentrations below the predicted non-effect concentration (PNEC). Meanwhile, sulfadiazine and metronidazole removals were lower, achieving around 50% (Carbajo et al., 2015; Kovalova et al., 2013). In addition, the antineoplastics irinotecan, ifosfamide, and capecitabine found in raw hospital wastewater could easily be 100% removed with a short contact time (10 min) and an ozone concentration of 45 mg/Nm^3 (0.9 mg O_3/mg TOC). However, cyclophosphamide is slightly more reluctant, but total removal was achieved with an ozone concentration of 55 g/Nm^3 (Ferre-Aracil et al., 2016).

The β-blockers compounds metoprolol and propranolol in HWW were removed with efficiencies higher than 93% using an ozone dose of 0.64 mg O_3/mg DOC (Kovalova et al., 2013). Moreover, the β-blockers atenolol, metoprolol and propranolol were removed from a HWW pretreated in a septic tank followed by an anaerobic filter for 120 min with an ozone inlet of 380 mg/L·h (Wilde et al., 2014). Table SM-5 shows recent research results of O_3 treated-HWW at the pilot-plant scale.

2.3.2. Fenton and photo-Fenton systems

Among AOPs, oxidation systems based on traditional Fenton's reagents have been widely investigated to remove recalcitrant organic compounds in wastewater treatment. This process is based on the generation of hydroxyl and hydroperoxyl radicals from the decomposition of hydrogen peroxide in the presence of dissolved iron in acidic conditions. The main advantages of this process are: (i) high cost-efficiency, (ii) environmentally friendly reagents, and (iii) simplicity of the equipment (Pignatello et al., 2006). The use of solid Fe-based catalysts represents a more efficient approach, as it allows to operate under a wider pH range, and the loss of catalyst and subsequent formation of sludge at the end of the treatment are avoided to a great extent.

One of the most critical challenges in treating hospital wastewaters is the removal the wide range of PhCs in this complex matrix. Effective and relatively fast removal of the drugs is usually achieved, but it is accompanied by low mineralisation degrees and, thus, the formation of a wide range of oxidation by-products, that must be carefully assessed. The feasibility of Fenton oxidation for PhCs treatment has been addressed as this technology has been scarcely explored for HWW. However, Fenton oxidation has been extensively investigated in the literature for synthetic matrices, as summarised in Table SM-6. As seen in this Table, most of the works have been carried out under ambient conditions.

In some cases, the intermediate species formed might be even more toxic than the target pollutants, so the ecotoxicity of the oxidation effluents is usually determined. Nevertheless, as PhCs appear at relatively low concentrations, hydrogen peroxide doses are commonly in excess. Operating under those conditions allows obtaining short-chain organic acids at the end of the treatment, and thus, most works have reported insignificant ecotoxicity values as well as negligible estrogenic and antimicrobial activities for the Fenton-treated effluents (Luo et al., 2014; Su et al., 2016; Zeng et al., 2015).

Although it has been demonstrated that Fenton oxidation represents a successful approach for the removal of isolated pharmaceuticals in simple water matrices, its feasibility for treating hospital wastewater cannot be directly extrapolated as it is a more complex scenario. HWW contains many substances apart from the PhCs, consuming reagents, acting as radical scavengers, and deactivating the catalyst during the Fenton reaction (Pignatello et al., 2006).

The Fenton process can be applied as polishing post-treatment or even as a sole process if the effluent is released into the sewer system. Recently, Munoz et al. have explored the alternative of increasing the temperature for the on-site treatment of HWW before its discharge to the sewer system (Munoz et al., 2016). This intensified approach would allow taking advantage of the heat energy contained in the laundry stream, as laundering procedures usually imply the use of high temperatures. COD, TOC and the phenolic compounds concentration were measured in this work, and the ecotoxicity and Total Coliforms concentration were also followed. It was proved that increasing the temperature above the ambient (70–90 °C) constitutes an efficient alternative for actual HWW (COD_0 = 365 mg/L) treatment. It significantly improved the degradation efficiency using relatively low iron concentration (25 mg/L) and H_2O_2 dose (1 g/L). A 70% of COD reduction, 50% of TOC mineralisation, and the complete degradation of phenolic compounds were reached, obtaining non-toxic effluents. Furthermore, disinfection of the wastewater was also achieved, as confirmed by the complete removal of Total Coliforms. From an economic point of view, this alternative was more cost-efficient than that previously performed with the polishing treatment as it implied a significantly lower addition of H_2O_2 per gram of COD removed (in this case, 265 *vs.* 128 mg COD removed per g H_2O_2).

To our knowledge, the treatment of HWW by heterogeneous Fenton oxidation has been scarcely addressed. However, some approaches have been carried out by fortifying the hospital effluent with several pharmaceuticals to evaluate the water matrix composition's effect on removing micropollutants. Munoz et al. (2017) investigated the elimination of six pharmaceuticals (metronidazole, sulfamethoxazole, atenolol, trimethoprim, diltiazem, and ranitidine) in real hospital wastewater spiked with 25 mg/L of each compound by heterogeneous Fenton oxidation using a synthetic ferromagnetic catalyst ($Fe_3O_4/\gamma\text{-}Al_2O_3$). The oxidation rate of the pollutants was decreased by around 50%, but the drugs were completely removed after 90 min reaction time at the optimum operating conditions (75 °C, $pH_0 = 3$; $[H_2O_2]_0 = 730$ mg/L; $[Fe_3O_4/\gamma\text{-}Al_2O_3] = 2$ g/L). In other relevant work, a fortified HWW (sulfamethoxazole, 5 mg/L) was treated by a low-cost mineral magnetite under ambient temperature and circumneutral pH (5) using a stoichiometric dose of H_2O_2 (25 mg/L) (Munoz et al., 2018). In line with the previous results, the HWW matrix led to partial inhibition of the reaction, attributing it to hydroxyl radicals' scavenging and the high conductivity value of HWW (1185 mS/cm). On the other hand, the possible consumption of hydroxyl radicals by other organic species present in the raw HWW was also noticed. In a recent contribution, del Álamo et al. (2020) investigated the treatment of a HWW (Spain) fortified with carbamazepine (15 mg/L) in continuous operation using an innovative reticulated macroporous perovskite ($LaCu_{0.5}Mn_{0.5}O_3$). The catalytic system showed a high activity together with reasonable stability for 70 h under relatively soft conditions ($pH_0 = 5.5$, 70 ºC, $[H_2O_2]_0 = 700$ mg/L). In this work, the actual HWW unfortified with PhCs was also assessed, being the first work reporting a heterogeneous Fenton treatment for real HWW. It was concluded that, apart from eliminating carbamazepine, high removal of the PhCs (at μg/L concentration) was also achieved (90–95%). Remarkably, their residual concentration in the treated effluent was below the predicted non-effect concentration (PNEC) for aquatic organisms, concluding that the Fenton effluent does not pose any significant threat to the environment. It is important to note that in this study iohexol (contrast media) was removed in 97%. Up to now, there are not treatment achieving that high elimination for contrast media PhCs.

