CHAPTER

Anticancer drugs in the environment: environmental levels and technological challenges

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3.1 Introduction

Cytostatic drugs are pharmaceutical compounds designed and manufactured to treat several diseases, particularly cancer (Yadav, Rene, Mandal, & Dubey, 2021). These drugs inhibit the proliferation of cells that have a high dividing rate or growth, two of the characteristics of cancer cells. However, these characteristics are very general, being shared by many cell types, which means that cytostatic drugs can damage healthy cells due to their low selectivity, by blocking, for example, DNA replication through the inhibition of topoisomerase activity (Rout, Zhang, Bhunia, & Surampalli, 2021). Additionally, cytotoxic, genotoxic, mutagenic, and teratogenic effects were observed, even at low concentrations (Johnson et al., 2008; Kümmerer, Haiß, Schuster, Hein, & Ebert, 2016; Negreira, de Alda, & Barceló, 2014; Novak, Žegura, Modic, Heath, & Filipič, 2017). Considering their potential to harm organisms along with their very narrow therapeutic index (i.e., therapeutic and toxic doses are very close) and the low selectivity to exclusively target cancer cells (Wormington et al., 2020) these drugs should arguably be treated as hazardous class of contaminants. The European Commission has recognized the ability of cytostatics to interact with the physiology of the endocrine system with effects sometimes being observed long after the exposure ceased (European Commission, 2016). It was reported that these compounds damage the uterus, which has evident consequences to future generations (de Oliveira et al., 2020; Deblonde, Cossu-Leguille, & Hartemann, 2011; Sim, Lee, & Oh, 2010). Nonetheless, no policies or guidelines were put in place to attempt to prevent or limit exposure to cytostatics. This is particularly relevant if we consider the number of cytostatic drugs currently used and the projected increase for the future. In fact, over the last years, the incidence of cancer has been increasing, with 18.07 million new cases in 2018 (Bray et al., 2018) and the consequent demand for anticancer drugs growing significantly (Sun et al., 2017). In Germany, for example, an increase in the consumption of these drugs from 22,000 kg in 2001 to 50,000 kg in 2012 was registered (Cristóvão et al., 2020). This demand will likely continue to rise, as the incidence of cancer is expected to continue increasing, reaching 29.5 million cases in 2040 (IARC, WHO−GCO).

Emerging Contaminants in the Environment. DOI: https://doi.org/10.1016/B978-0-323-85160-2.00006-8

Upon administration, cytostatic drugs (as any chemical in general) go through a series of processes within the organism, conceptualized as adsorption, distribution, metabolism, and excretion (ADME). Nevertheless, some drugs are not metabolized and are excreted through urine, ending up in sewage (Biel-Maeso, Baena-Nogueras, Corada-Fernández, & Lara-Martín, 2018; Cristóvão et al., 2020; Dubey, Kumar, Labrou, & Shukla, 2017; Rout et al., 2021; Santana-Viera, Montesdeoca-Esponda, Sosa-Ferrera, & Santana-Rodríguez, 2016). The low vapor pressure of cytostatic drugs, which prevents their volatilization, and their high solubility contribute to their widespread dispersion in water (Pruijn & DeWitte, 2004; Yadav et al., 2021). In addition, wastewater treatment plants (WWTPs) are not capable of efficiently removing this type of compound (Cristóvão et al., 2020; Franquet-Griell, Medina, Sans, & Lacorte, 2017a; Rout et al., 2021). Typically, WWTP treatments include chlorination and ultraviolet light, which are not completely effective against pharmaceutical compounds. Methods that are more efficient include, for example, ozonation, but this technology is not widely used or available around the world. Also, in developed countries, 30% of the industrial wastewaters are not treated (United Nations 2017). Thus cytostatics are continuously being discharged into the aquatic environment (Kosjek & Heath, 2011). Antineoplastic compounds, such as fluorouracil, tamoxifen, cyclophosphamide, ifosfamide, mycophenolic acid, cyclophosphamide, and tamoxifen have been detected in several water sources, including hospital effluents, wastewater influents and effluents, surface waters, groundwater, rivers, and even in potable water (Gouveia, Alves, & Santos, 2019; López-Serna et al., 2013; Mahnik, Lenz, Weissenbacher, Mader, & Fuerhacker, 2007; Negreira et al., 2014; Roberts & Thomas, 2006; Valcárcel, Alonso, Rodríguez-Gil, Gil, & Catalá, M., 2011).

3.2 Characterization of cytostatics

The World Health Organization adopted the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD), which classifies cytostatic drugs into four major groups: antineoplastic drugs (L01), endocrine therapy (L02), immunostimulants (L03), and immunosuppressants (L04) (Fig. 3.1).