The Fenton process assisted by ultraviolet or visible light irradiation, *i.e.,* the photo-Fenton process, remarkably improves the degradation efficiency of the conventional treatments. Giannakis et al. (2017) investigated the application of the photo-Fenton process for the on-site treatment of hospital wastewater in developing countries, demonstrating the efficiency of this process for the removal of pharmaceuticals (iohexol, venlafaxine) as well as for the inactivation of pathogen microorganisms and viruses in relatively short reaction times ($\leq$1 h) operating under ambient conditions. To improve the overall efficiency of the photo-Fenton process, other strategies such as different reactor configurations, the use of solid catalysts, or even the combination with adsorption technology have been explored. Anjana Anand et al., 2016 studied the performance of fluidised bed solar photo-Fenton oxidation to treat hospital wastewater (India). A complete operating condition study evaluated the effect of pH_0, Fe^{2+} concentration, H_2O_2 dose, and silica carrier. Under the optimum conditions ($pH_0 = 3$; $[Fe^{2+}]_0 = 280$ mg/L; $[H_2O_2]_0 = 1.7$ g/L and [silica] = 40 g/L), COD removal was of 92% compared to the 67% percentage removal achieved in the conventional reactor configuration. The resulting effluent fulfilled the requirements for its direct discharge according to the regional regulations. García-Muñoz et al. (2017) investigated the treatment of HWW (Spain) by photo-assisted heterogeneous Fenton oxidation catalysed by a low-cost mineral ilmenite. Due to both, Fenton and photocatalytic reactions, the process was efficient (TOC conversion above 80% in 5 h reaction time), operating at 50 °C with a catalyst load of 1 g/L and the stoichiometric amount of H_2O_2 (780 mg/L).

2.3.3. *Photocatalytic systems*

Photocatalytic oxidation processes are of interest for wastewater treatment since they can operate at mild temperature and pressure conditions to remove recalcitrant organic compounds. However, up-to-date the number of photocatalytic studies focused on treating real hospital effluents is scarce. Lin et al. (2014), investigated the occurrence of ketamine and norketamine in 13 different HWW effluents. Ketamine was found at a concentration of 10 μg/L, with a ketamine/norketamine ratio of 0.3–4.6. Dark incubation experiments showed that ketamine was not degraded by microbial or hydrolysis. Thus, photolysis significantly reduced the concentration of ketamine and norketamine, but by-products, similar to human metabolites, are formed, such as norketamine and other by-products that showed high toxicity. The N-demethylation of ketamine formed these secondary products; so, an assessment of the ecotoxicity of ketamine and its photolysis by-products is critical to attaining a global understanding of its impact.

Van Doorslaer et al. (2015), investigated the photocatalytic degradation mediated of the fluoroquinolone antibiotic moxifloxacin (MOX) in a HWW using titanium dioxide as a catalyst. They found that photocatalytic degradation of MOX was about twice slower in the hospital effluent matrix than in demineralised water. To find out the influence of the matrix constituents on the degradation rate of MOX, the authors compared the results obtained adding suspended particulate matter and selected inorganic and organic matrix constituents. Both inorganics and organics had a detrimental influence on the photocatalytic degradation rate, with the highest effect observed for humic and fulvic acids (factor of 1.3–1.4 at 15 mg C/L TOC). This fact was explained by the limited accessibility to reactive species and the light-shielding in dissolved organics. The results highlighted the importance of using real water matrices for photocatalytic applications.

Sponza and Güney (2017), evaluated the removal of 2,3,4,5,6-pentabromotoluene (PBT), 2,3,4,5,6-pentabromoethyl benzene (PBEB), triclosan (TCS) and gemfibrozil (GFZ) present in a raw hospital wastewater using cerium (IV) and titanium (IV) oxide nanoparticles as catalyst. They investigated the influence of the catalyst dose, irradiation time, UV light power and pH on the photodegradation yields of the micropollutants. It was found that the photodegradation of PBT, PBEB, TCS and GFZ with nano-CeO_2 slightly improved compared to nano-TiO_2 under the optimum experimental conditions (0.50 g/L nano-CeO_2, 45 min irradiation time, 25 °C temperature, pH = 8.50, and 210 W UV light power). The reutilization of the nanoparticles was also evaluated. After six sequential runs using nano-TiO_2, the photodegradation yields slightly decreased with nano-TiO_2. Finally, the economic evaluation of the process indicated that the cost was much lower for the treatment using nano-CeO_2. Also, it was studied the ofloxacin removal from an HWW using nano-GO/M composite as a photocatalyst (Sponza and Alicanoglu, 2018). At a pH value of 7.8 in 60 min irradiation time using a UV power of 300 W and using 2 g/L of nano-GO/M, the authors obtained high removal efficiencies of COD (88%), TSS (82%), TKN (95%) and ofloxacin (97%). The quality of the treated HWW was first class according to the Turkish Water Pollution Control Regulations criteria, and the treated water could also be used for irrigation purposes.

Konstas et al. (2019), investigated the photocatalytic degradation of PhCs present in unspiked secondary wastewater effluent from the University Hospital of Ioannina city (Northwestern Greece). They compared the performance of TiO_2–P25, graphitic carbon nitride (g-C_3N_4, CN) and a heterojunction of perovskite strontium titanate and graphitic carbon nitride, $SrTiO_3$/g-C_3N_4 (20% g-C_3N_4, 20CNSTO), using simulated solar irradiation. The PhCs contained in the wastewater were discriminated based on their initial concentrations and removal efficiencies in two main groups. The first one consisted of the PhCs frequently present in HWW (venlafaxine, VNX; O-desmethyl venlafaxine, ODV; amisulpride, AMS; sulfamethoxazole, SMX; and carbamazepine, CBZ). In this group, the photocatalytic degradation kinetics were systematically assessed. The second group was formed by the compounds sporadically detected in the effluent, so it was not possible a systematic study of their photocatalytic degradation. In addition, the second group included two differentiated sub-classes: PhCs successfully removed within 45 min from the aqueous solution *(i.e.,* haloperidol, paroxetine, clozapine, amitriptyline, sertraline, diclofenac, fluoxetine, and mirtazapine); and PhCs, whose initial concentrations (traces in most cases) remained nearly stable during the photocatalytic process (*i.e.*, trimethoprim, citalopram, fluvoxamine, bupropion, fenofibrate and salicylic acid). The photocatalytic degradation patterns observed for VNX, ODV, AMS, SMX and CBZ depended on the samples collected (February, March and May) and the photocatalyst used. All compounds presented higher photocatalytic degradation rates for May samples, attaining after 120 min an average degradation value higher than 80% after 120 min reaction time. In February, AMS and CBZ presented after 120 min 42% and 57% removal values, respectively, after 120 min. In general, 20CNSTO material showed lower photocatalytic performance than TiO_2 and CN, with CN presenting similar or better degradation rates than TiO_2, depending on the pharmaceutical compound treated.

2.3.4. Electrochemical advanced oxidation processes

Electrochemical advanced oxidation processes (EAOP) have been successful for the degradation of several pharmaceutical pollutants. Hydroxyl radicals are formed by the anode over-potential (Kapałka et al., 2010). Only one study is focused on the treatment of HWW by EAOP using Nb/BDD anodes in terms of PhCs degradation (Ouarda et al., 2019). Results showed that PhCs abatement rates were greater than 50% after 120 min of electrolysis at the higher current density (35.4 mA/cm^2) as more hydroxyl radicals were produced (Ouarda et al., 2018). The PhCs can be divided into two groups: the first one comprised desvenlafaxine, sulfamethoxazole, 4-hydroxy diclofenac, diclofenac, and clarithromycin, with abatement rates higher than 80%. The second one contained six pollutants: venlafaxine, carbamazepine, caffeine, ibuprofen, dihydrocarbamazepine and 2-hydroxyibuprofen, whose abatement rates ranged between 50 and 80%.

Some approaches have been evaluated using fortified wastewater. In this regard, Esfandyari et al. (2019) used the electrochemical process to remove cefazolin and COD from spiked hospital wastewater. The tests were performed at three different voltages (15, 30, 50 V) and periods (10, 30, 50 min). Results showed that the higher efficiency of PhCs removal (more than 92%) was achieved in 50 min of reaction time.

In conclusion, AOPs are promising alternatives to PhCs removal from hospital wastewater, but more studies about the costs associated with the pilot plant scale are required.

2.4. Combined treatments

Conventional processes are often insufficient to ensure high removals for most pharmaceuticals in HWW. Moreover, AOPs are usually very expensive due to the high organic load of raw hospital wastewater. Consequently, different alternative technologies, such as hybrid processes that combine two or more treatments, have also been studied to remove such micropollutants.

2.4.1. Physical and chemical combined treatments

Generally, advanced oxidation processes can lead to the complete mineralisation of some organic compounds to CO_2, H_2O, and inorganic ions. However, these processes usually involve a significant excess in chemicals and, consequently, high costs. In addition, those treatments could lead to the release of toxic by-products. Thus, combined processes have been suggested to overcome the disadvantages of individual processes. Several studies proved that combined schemes are feasible and practical tools for enhancing treatment efficiency.

Treating raw hospital wastewater by ozonation is technically and economically viable for the chemical abatement of antineoplastic compounds and other dissolved organics in HWW (Ferre-Aracil et al., 2016). However, some authors have demonstrated that the pre-treatment of hospital wastewater improved the efficiency obtained in the subsequent treatments, e.g., O_3, O_3/H_2O_2, O_3/US or UVC/UVV/O_3 (Arslan et al., 2014; de Oliveira Schwaickhardt et al., 2017; Hansen et al., 2016; Souza et al., 2018). These treatment methods alone, or hybrid treatments, show a stronger oxidative capacity in the degradation of organic compounds that are refractory to biological treatments, improving the degradation efficiency and reducing the treatment costs.

In this sense, Wilde et al., 2014b have studied the degradation of β-blockers from HWW with O_3 and Fe^{2+}/O_3 in a semi-batch bench-scale column reactor. The organic matter removal reached 31% and 49% values for O_3 and Fe^{2+}/O_3, respectively (Figure SM-2a). Figure SM-2a, shows the influent and effluent of the O_3/UV treatment. This process was efficient for the complete removal of the β-blockers detected (Souza et al., 2018).

Moreover, applying abiotic treatment and UV/O_3, UV/H_2O_2, O_3/H_2O_2 and UV/O_3/H_2O_2 processes for a hospital effluent containing ifosfamide and cyclophosphamide drugs resulted in an almost total removal of these cytostatic compounds (>99% for both cases). After applying chemical treatments, different results were obtained for removing both PhCs (Česen et al., 2015). The study by Somensi et al. (2015) demonstrated that the association of ozonolysis with sonolysis is more efficient in terms of the disinfection and denaturation of the genetic material present in the hospital wastewater than the ozonolysis treatment alone.

The application of ozone-based advanced oxidation processes (AOP), like O_3/H_2O_2, has been studied to increase the removal of the PhCs. Nevertheless, the PhCs removal was not significantly improved (El Morabet et al., 2020; Ferre-Aracil et al., 2016). Meanwhile, AOPs are useful for water with low DOC contents; in contrast, in a water matrix with DOC higher than 3 mg/L, the increase of hydroxyl radical is negligible due to the relatively high DOC content (Acero and Von Gunten, 2001; Kovalova et al., 2013; Van Geluwe et al., 2011). AOP based on Fe^{2+}/O_3 or UV/O_3 improved the mineralisation of the COD up to values around 64% (Souza et al., 2018; Wilde et al., 2014), and many PhCs were completely degraded at high pH, but ozonation accomplished at a high pH could present higher acute toxicity in the final effluent.

More recently, Della-Flora et al. (2020) studied the combination of solar photo-Fenton reaction and adsorption (using an activated carbon obtained from avocado seeds) to treat HWW fortified with the anticancer drug flutamide spiked in the hospital effluent ($C_0 = 5$ mg/L). The oxidation treatment allowed 58% degradation of the pharmaceutical using three additions of 5 mg/L Fe^{2+} and an initial H_2O_2 concentration of 150 mg/L in 2 h of reaction time. Moreover, up to thirteen by-products were also followed along the reaction.