Group L01, antineoplastic drugs, includes alkylating agents (L01A), antimetabolites (L01B), alkaloids and other products (L01C), cytotoxic antibiotics and related substances (L01D), protein kinase inhibitors (L01E), and other antineoplastic agents (L01X). The *alkylating agents (L01A)* are the largest group of antineoplastic drugs and include cyclophosphamide and ifosfamide. These drugs are responsible for the alkylation of intracellular nucleophilic targets in DNA, RNA, and enzymes (WHO Collaborating Centre for Drug Statistics Methodology, 2021; Zhang, Chang, Giannis, & Wang, 2013). The *antimetabolites (L01B)* are analogs of folic acid, purine, and pyrimidine, and include 5-fluorouracil and capecitabine (WHO Collaborating Centre for Drug Statistics Methodology, 2021). The *alkaloids (L01C)* are subdivided into vinca alkaloids and analogs, podophyllotoxin derivatives, colchicine derivatives, taxanes, topoisomerase I inhibitors, and other plant alkaloids and natural products, such as etoposide and paclitaxel (WHO Collaborating Centre for Drug Statistics Methodology, 2021). The *cytotoxic antibiotics and related substances (L01D)* include actinomycines, anthracyclines, and related substances,

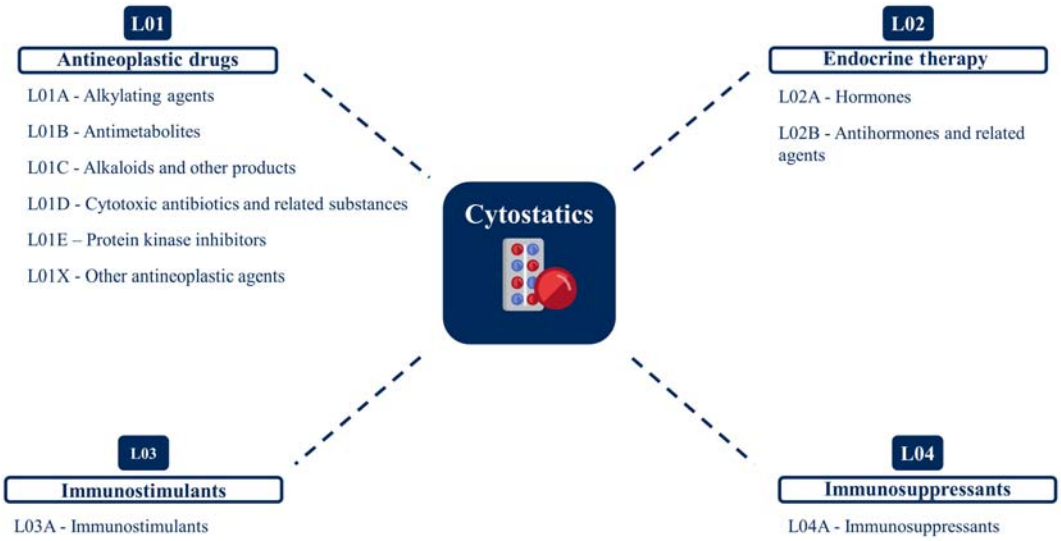

FIGURE 3.1

Classification of cytostatic drugs according to the anatomical therapeutic chemical classification system and the defined daily dose.

and other cytotoxic antibiotics such as doxorubicin and epirubicin (WHO Collaborating Centre for Drug Statistics Methodology, 2021). The *protein kinase inhibitors (L01E)* are a vast set of inhibitors such as imatinib and erlotinib (WHO Collaborating Centre for Drug Statistics Methodology, 2021). The *other antineoplastic agents (L01X)* includes the remaining antineoplastic drugs that cannot be included in the groups described above, including platinum compounds, methylhydrazines, monoclonal antibodies, sensitizers, retinoids, and some inhibitors, such as carboplatin and cisplatin (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

Group L02, endocrine therapy, includes hormones (L02A) and antihormones and related agents (L02B). *Endocrine therapy hormones (L02A)* are estrogens, progestogens, and gonadotropin-releasing hormone analogs like megestrol and fosfestrol. *Hormone antagonists and related agents (L02B)* include tamoxifen and bicalutamide. This group includes compounds that block the action of estrogens and androgens and also includes aromatase inhibitors (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

Group L03, immunostimulants (L03A), are colony-stimulating factors, interferons, interleukins, and others, and include filgrastim and aldesleukin (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

Group L04, immunosuppressants (L04A), are selective immunosuppressants, tumor necrosis factor-alpha, interleukin, and calcineurin inhibitors and include mycophenolic acid and methotrexate (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

3.3 Environmental levels of cytostatics

Cytostatic drugs, after being excreted by patients, will enter the sewage system, having been detected in hospital effluents, WWTP influents/effluents, and surface waters (Kosjek & Heath, 2011). Besides this continuous input, cytostatics can also enter the environment through the mishandling of pharmaceutical residues (Yadav et al., 2021).