Another interesting approach to enhance the efficiency of the conventional Fenton process is its combination with electrochemistry (electro-Fenton). However, this alternative has been scarcely investigated for treating HWW. Ahmadzadeh and Dolatabadi (2018) explored the efficiency of this system for treating HWW spiked with acetaminophen (5.8 mg/L). Remarkably, a high removal of the drug (ca. 99%) was achieved in a short reaction time (10 min) operating under optimized conditions ($[H_2O_2]_0 = 0.04$ mg/L; 3-cm interelectrode distance; [KCl electrolyte] = 100 mg/L; 8 mA/cm^2; $pH_0 = 2.75$). In a more recent contribution, Dolatabadi et al. (2020) investigated the elimination of the nonsteroidal anti-inflammatory drug mefenamic acid spiked in a HWW (7 mg/L) using the electro-Fenton process. The removal efficiency was above 95% after 12 min reaction time using an H_2O_2 dose of 233 mg/L and a current density of 6.6 mA/cm^2.

Mahdavi et al. (2020), have evaluated the combination of coagulation, flocculation, sedimentation, and ultrafiltration processes for removing total dissolved solids, COD, and Total Coliforms present in hemodialysis wastewater. With a combination of sedimentation and ultrafiltration processes, the removal efficiency of the studied parameters was enhanced to >99%.

Based on these results, further research is required in this field to assess the efficiency of the intensified Fenton technologies for the treatment of HWW, not only focusing on spiked-hospital wastewaters but evaluating the removal of both, the pollutants and the pathogens contained in the real effluents.

2.4.2. Biological and physico-chemical hybrid treatments

During the last years, hybrid technologies have been extensively studied and improved for their application in HWW treatment, preventing the release of PhCs into the aquatic environment. Most hybrid systems consist of biological-based treatments followed by physical or chemical processes. Ozonation is the most widely used process to combine with biological treatments, such as conventional activated sludge treatment or membrane bioreactors.

Lin et al. studied the combination of ozonation and hydrogen peroxide with an MBR system. Still, this work was mainly focused on the polishing treatment, without any information on the overall degradation process. For the ozonation treatments, two-thirds of the micropollutants (38 out of 56) present in the hospital wastewater effluent were eliminated at low specific ozone doses. Another combination using ozonation as a polishing step was evaluated by Wigh et al. (2016). In this study, a mixture of urban and hospital effluents was treated using a biological treatment (CAS) followed by ozonation. However, in this work, the authors focused on investigating some fitness traits and DNA integrity in several aquatic organisms that are relevant for assessing ecosystem health through a multi-parametric approach.

Some papers are based on a biological and membrane treatment studying PhCs removal (Domenjoud et al., 2017; Mousaab et al., 2015). Mousaab et al., (2015) evaluated pharmaceuticals removal by biological treatment coupled with membrane filtration. They observed that the global quality of the treatment was slightly increased due to the increase in biomass concentration, solid residence time, and sorption capacity. The main characteristics of these systems and the effluents are shown in Table SM-7.

Other investigations deal with the PhCs removal from an HWW coupling biodegradation and ozone oxidation (Domenjoud et al., 2017; Vo et al., 2019a). An innovative approach was proposed based on the high selectivity of molecular ozone reactions involving fast-reacting molecules.

Domenjoud et al. (2017) studied the integration of ozone oxidation within a CAS process by applying ozone to the wastewater entering the biological treatment and the mixed liquor recycle loop. Performance assessment was carried out at a pilot scale and covered the full treatment line, considering chemical and biological oxidations of PhCs. The capacity of the pilot line was 60 L/h with 23 h of HRT in the biological reactor and 250% of the recirculation rate. The CAS treatment was operated to achieve complete nitrification at a minimal sludge residence time (SRT), ranging from 4 to 12 days according to the mixed liquor temperature, that varied from 8 to 20 °C. The ozone injection in the CAS influent or the recycled mixed liquor led to significant improvements in the removal of PhCs from the water stream. The average overall reduction achieved by the nitrifying CAS treatment was 49% for the ten substances quantified in the influent. This removal efficiency increased to 71 and 80% when the biological treatment was combined with the ozone injection in the recycled mixed liquor at a transferred ozone dose of 1.1 mg O_3/gTSS or in the influent at a higher transferred ozone dose of 3 mg O_3/L (Table SM-8).

Taking advantage of the MBR systems and ozonation process, Vo et al., 2019a studied the performance of a sponge-MBR coupled with an ozonation process for antibiotics removal from hospital wastewater. Among seven investigated antibiotics, an effective reduction (more than 90%) of norfloxacin, erythromycin, tetracycline and trimethoprim were achieved since ciprofloxacin and ofloxacin were highly removed (over 80%). However, the sulfamethoxazole removal efficiency was only 66%. The authors concluded that the combination of sponge-MBR and ozonation treatment could be a prospective technology for removing antibiotics compared to other biological wastewater treatment processes, as the presence of sponges has significantly improved the removal efficiency of some pharmaceuticals.

Rodrigues-Silva et al. (2019) studied an ozonation process to degrade fluoroquinolone compounds in pretreated samples using an up-flow anaerobic sludge blanket (UASB). Ciprofloxacin was the only fluoroquinolone identified in the pretreated biological samples. After 5 min of ozonation, no fluoroquinolone concentration was detected in the effluent sample, concluding that ozone-based processes are good prospects for degrading fluoroquinolones.

Tang et al. (2019) studied a pilot-scale ozonation system post-treatment to reduce the PhCs and toxicity in the effluent of a pilot-scale MBBR treating hospital wastewater. The HRT of the reactor was 13.1 min, using a flow rate of 1 L/min and a volume of 13.1 L. The pre-treated effluent was polished further by suspended biofilm carriers to remove biodegradable organic matter and toxic by-products generated during the ozonation process. Moreover, pharmaceutical concentrations decreased with the increase of ozone dosage, achieving 90% removal of PhCs and DOC in the treated wastewater.

Finally, the application of a biological treatment followed by a sonochemical process was also evaluated to treat an HWW in Colombia (Serna-Galvis et al., 2019). The biological system removed the biodegradable organic matter from the HWW, but most pharmaceuticals were recalcitrant towards the bio-treatment. So, both systems reinforce each other. The sono-photo-Fenton system eliminated several micropollutants from the HWW, such as diclofenac, carbamazepine, venlafaxine, sulfamethoxazole, trimethoprim and irbesartan. This process combination also decreased the concentration of acetaminophen and erythromycin below their PNEC values, achieving removal values of 98 and 44%, respectively.

Khan et al. (2020b) studied the coupling of two treatment technologies (MBR and CW) with an advanced oxidation process in semi-batch mode (O_3 and O_3/H_2O_2). This coupling enhances the reduction of pharmaceuticals to overcome the shortcomings of conventional treatments, as diclofenac and furosemide were removed entirely with both processes. The lowest removal values were detected for ofloxacin and ibuprofen, although these values significantly increased with higher O_3 dosages without any influence of the hydrogen peroxide concentration. The results confirmed that the MBR system coupled with the ozone process proved to be an optimal technology among the four combined technologies for the pretreatment of HWW.

Other studies are focused on the disinfection of HWW after biologically-treated wastewater. In this way, Moussavi et al. (2019) found that the vacuum UV (VUV) treatment was much more efficient than the UVC one in the inactivation of *E. coli*. A 6.4 and 3.7 log *E. coli* inactivation (from an initial concentration of $1.09{\cdot}10^{10}$ CFU/mL) was achieved in the VUV and UVC photoreactors, respectively, operated under similar conditions at neutral solution pH. They also studied the process in a continuous-flow reactor with the addition of H_2O_2 to the process. This combined system (VUV/H_2O_2) attained the highest performance and complete bacterial inactivation and detergent removal along with ca. 94% of TOC reduction in 10 min. Most trace chemicals were degraded, and the biotoxicity decreased markedly after treatment in the VUV/H_2O_2 process.

To conclude, although MBRs generally led to high PhCs removal, most of the combination processes led to a higher trimethoprim degradation (93–100%) (a critical antibiotic due to its high toxicity, Table SM-8). However, higher PhCs degradations for those PhCs present at high concentrations (analgesics, such as diclofenac, ibuprofen, and ketoprofen) were obtained for the system combined with ozone (Khan et al., 2020b). A new approach combining the biological treatment with a sono-photo-Fenton process led to the total removal of carbamazepine, diclofenac, and sulfamethoxazole, characterised for the low degradation values in the biological processes. Moreover, biological wastewater treatment in combination with membrane achieved higher degradation values of iohexol, one of the main challenging tasks, considering the recalcitrant character of the contrast media. Thus, these combined options are motivating alternatives for achieving high PhCs degradation with a lower cost since the oxidant doses substantially decrease. However, some other options including Fenton-like processes should be considered in future works.

3. New goals in the hospital wastewater characterization and treatment: antibiotic bacterial resistance (ARBS), antibiotic resistant genes (ARGS) and sars-Cov-2

As it has been previously mentioned, hospital wastewater is of interest as it contains high levels of antibiotics, but also antibiotic resistance bacteria (ARBs) and antibiotic resistance genes (ARGs) can occur (Adekanmbi et al., 2019; Barancheshme and Munir, 2018; Chandran et al., 2014; Hocquet et al., 2016). Furthermore, the outbreak of the

Table 3

Characterisation parameters in influent and effluent hospital wastewaters focused on detecting ARBs and ARGs.

HWTPs	Treatment	Influent	Effluent	Reference
Five HWWTPs in Xinjiang (China)	Membrane bioreactor, anaerobic/oxic, or oxidation ditch.	number of copies of genes/16 S rRNA genes copy number: *sul1*: 4.23 ± 3.45 × 10^{-1} *sul2*: 2.06 ± 1.87 × 10^{-1} *sul3*: 7.56 ± 2.35 × 10^{-1} *tetQ*: 5.10 ± 3.25 × 10^{-1} *intI*: 1.91 ± 1.56 × 10^{-2} *intI2*: 5.50 ± 6.36 × 10^{-4}	No removal	Li et al. (2016)
Three HWWTPs in Iran	Chlorination (H1) Chlorination + absorption well (H2) Activated sludge + chlorination + UV + absorption well (H3)	Resistant bacteria to (CFU/100 mL): GM: 1.24 × 10^{7} CHL: 3.29 × 10^{7} CAZ: 5.54 × 10^{7}	Resistant bacteria to (CFU/100 mL): GM: Not detectable (Removal efficiency 100%) CHL: 5 × 10^{5}, >98% CAZ: 1 × 10^{6}, >98%	Aali et al. (2014)
Two HWWTPs of Riyadh (Saudi Arabia)	Conventional activated sludge tank + secondary clarifier + sand filtration + chlorination (H1) Activated sludge tank in anoxic/oxic mode + secondary clarifier + sand filtration + chlorination (H2) Chlorine dosage: ca. 10 mg/L	*Pseudomonas* sp. (ARB): 3.75 × 10^{7} CFU/L (H1) 3.05 × 10^{5} CFU/L (H2) ARGs (copies/mL) *tetO*: 9.43 ± 5.77 × 10^{2} (H1) & 4.08 ± 3.13 × 10^{2} (H2) *tetZ;* not reported *sul1*:1.59 ± 1.41 × 10^{5} (H1) *sul2*: 3.69 ± 2.24 × 10^{3} (H1) *intl1*: 3.57 × 10^{5} (H1 & H2) *intl2*: 10^{3} (H1 & H2)	*Pseudomonas* sp. (ARB): 1.73 × 10^{6} CFU/L (H1), >95% Not detected (H2) (Removal efficiency >99.999%) ARGs (copies/mL): *tetO*: Not detected (H1 & H2) (Removal efficiency >99%) *tetZ*: 1.84 and 0.475 log removal (>98% and <90%) (H1 & H2) *sul1*:1.82 ± 1.18 × 10^{5} (H1); 0.785 log removal (<90%) (H2) *sul2*: 9.29 × 10^{3} ± 1.59 × 10^{4} (H1); 0.506 log removal (<90%) (H2) *intl1:* 1.40 × 10^{5} (<90%) (H1); 3.43 × 10^{4} (90%) (H2) *intl2*: 2.60 × 10^{1} (97%) (H1); 1.43 × 10^{1} (>98%) (H2)	Timraz et al. (2017)
Veterinary hospital effluent in University Autónoma of Barcelona (Spain)	Fungal treatment of *Trametes versicolor* in bioreactors		Removal rate (%): 100% for *bla*$_{TEM}$, *ermB* and *tetW* genes 56% for *sulI* −843% for *bla*$_{SHV}$ −163% for *qnrS*	Lucas et al. (2016)
Inoculated natural spring water and wastewater effluent (Zagreb)	Natural zeolite clinoptilolite enriched with: AgNZ: 35.5 mg Ag^{+}/g; CuNZ: 16.2 mg Cu^{2+}/g; ZnNZ: 18.7 mg Zn^{2+}/g	Hospital pathogenic isolated bacterium *Acinetobacter baumannii* (ARB) from WWTP in natural spring water: (i) 1 × 10^{3} CFU/mL (ii) 1 × 10^{5} CFU/mL In real WWTP effluent: Not reported	*Acinetobacter baumannii* (ARB) AgZN: (i) 99.5%; (ii) > 99.999% CuZN: (i&ii): <90% In real WWTP effluent: AgZN: Total removal < Bacterial detection limit	Ivankovic et al. (2019)
Hospital wastewater in Delft	Pharmafilter: sequential advanced processes: MBR + O_3+GAC + UV	Gene copies/mL *bla*$_{KPC}$: 10^{3}-10^{4} *bla*$_{SHV}$: 10^{5} *bla*$_{OXA}$: 10^{5}-10^{6} *aph(III)a*: 10^{6} *ermB*: 10^{6}-10^{7} *ermF*: 10^{5}-10^{6} *int1:* 10^{7}-10^{8} *qnrS*:10^{3} *sul1*: 10^{7}-10^{8} *tetB*: 10^{7}-10^{8} *tetM*: 10^{5} *vanA*: 10^{3}-10^{5}	Log_{10} fold reduction: *bla*$_{KPC}$: > 1.7 (<LOD) *bla*$_{SHV}$: > 3.1 (<LOD) *bla*$_{OXA}$: > 3.6 (<LOD) *aph(III)a*: > 3.8 (<LOD) *ermB*: > 4.4 (<LOD) *ermF*: 4.0–5.0 *int1:* 4.0–5.0 *qnrS*: > 0.9 (<LOD) *sul1*: 1.7 *tetB*: > 3.1 (<LOD) *tetM*: > 3.1 (<LOD) *vanA*: > 2.4 (<LOD)	Paulus et al. (2019)
Hospital wastewaters in Slovakia and Czechia	Fenton reaction Fenton-like reaction Ferrate (VI) BDDE	Log10 CFU/mL Coliform bacteria: 5.0 *Escherichia coli:* 1.6 *Staphylococci:* 2.5 *Staphylococcus aureus:* 2.2	Total removal (<LOQ)	Mackuľak et al. (2019)