In general, the concentrations of cytostatics in the environment are low, in the micrograms or nanograms per liter range, and therefore their analysis/quantification is very difficult. Furthermore, when cytostatics are associated with other compounds in mixtures, byproducts and coproducts, it is even more difficult to identify and quantify the different compounds present in environmental samples. This reinforces the importance of sample preparation and the selection of adequate methodologies for the identification and quantification of the different compounds (Brack et al., 2015; Garcia-Ac et al., 2009; Gouveia, Silva, Ribeiro, Alves, & Santos, 2020; Pessoa, Santos, Souza, Alves, & Nascimento, 2012; Pieczyńska, Borzyszkowska, Ofiarska, & Siedlecka, E.M., 2017; Santana-Viera et al., 2016; Santos, Franquet-Griell, Lacorte, Madeira, & Alves, 2017). Most protocols require an extraction process, such as solid-phase extraction (SPE) or liquid-liquid extraction (LLE). LLE provides good repeatability, high recoveries, simpler steps, and the cartridges used are affordable (Gouveia et al., 2020). However, SPE is more widely used as it generates cleaner extracts with less contamination while using smaller volumes of organic solvents (Gouveia et al., 2020; Kumari, Varughese, Ramji, & Kapoor, 2016; Rawa-Adkonis, Wolska, Przyjazny, & Namieśnik, 2006; Saar, Gerostamoulos, Drummer, & Beyer, 2009; Santana-Viera et al., 2016; Tauxe-Wuersch, Alencastro, Grandjean, & Tarradellas, J., 2006). The quantification is frequently performed by liquid chromatography-tandem mass spectrometry (LC-Ms/MS) since it provides lower limits of detection (LODs), a fundamental requisite when dealing with such low environmental levels (Calamari, Zuccato, Castiglioni, Bagnati, & Fanelli, 2003; Zhang & Zhou, 2007; Zhou, Zhang, Banks, Grover, & Jiang, 2009).

These technical difficulties in the quantification of cytostatics from complex matrices can explain the reduced number of studies published (42) and the reduced number of countries studied (16) (Fig. 3.2).

The vast majority of the studies were performed in Europe (83.1%), followed by Asia (13.6%) and America (3.3%). In general terms, and as could be expected, the levels are higher in hospital effluents and in WWTP influents/effluents and lower in surface waters. The levels of the most common cytostatics reported over the last five years in the different types of samples are provided in Tables 3.1–3.3 and described in the following sections.

3.3.1 Hospital effluents

The concentrations detected in hospital effluents, that is, hospital sewage, are expected to be higher, as these drugs are administered at hospitals in high doses and generally no treatment is applied (Isidori et al., 2016). The concentrations registered in hospital effluents ranged from 1 to 61,600 $ng.L^{-1}$ (Table 3.1). The highest value was detected in a hospital effluent from Slovenia (Isidori et al., 2016). This maximum value corresponds to carboxy-cyclophosphamide, a metabolite of cyclophosphamide which was, simultaneously, the cytostatic with higher detection frequency in hospital effluents (Czerwiński & Skupiński, 2020; Isidori et al., 2016; Olalla, Negreira, López de

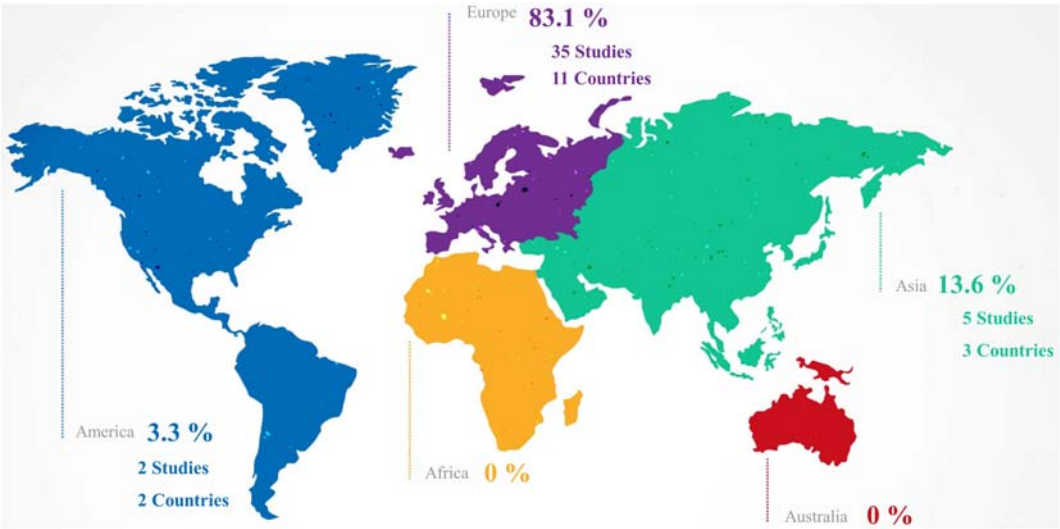

FIGURE 3.2

Global distribution of the studies reporting the occurrence of cytostatic drugs in environmental samples.

Data from 1990 to 2020. Image font adapted from the website vexels.com.

Alda, Barceló, & Valcárcel, 2018; Santana-Viera, Hernández-Arencibia, Sosa-Ferrera, & Santana-Rodríguez, 2019).

Isidori et al. (2016) reported the occurrence of 20 pharmaceutical compounds in hospital effluents from Spain and Slovenia, ranging from 0.3 to 61,600 ng L^{-1} and found a significant correlation between their levels and the results of toxicity tests. Another study from Spain detected irinotecan, imatinib, and ifosfamide at maximum concentrations of 273, 577, and 4761 ng L^{-1}, respectively (Olalla et al., 2018). Czerwiński & Skupiński, 2020 detected cyclophosphamide and ifosfamide in hospital effluents from Poland at concentrations ranging from 375−5141 ng L^{-1} to 56−1413 ng L^{-1}, respectively. On Gran Canaria Island (Spain), three different cytostatic drugs were detected, namely etoposide, cyclophosphamide, and vincristine at maximum concentrations of 619.9, 1218, and 1851 ng L^{-1}, respectively (Santana-Viera et al., 2019). Across the Atlantic, in Brazil (Santa Maria, Rio Grande do Sul), high levels of irinotecan, doxorubicin, and epirubicin were found (3400, 4640, and 6220 ng L^{-1}, respectively). In Japan, cytostatic drugs such as 4-hydroxy-N-desmethyltamoxifen (0.3 ng L^{-1}; tamoxifen metabolite), capecitabine (4 ng L^{-1}), etoposide (42 ng L^{-1}), tamoxifen (82 ng L^{-1}), and bicalutamide (1010 ng L^{-1}) presented a wide range of concentrations, with tamoxifen being the highest reported (Azuma, 2018).