COVID-19 pandemic has globally and urgently demanded the control and monitoring of viruses and other pathogens in wastewater and their efficient removal.

The on-site treatment of HWW before discharging to municipal WWTPs is highly required. Although, it is crucial to consider that even in existing HWWTPs, ARBs and ARGs are still released into streams and rivers (Devarajan et al., 2016; Magalhães et al., 2016). Hence, antibiotic resistance among pathogens increases the demand for novel treatment strategies. In addition, a positive correlation between ARGs and metals was determined by Devarajan et al. (2016). Metals concentration values are generally found in high concentrations in HWW (Table 1), being a critical point to be highlighted (Varela et al., 2014). Table 3 shows the studies conducted to determine ARBs and ARGs from HWW and the correspondence degradation values obtained in several proposed treatments.

Perry et al. (2019) used metagenomics to study whether the abundance of resistance genes in HWW reflects clinical activity within a hospital located in Scotland. 1047 bacterial genes and 174 different AMR genes were detected across all samples. They showed that antimicrobial usage is a significant driver of AMR gene outflow from hospitals into the sewage environment. Moreover, a positive relationship between the length of stay and AMR gene abundance can be established, being a risk factor for carriage and infection with resistant microorganisms.

Narciso-Da-Rocha et al. (2014) evaluated four indicator genes in a hospital effluent (1000 m^3/day) and in the raw and treated wastewaters of municipal WWTP receiving the hospital discharge located in the northern region of Portugal. Wastewater treatment mainly consisted of a preliminary system, a primary settling tank as physico-chemical treatment, and a biological reactor based on an anoxic (denitrification), an aerated (nitrification) and an endogenous (phosphorous removal) zone. The tertiary treatment was composed of a sand-bed filtration system. The indicator genes were the class 1 integrase gene *intI1*, responsible for horizontal gene transfer processes; bla_{TEM}, one of the most extensive antibiotic resistance genes in the environment, conferring resistance to β-lactam antibiotics like penicillins and extended-spectrum cephalosporins; *vanA*, an antibiotic resistance gene uncommon in the environment but often found in clinical isolates due to the use of vancomycin; and *marA*, involved in several resistance phenotypes associated to antibiotics, household disinfectants, and survival under stress conditions. The *intI1* gene prevailed in all effluents, and its relative abundance (normalised by 16 S rRNA copy number) was hardly affected. This fact suggests that *intI1* may be stable in wastewater. In this case, wastewater treatment failed to remove the gene *vanA* and *marA* either. On the contrary, the treatment led to a significant reduction of bla_{TEM} up to 165 copies/16 S rRNA. However, this concentration may still be a high-dose level for a resistance gene to be spread in the aquatic environment. Different results were observed by Rodriguez-Mozaz et al. (2015) that examined the removal efficacy against ARGs by using an activated sludge treatment in WWTP in Gerona (Spain) that receives the hospital effluent without any previous treatment (1000–1500 m^3/day^{-1}). Considering relative concentration values, only *ermB* (resistance to macrolides) and *tetW* genes (resistance to tetracyclines) decreased downstream because of the wastewater treatment, whereas bla_{TEM} (resistance to β-lactams), *qnrS* (resistant to fluoroquinolones), and *sulI* (resistance to sulfonamides) genes showed significantly higher values in water samples collected downstream of the WWTP discharge than in upstream waters. Therefore, it is thought that the spread of some ARGs among bacterial cells may occur during wastewater treatment. In addition, high fluoroquinolone concentrations detected in wastewater may cause the promotion of these antibiotic-resistant bacteria and the *qnrS* gene.

Although deeper insight has been recently accomplished into the fate of ARGs and ARBs in HWW once discharged into WWTPs, only a few research groups have addressed the existing knowledge gap regarding on-site hospital WWTPs in removing ARBs, ARGs and integrase genes. Thus, Li et al. (2016) have evaluated the efficiency against ARGs of five HWWTPs located in Xinjiang (China). In this case, integron genes such as *intl1* and *intl2* were also present in wastewater influents. The primary wastewater treatment responsible of ARGs elimination for each hospital corresponded to a membrane bioreactor, anaerobic oxic, and oxidation ditch. However, this treatment was not enough to effectively remove the ARGs released into the aqueous environment. The highest relative ARG concentrations corresponded to *sul1*, *sul2*, *tetQ*, and *qnrS*. It is worth noting that the high concentration of sulphonamide resistance genes (*sul1*, *sul2*) suggested that their spread was likely to be linked to mobile genetic elements (*intl1* and *intl2).*

Aali et al. (2014) reported the study of three different HWWTPs based on a disinfection process (chlorination, H1; chlorination/adsorption, H2; activated sludge/chlorination + UV/adsorption, H3). So, the effect of HWWTPs on the removal of antibiotic-resistant bacteria to gentamicin (GM), chloramphenicol (CHL), and ceftazidime (CAZ) was determined. The mean concentration of ARBs in the raw inflow of the three HWWTPs was ca. 10^7 CFU/100 mL. Among the ARBs, ceftazidime resistant bacteria showed the highest concentration in HWWTPs. In addition, it could be concluded that H3 was the most efficient treatment plant for removing ARBs. Thus, the concentration of gentamicin resistant bacteria was significantly reduced in this HWWTP. However, chloramphenicol and ceftazidime ARBs were decreased by almost ca. 2 log units. In contrast, Li et al. (2015) observed low concentration values of tetracycline and sulfamethoxazole-resistant bacteria in effluents from 7 hospitals in Linan (China). This behavior could be a consequence of the use of effective disinfectants.

Timraz et al. (2017) evaluated the efficiency of on-site HWWTPs operating on-site in two hospitals (H1 and H2) in Riyadh (Saudi Arabia) to eliminate antibiotic-resistant bacteria (ARBs) predominantly identified to be *Pseudomonas* spp.; ARGs as *tetO*, *tetZ* (resistance to tetracyclines), *sul1* and *sul2* (resistance to sulfonamides); and integrase genes (mobile genetic elements responsible for HGT) as *intl1* and *intl2*. Although both HWWTPs use the conventional biological activated sludge process and sand filtration with chlorination as tertiary treatment, different removal efficiencies were observed. Likely, longer HRT and SRT in H2 may result in higher removal efficiencies, enhancing sedimentation and a longer contact time for natural attenuation within the activated sludge. The average concentration of ARBs recovered from influent samples of the first HWWTP was 3.75×10^7 CFU/L. After the wastewater treatment process, approximately a 1.34-log reduction was achieved. A lower concentration of ARBs was observed in the second HWWTP, with an average value of 3.05×10^5 CFU/L. Furthermore, the inactivation of ARBs was complete. Considering ARGs, total removal of *tetO* was detected at the effluent samples of both HWWTPs, whereas *tetZ* genes were only reduced by 1.84-log and 0.475-log by H1 and H2, respectively. Negligible removal of *sul1* and *sul2* genes was achieved by H1, although H2 led to ca. 0.785-log and 0.506-log removal for *sul1* and sul2, respectively. A 2-log reduction was reported for *intl2* by both HWWTPs but not for the *intl1* gene. Hence, the persistence of *intl1* genes leads to increasing concerns about the potential horizontal dissemination of ARGs in the environment. Li et al. revealed that sulfonamide resistance could be associated with class 1 integron genes in bacterial isolates (Li et al., 2015, 2016).

A fungal treatment with *Trametes versicolor* in bioreactors was performed by Lucas et al. (2016) to determine its effect on removing some antibiotic resistance genes (ARGs). Wastewater samples were collected from a veterinary HWW located at University Autónoma de Barcelona (Spain). The fungal treatment was efficient in removing ARGs, such as *ermB* (resistance to macrolides), *tetW* (resistance to tetracyclines), bla_{TEM} (resistance to β-lactams), and *sulI* (resistance to sulfonamides). The complete removal was achieved for bla_{TEM}, *ermB* and *tetW* genes, and a removal rate of 56% was obtained for *sulI*. It is important to note that removal rates of *sulI* are generally low in conventional WWTP isolates (Li et al., 2015, 2016; Timraz et al., 2017). In contrast, negative removal rate values of −843% and −163% for bla_{SHV} and *qnrS* (reduced susceptibility to fluoroquinolones), respectively, were found. Thus, fungal treatment is a promising technology, but variables such as the operational parameters of the bioreactors, the wastewater bacterial communities and their interaction with fungi should also be optimized.

An electro-peroxone reactor was reported by Zheng et al. (2018) to be used as a pretreatment for subsequent Sequencing Batch Reactor (SBR) treatment of a simulated HWW. It was based on a mixture of municipal wastewater with a high concentration of representative antibiotics such as ciprofloxacin 200 mg/L, TOC 103.9 mg/L, COD 510 mg/L and total nitrogen (TN) 20.96 mg/L. The O_2 and O_3 mixture was supplied into the reactor with a constant flow rate of 1 L/min for 30 and 75 min. Thus, the removal rates of genes resistant to quinolones (*aac (6′)-Ib-cr*, *qepA*, *qnrA*, *qnrB*, *qnrD*, *qnrS*) were quantified. The optimal removal for *aac(6′)-Ib-cr* genes after SBR with 30 and 75 min of E-peroxone pretreatment led to 2.1 fold and 3.7 fold reduction, respectively, corresponding to a removal rate of 73%. Similar removal rates for *qepA* were reached. Four *qnr* genes were reduced after SBR with 75 min E-peroxone pretreatment. Although this technology seems effective, the effects of ciprofloxacin degradation products or intermediates on ARGs selection and bacteria in SBR should be fully understood.