3.3.2 Wastewater treatment plants influents

The final destination of domestic, and most of the time hospital, sewage is WWTP. The influent enters these WWTPs and, after being treated, the effluent is generally discharged into the environment. As a result of the different treatments performed at the WWTP, the final effluent generally

Table 3.1 Concentrations of cytostatic drugs (ng.L^{-1}) detected in *hospital effluents* between 2016 and 2021.

Cytostatic	Concentration (ng.L^{-1})	Location	Reference
5-Fluorouracil	2.4	Spain	Isidori et al. (2016)
	7.9	Slovenia	Isidori et al. (2016)
Bicalutamide	1010	Japan	Azuma et al. (2019)
Capecitabine	112	Slovenia	Isidori et al. (2016)
	4	Japan	Azuma et al. (2019)
	1749	Spain	Olalla, Negreira, López de Alda, Barceló, & Valcárcel (2018)
Cyclophosphamide	1218 ± 45 (Mean)	Canarias	Santana-Viera, Hernández-Arencibia, Sosa-Ferrera, & Santana-Rodríguez (2019)
	22,900	Slovenia	Isidori et al. (2016)
	435 ± 26 (Mean)	Poland	Czerwiński and Skupiński, (2020)
	33	Spain	Isidori et al. (2016)
	3000	Spain	Olalla et al. (2018)
Carboxy-cyclophosphamide	61,600	Slovenia	Isidori et al. (2016)
4-Ketocyclophosphamide	1350	Slovenia	Isidori et al. (2016)
N-dechloroethylcyclophosphamide	5630	Slovenia	Isidori et al. 2016
Doxorubicin	4.64 ± 0.37	Brazil	Souza, Reichert, & Martins, (2018)
Epirubicin	6.22 ± 043	Brazil	Souza, Reichert, & Martins, (2018)
Erlotinib	4.2	Slovenia	Isidori et al. (2016)
	2.5	Spain	Isidori et al. (2016)
Etoposide	619.9 ± 48 (Mean)	Canarias	Santana-Viera et al. (2019)
	42	Japan	Azuma et al. (2019)
Ifosfamide	48	Slovenia	Isidori et al. (2016)
	4761	Spain	Olalla et al. (2018)
	232 ± 20 (Mean)	Poland	Czerwiński & Skupiński (2020)
Irinotecan	273	Spain	Olalla et al. (2018)
	3.40 ± 0.32	Brazil	Souza, Reichert, & Martins, (2018)
	11.6	Slovenia	Isidori et al. (2016)
Methotrexate	3990	Slovenia	Isidori et al. (2016)
	36	Spain	Isidori et al. (2016)
	4756	Spain	Olalla et al. (2018)
Hydroxymethotrexate	539	Slovenia	Isidori et al. (2016)
Platinum-based	360	Slovenia	Isidori et al. (2016)
Tamoxifen	10	Slovenia	Isidori et al. (2016)
	7.5	Spain	Isidori et al. (2016)
	82	Japan	Azuma et al. (2019)

Table 3.1 Concentrations of cytostatic drugs (ng.L^{-1}) detected in *hospital effluents* between 2016 and 2021. *Continued*

Cytostatic	Concentration (ng.L^{-1})	Location	Reference
Vincristine	1851	Canarias	Santana-Viera et al. (2019)
4-hydroxy-N-desmethyltamoxifen	11	Spain	Isidori et al. (2016)
	10	Slovenia	Isidori et al. (2016)
	0.3	Japan	Azuma et al. (2019)

Table 3.2 Concentrations of cytostatic drugs (ng.L^{-1}) detected in *wastewater treatment plants influents and effluents* between 2016 and 2021.

	Concentrations (ng.L^{-1})			
Cytostatic	Influent	Effluent	Location	Reference
5-fluorouracil	3.5		Slovenia	Isidori et al. (2016)
	4		Spain	Isidori et al. (2016)
Bicalutamide	156		Japan	Azuma et al. (2019)
	79	60	Portugal	Gouveia et al. (2020)
		1032	Japan	Azuma (2018)
Capecitabine	87	24	Portugal	Gouveia et al. (2020)
	171		Slovenia	Isidori et al. (2016)
	81 ± 46 (Mean)	13 ± 3 (Mean)	Spain	Franquet-Griell, Cornadó, Caixach, Ventura, & Lacorte (2017)
		11	Japan	Azuma (2018)
Carboplatin	1600	1200	Iran	Ghafuri et al. (2018)
Cisplatin	1120	430	Iran	Ghafuri et al. (2018)
Cyclophosphamide	110		Japan	Azuma et al. (2019)
	80	45	Portugal	Gouveia et al. (2020)
	34	22	Slovenia	Isidori et al. (2016)
	8.5		Spain	Isidori et al. (2016)
	15 ± 9 (Mean)	19 ± 3 (Mean)	Spain	Franquet-Griell et al. (2017)
		91 ± 14 (Mean)	Canarias	Santana-Viera et al. (2019)
		22	Japan	Azuma (2018)
		17	Portugal	Santos, Franquet-Griell, Alves, & Lacorte (2018)
Doxorubicin	139		Portugal	Gouveia et al. (2020)
Erlotinib	10.3	4.1	Slovenia	Isidori et al. (2016)
	7.8	3.4	Spain	Isidori et al. (2016)

(*Continued*)

Table 3.2 Concentrations of cytostatic drugs (ng.L^{-1}) detected in *wastewater treatment plants influents and effluents* between 2016 and 2021. *Continued*

	Concentrations (ng.L^{-1})			
Cytostatic	**Influent**	**Effluent**	**Location**	**Reference**
Etoposide	582		Japan	Azuma et al. (2019)
	5141 ± 256 (Mean)		Canarias	Santana-Viera et al. (2019)
	62		Portugal	Gouveia et al. (2020)
Gemcitabine	62		Slovenia	Isidori et al. (2016)
Ifosfamide	50	71	Portugal	Gouveia et al. (2020)
Imatinib	149		Portugal	Gouveia et al. (2020)
Irinotecan	59		Slovenia	Isidori et al. (2016)
Megestrol	19		Portugal	Gouveia et al. (2020)
Methotrexate	308		Slovenia	Isidori et al. (2016)
	31		Spain	Isidori et al. (2016)
Hydroxymethotrexate	401		Slovenia	Isidori et al. (2016)
Mycophenolate mofetil	70		Portugal	Gouveia et al. (2020)
Mycophenolic acid	3099 ± 500 (Mean)	195 ± 72 (Mean)	Spain	Franquet-Griell et al. (2017)
	1624		Portugal	Gouveia et al. (2020)
		874	Portugal	Santos et al. (2018)
Oxaliplatin	430	120	Iran	Ghafuri et al. (2018)
Platinum-based drugs	30		Slovenia	Isidori et al. (2016)
Tamoxifen	15		Japan	Azuma et al. (2019)
	74	7.5	Slovenia	Isidori et al. (2016)
	19		Spain	Isidori et al. (2016)
		9	Japan	Azuma (2018)
(Z) − 4-Hydroxytamoxifen	8.6		Slovenia	Isidori et al. (2016)
	8.6		Spain	Isidori et al. (2016)
4-Hydroxy-N-desmethyltamoxifen	49		Slovenia	Isidori et al. (2016)
	83	14	Spain	Isidori et al. (2016)
N-desmethyltamoxifen	24		Japan	Azuma et al. (2019)

exhibits lower levels than the initial influent. Table 3.2 describes the levels of cytostatics detected in WWTP influents and effluents. The concentrations varied between 3.5 and 5141 ng L^{-1}, with etoposide sampled in Gran Canaria Island registering the highest concentration (Santana-Viera et al., 2019) and tamoxifen (and metabolites) being the most common drug detected in WWTP influents (Azuma, 2018; Isidori et al., 2016). Furthermore, total cytostatics identified in WWTP influents were very similar to those found in hospital effluents with small differences in the type of cytostatics found, namely Carboxycyclophosphamide (cyclophosphamide metabolite), N-Dechloroethyl Cyclophosphamide (cyclophosphamide metabolite), 4-Ketocyclophosphamide (cyclophosphamide metabolite), vincristine,

Table 3.3 Concentrations of cytostatic drugs detected in *surface waters* between 2016 and 2021.

Cytostatic	Concentration (ng.L^{-1})	Type of sample	Location	Reference
Bicalutamide	38	River	Japan	Azuma et al. (2019)
	254	River	Japan	Azuma (2018)
Cyclophosphamide	13.7	River	Spain	Franquet-Griell et al. (2017a)
	17	River	Japan	Azuma et al. (2019)
	20	River	Japan	Azuma (2018)
Capecitabine	20	River	Japan	Azuma (2018)
Erlotinib	3.9	River	Spain	Franquet-Griell et al. (2017a)
Ifosfamide	13.9	River	Spain	Franquet-Griell et al. (2017a)
Megestrol	6	River	Spain	Franquet-Griell et al. (2017a)
Mycophenolic acid	210 ± 9 (Mean)	River	Portugal	Santos et al. (2018)
	211 ± 6 (Mean)	River	Portugal	Santos et al. (2018)
	541 ± 85 (Mean)	River	Portugal	Santos et al. (2018)
	656	River	Spain	Franquet-Griell et al. (2017a)
Tamoxifen	76	River	Japan	Azuma (2018)
	25.1	River	Spain	Franquet-Griell et al. (2017a)