Ivankovic et al. (2019) collected environmental isolates of hospital pathogenic bacterium *Acinetobacter baumannii* (carbapenem-resistant bacteria) from the influent and effluent of a WWTP in the city of Zagreb to test the antibacterial activity of a natural zeolite (clinoptilolite, NZ) (70 wt%) enriched with silver (AgNZ), zinc (ZnNZ), and copper (CuNZ) to improve the clinoptilolite cation exchange capacity. NZ or CuNZ, ZnNZ and AgNZ were tested in batch (stationary) conditions, ranging from 1024 to 0.062 mg/L. These materials were added into inoculated bacterial suspensions of natural spring water at concentrations of $\sim 10^5$ CFU/mL; and kept in contact for 1, 5, 7 and 24 h. The antibacterial activity was also tested in a flow system for CuNZ and AgNZ, as ZnNZ achieved no antimicrobial performance in the former configuration. Bacterial suspension ranging between 10^3-10^5 CFU/mL was pumped through a glass column filled with 5 g of NZ, CuNZ or AgNZ at a flow rate of 30 mL/h. Samples were collected every 24 h for 4 consecutive days and up to 14 days. The AgNZ showed excellent antibacterial activity with a total reduction of viable bacterial concentration within 4 days, observing that adsorption phenomena were involved in the process only during the first 24 h. Antibacterial activity was maintained throughout the following 10 days. Thus, 5 g of AgNZ effectively reduced total bacterial concentration in 10.1 L of suspension. Moreover, after 14 days, no viable bacterial cells were adsorbed on AgNZ (detection limit <10 CFU g^{-1}). NZ and AgNZ materials were tested with real effluents from a WWTP in Zagreb. The flow system showed the ability to completely inactivate *A. baumannii* in 2.9 L of effluent wastewater after 4 days of treatment. In this case, 80% of adsorption on NZ was observed.

Paulus et al. (2019) reported the on-site treatment of an HWW in Delft using sequentially advanced technologies in an installation called Pharmafilter, which includes a MBR, an ozonation granulated activated carbon system, and finally UV radiation process. The authors pointed out the reduction of gene presence in the receiving UWW, emphasising the efficiency of advanced processes compared to activated sludge technology, traditionally used in urban WWTPs. MBR treatment was the most efficient for ARG reduction. bla_{KPC} and *vanA* were identified as hospital-related genes, and reduced below the detection limit (LOD = 10^{-1} genes copies/mL) during the on-site treatment, together with other genes also conferring resistance to β-Lactam antibiotics (bla_{SHV}, bla_{OXA}), to aminoglycosides (*aph(III)a*), to macrolides (*ermB*), to quinolones (*qnrS*), and tetracyclines (*tetB*, *tetM*). The obtained $\log_{10}$-fold gen reduction values were of >1.7; >2.4; >3.1; > 3.6; >3.8; >4.4; >3.1; >3.1, respectively. Mackuľak et al. (2019) studied the efficiency of several AOPs to inactivate ARB detected in five HWW located in Slovakia and Czechia. Fenton, Fenton-like and Boron-Doped Diamond (BDD) electrooxidation processes were compared. It was concluded that all applied methods decreased the amount of susceptible and resistant bacteria under the established Limit of Quantification.

As mentioned above, the discharge of HWWs exposes the population to a danger of infection. Then, it is important to reduce risks to public health and the environment, notably, during the COVID-19 pandemic. So far, most wastewater-based SARS-CoV-2 RNA surveillance has focused on monitoring the population disease by sampling WWTP (D'Aoust et al., 2021). More recent approaches opt for exploring single-facility assessments (Gibas et al., 2021). Also, it has been recently demonstrated by Acosta et al. (2021) that both, the frequency of positive trials and the abundance of SARS-CoV-2 RNA in HWW systems, can be correlated with an increase of hospitalised cases, alike to WWTP levels associate with the COVID-19 diagnosed cases in general population (D'Aoust et al., 2021).

Some publications (Acosta et al., 2021) suggest that wastewater-based monitoring of SARS-CoV-2 may be more sensitive for identifying severe cases in hospitals, providing more detailed information. That means that wastewater sampling can potentially identify areas where the COVID incidences are increasing but undetected by conventional means such as individual tests. However, they are still problems related to the complexity of the sample collection that needs to be solved, and also, the difficulties involved with the analysis. In this sense, it should be considered that samples need to be concentrated as they are diluted in significant volumes of wastewater. Thus, ways to obtain suitable protocols, such as the improvement of the sampling collection or the sensitivity of wastewater SARS-CoV-2 detection, are currently being explored.

Treatment methods are needed for the investigation to ensure virus-free treated water. In general, the removal of viruses in the biological treatment is higher than in the primary processes, wherein in the latter case, the treatment is only sedimentation compared to adsorption on the sludge for the biological wastewater treatment. Virus inactivation during the tertiary treatment can avoid infections, although each process has its mode of action. Since faecal shedding of SARS-CoV-2 RNA is widely reported, HWW containing viral particles might contaminate drainage systems. Although more efficient treatment systems must be developed, existing wastewater treatment techniques can decrease the virus load. Thus, treating hospital wastewater at the source of production could be an option to prevent viral transmission. So far, there are a few studies on the inactivation of SARS-Cov-2. These studies showed that chlorine disinfection and ultraviolet irradiation were the most efficient treatments. However, the effectiveness of ozone disinfection has not proven yet good results (Wang et al., 2020). Thus, more studies regarding ARBs, ARGs and SARS-CoV-2 are still required.

4. Future perspective and remarks

Hospitals are an essential source contributing to releasing PhCs, ARGs/ARBs, and viruses into surface waters. Moreover, treating HWW at the production source before entering drainage systems could prevent viral transmission, reduce ARGs/ARBs concentration, and remove PhCs. In general, there is no single practice for managing HWWs that could solve the problem. There is a great need for research in HWW treatments, as not all of them are efficient in removing every PhCs. Indeed, in many cases, several strategies are used in combination. MBRs have provided interesting results at the pilot plant scale with significant removals between 80 and 95% for analgesics and anti-inflammatories, cardiovascular PhCs and some antibiotics. However, psychiatric drugs, contrast agents, and some recalcitrant antibiotics are still present in the treated effluent. The latter are very important due to their effect on ARBs and ARGs. Advanced oxidation processes are very effective for removing PhCs from different families, including the contrast media, recalcitrant to biological and O_3 treatments. However, the cost of reagents and the energy consumed could be prohibitive due to the high flow rates of HWW. Thus, it can be concluded that combined technologies are highlighted to be the best option for PhCs, ARBs, ARGs, and indeed viruses such as SARS-CoV-2 removal in hospital effluents. The coupling strategy could improve the quality of the treated wastewater and reduce the toxicity of the effluent before it is discharged into the environment. MBR coupled with ozonation treatment appears to be an optimal technology for the pre-treatment of hospital effluents at full scale. However, other options such as fungal bio-oxidation combined with Fenton-like treatments must be studied at the pilot plant scale to verify the excellent results obtained at the bench scale.

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

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvman.2022.115769.

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