epirubicin, (Z) − 4-Hydroxytamoxifen (tamoxifen metabolite), cisplatin, gemcitabine, megestrol, mycophenolate mofetil, mycophenolic acid, and N-desmethyltamoxifen (tamoxifen metabolite) (Tables 3.1 and 3.2). In Spain, different pharmaceutical drugs were identified in a study conducted in 2016 (capecitabine, cyclophosphamide, and mycophenolic acid) with concentrations ranging from 15 to 3099 ng L^{-1} (Franquet-Griell, Pueyo, Silva, Orera, & Lacorte, 2017b), which contrasts with a previous study where concentrations varied between 3.5 and 83 ng L^{-1} for (Z) − 4-Hydroxytamoxifen, 4-Hydroxy-N-desmethyltamoxifen, 5-fluorouracil, cyclophosphamide, erlotinib, methotrexate, and tamoxifen (Isidori et al., 2016). Despite both samplings taking place in Barcelona, and the use of the same extraction processes, the differences obtained can be explained by the sampling procedure. For the first study, the sampling time was 4 days whereas, in the second, it was only 24 h. The daily wastewater inflow for each WWTP was also different, with 525,000 m^3 day^{-1} and 234,000 m^3 day^{-1}, respectively. This second study also analyzed wastewater (hospital and municipal) from Slovenia and the levels there were relatively higher than the ones detected in Barcelona (Isidori et al., 2016). In Portugal, the highest level was detected for mycophenolic acid (1624 ng L^{-1}). Also in Portugal, the mycophenolic acid prodrug, mycophenolate mofetil was also detected in WWTP influents (70 ng L^{-1}; Gouveia et al., 2020). The detection of both compounds in Portuguese WWTP influents is probably a consequence of its high use, since this cytostatic is also used as an immunosuppressant to prevent organ rejection after transplantation and Portugal has the third-highest rates of transplantation in Europe (IRODaT, Worldwide Actual Deceased Organ Donors, 2019). On the other hand, in Gran Canaria Island, a concentration of 5141 ng L^{-1} for etoposide was registered, which is very high (Santana-Viera et al., 2019). In Asia, results obtained in Japan and Iran registered different concentrations ranges, with 15−582 ng L^{-1} in Japan and higher values in Iran (720−1600 ng L^{-1}; Azuma et al., 2019; Ghafuri et al., 2018).

3.3.3 Wastewater treatment plants effluents

After WWTP treatments, it is reasonable to expect that the concentration of pharmaceutical drugs should be reduced and, ideally, the drugs efficiently removed in the final effluent. However, it has been reported that conventional WWTP treatments cannot remove these compounds due to their recalcitrant nature (Franquet-Griell et al., 2017a; Yadav et al., 2021). Concentrations in effluents varied between 3.4 and 1200 ng L^{-1} (Table 3.2), the highest being identified for bicalutamide in Japan (Azuma, 2018). The authors of the Japanese study explained the obtained result as a consequence of the high consumption rate of these pharmaceuticals (Ministry of Health Labour & Welfare Japan, 2013) and to low investment in research and development of wastewater treatment facilities (Verlicchi, Aukidy, & Zambello, E., 2015; Yadav et al., 2021). Furthermore, in a study conducted one year later the concentration of bicalutamide decreased to 127 ng L^{-1}, which could be related to an upgrade in the wastewater treatment, such as, for example, ozonation (Azuma et al., 2019).

Generally, and similarly to hospital effluents, the cytostatic cyclophosphamide was the most detected compound (total of nine studies, Azuma, 2018; Franquet-Griell et al., 2017a; Gouveia et al., 2020; Isidori et al., 2016; Santana-Viera et al., 2019; Santos et al., 2018). In European countries such as Portugal, Slovenia, and Spain, the concentration of cytostatics pharmaceutical drugs identified ranged from 3.4 to 874 ng L^{-1} (Franquet-Griell et al., 2017b; Gouveia et al., 2020; Isidori et al., 2016; Santos et al., 2018). Likewise, in Japan, the concentrations of cytostatics were in the range of 9−1032 ng L^{-1} (Azuma, 2018). In Iran, relatively higher concentrations were found by Ghafuri et al. (2018), with levels varying between 310 and 1200 ng L^{-1}. On Gran Canaria Island, cyclophosphamide was found with a maximum concentration of 105 ng L^{-1} (Santana-Viera et al., 2019).

3.3.4 Surface waters

As previously mentioned, cytostatic drugs exhibit low biodegradability and high stability (Franquet-Griell et al., 2017a), and are extremely difficult to remove with the current WWTP technologies. Consequently, these toxic compounds will end up in water bodies, including rivers, lakes, and channels (Verlicchi, Campos Garrigós, & Al Aukidy, 2020). Nevertheless, few studies reported their occurrence in the aquatic environment and are restricted to Japan, Spain, and Portugal. Globally, as can be seen in Table 3.3, the cytostatics in surface waters exhibited low concentrations.

Cyclophosphamide was once again the cytostatic with the highest detection frequency (Azuma, 2018; Azuma et al., 2019; Franquet-Griell et al., 2017), whereas the cytostatic with the highest concentration was mycophenolic acid with 656 ng L^{-1} detected in a Spanish river (Besòs River, Franquet-Griell et al., 2017). In Japan, several different pharmaceuticals were detected in the Yodo River Basin, including bicalutamide, capecitabine, cyclophosphamide, N-desmethyltamoxifen, and tamoxifen (Azuma, 2018; Azuma et al., 2019). In this river, WWTPs were identified as the principal sources of pharmaceutical drugs and, consequently, of cytostatics as well (Azuma, 2018; Azuma et al., 2019).

In Spain, in the Besòs River, a comprehensive survey of 19 cytostatics was performed, and of those, seven were detected, including cyclophosphamide, erlotinib, ifosfamide, megestrol, mycophenolic acid, and tamoxifen (Franquet-Griell et al., 2017). Likewise, Santos et al. (2018) collected

water samples from three rivers in Portugal, namely Uíma, Douro, and Leça and, monitored seven pharmaceuticals, but only mycophenolic acid (210, 211, and 541 ng L^{-1}, respectively) was detected (Santos et al., 2018).

Overall, based on the studies reported, in terms of WWTP influents, effluents, and surface waters, the most relevant cytostatics are 5-fluorouracil, bicalutamide, capecitabine, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, erlotinib, etoposide, gemcitabine, ifosfamide, imatinib, irinotecan, megestrol, methotrexate, mycophenolic acid, mycophenolate mofetil, paclitaxel, tamoxifen, and vincristine. In the next section an overview of the remediation technologies for these drugs are described.

3.4 Remediation strategies

Given the number of toxic compounds present in sewage and their potential impacts in ecosystems, several technologies have been developed to treat wastewater, in order to reduce the number of toxic compounds that can be carried by the effluents and to minimize the harmful effects in the environment (Nunes et al., 2019). Generally, common treatments can be classified as biological, physicochemical, and chemical.

Biological treatments are relatively cheap processes and involve microorganisms such as bacteria, yeast, fungi, and algae, but their effectiveness can be compromised by the effluent's toxicity (Nunes et al., 2019). In addition, some of the byproducts generated might be toxic and nonbiodegradable (Al-Khalid & El-Naas, 2012; Lavanya, Rajesh, Sunil, & Sarita, 2014; Quiton, Lu, & Huang, 2021).

Physicochemical treatments include processes that focus on adsorption, precipitation, coagulation/flocculation, filtration, ion exchange, and sedimentation of the targeted compounds. However, sometimes the products are not eliminated but rather concentrated in another phase, demanding a further treatment step (Quiton et al., 2021).

Chemical treatments are generally performed in the presence of oxygen or other oxidants, such as hydrogen peroxide, ozone, and permanganate, that will degrade the pollutants through an oxidative reaction. Yet, sometimes the compounds are not fully oxidized and therefore intermediate products may be formed, which can be even more toxic than the initial compounds (Quiton et al., 2021; Rodrigues, Silva, Carabineiro, Maldonado-Hódar, & Madeira, 2019).

Likewise, the treatments to remove cytostatics from the environment can also be divided into biological, physicochemical, and chemical treatments (Fig. 3.3) (Yadav et al., 2021). Treatment differences are highlighted in Figs. 3.3 and 3.4 and Table 3.4.

3.4.1 Biological treatment

Biological processes include microorganisms able to degrade cytostatic drugs. Traditionally this is performed in a bioreactor inoculated with *activated sludge* containing aerobic bacteria and often combined with membrane filtration (Buerge et al., 2006; Česen et al., 2015; Franquet-Griell et al., 2017a; Mahnik et al., 2007). Biological treatments were successfully employed to degrade some cytostatic drugs either in MilliQ water and simulated effluent or real effluent. Nevertheless, they

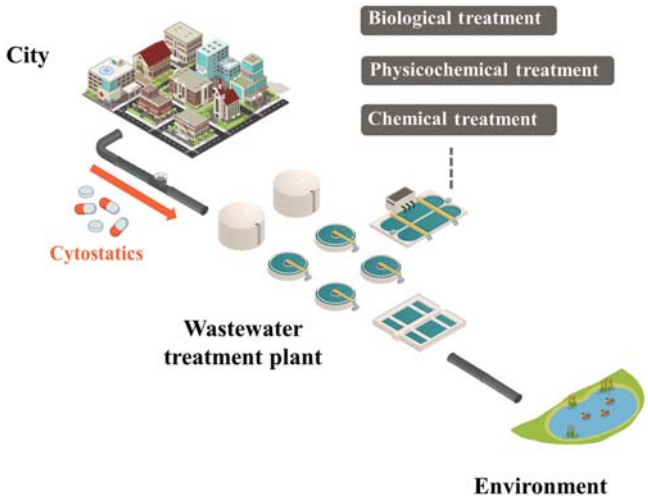

FIGURE 3.3

Overview of the fate of cytostatics with the types of wastewater treatment plants treatments available to prevent their introduction into the aquatic environment.

Icons from freepik.com.

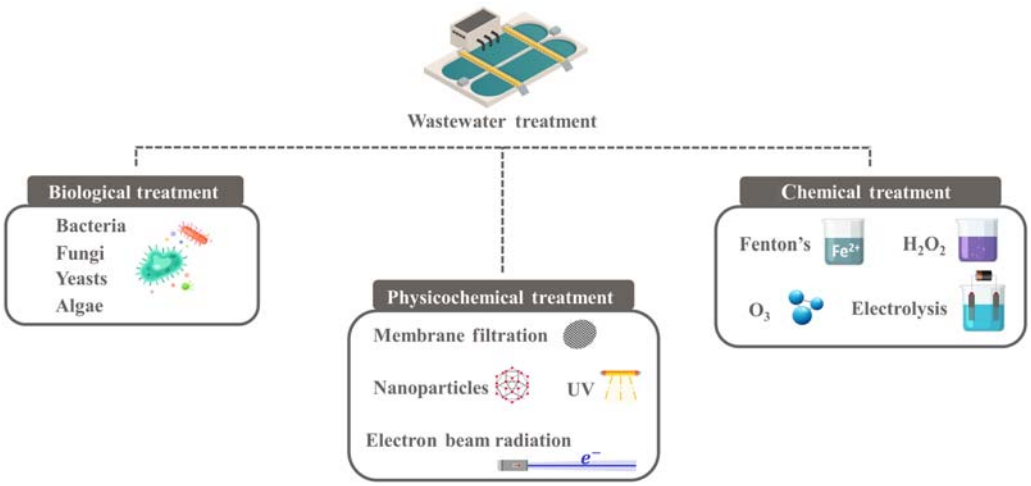

FIGURE 3.4

Schematic representation of the different types of wastewater treatments available.

Icons from freepik.com

Table 3.4 Remediation strategies used in the treatment of cytostatics with indication of the drug, the matrix tested, the treatment employed, and the removal efficiency (%). *na*, information not available; *WWTP*, wastewater treatment plant.

Cytostatic	Matrix	Treatment employed	Removal %	Reference
5-Fluorouracil	Hospital effluent	Biological	>99	Mahnik et al. (2007)
	Hospital effluent	Membrane bioreactor (MBR)	>99	Mahnik et al. (2007)
	Milli-Q water	Electrolysis	>99	Siedlecka et al. (2018)
	Milli-Q water	Electrolysis	77	Ochoa-Chavez, Pieczyńska, Fiszka Borzyszkowska, Espinoza-Montero, & Siedlecka (2018)
	Milli-Q water	UV/Fenton's reagent	96	Koltsakidou et al. (2017)
	Milli-Q water	Fenton's reagent	No significant removal	Koltsakidou et al. (2017)
	Milli-Q water	O_3	>99	Chen et al. (2019)
	Milli-Q water	UV (Hg lamp)	>99	Lutterbeck et al. (2016)
	Milli-Q water	UV (Xe Lamp)	No significant removal	Lutterbeck et al. (2016)
	Milli-Q water	UV	No significant removal	Zhang, Zhang, Xiao, Chang, & Lim (2017b)
	Milli-Q water	UV/H_2O_2	90.4	Zhang et al. (2017b)
	Milli-Q water	UV/$BiOCl_nBr_m$	>99	Wilczewska et al. (2021)
	Milli-Q water	UV/BiOClBr	>99	Wilczewska et al. (2019)
	Milli-Q water	UV/Fenton's reagent	>99	Emídio, Hammer, & Nogueira (2020)
	Milli-Q water	UV/H_2O_2	>99	Lutterbeck et al. (2015c)
	Milli-Q water	UV/Fenton's reagent	>99	Lutterbeck et al. (2015c)
	Milli-Q water	UV/TiO_2	>99	Lutterbeck et al. (2015c)
	Milli-Q water	UV/TiO_2	>99.9	Lin & Lin (2014)
	Milli-Q water	UV/TiO_2	>99	Borzyszkowska et al. (2016)
	Milli-Q water	UV/TiO_2	100	Mazierski et al. (2019)
	Milli-Q water	UV/TiO_2	>99	Koltsakidou et al. (2017)
	Milli-Q water + WWTP effluent	Electrolysis	80	Pieczyńska, Ochoa-Chavez, Wilczewska, Bielicka-Giełdoń, & Siedlecka (2019)
	Milli-Q water	Fenton's reagent	>99	Governo, Santos, Alves, & Madeira (2017)
	Milli-Q water	Fenton's reagent/ H_2O_2	>99	Governo et al. (2017)
	WWTP effluent	Fenton's reagent/ H_2O_2	>99	Governo et al. (2017)
	Milli-Q water	UV	>99	Governo et al. (2017)
	Milli-Q water	UV/Fenton's reagent/H_2O_2	>99	Governo et al. (2017)
	Milli-Q water	UV/H_2O_2	>99	Governo et al. (2017)
	Pharmaceutical wastewater and hospital effluent	O_3	>99	Lin, Hsueh, & Hong (2015)
	Synthetic waters and river waters	UV/$NaHCO_3$ + $NaNO_3$	93	Lin, Wang, & Lee (2013)
	Synthetic waters and river waters	UV (Solar)	No significant removal	Lin et al. (2013)
	Treated water and wastewater secondary effluent	UV	No significant removal	Zhang, Xiao, Zhang, Chang, & Lim (2017a)
	Treated water and wastewater secondary effluent	UV/H_2O_2	90	Zhang et al. (2017a)

(*Continued*)

Table 3.4 Remediation strategies used in the treatment of cytostatics with indication of the drug, the matrix tested, the treatment employed, and the removal efficiency (%). *na*, information not available; *WWTP*, wastewater treatment plant. *Continued*

Cytostatic	Matrix	Treatment employed	Removal %	Reference
Capecitabine	Hospital and WWTP effluent	Biological	No significant removal	Franquet-Griell et al. (2017b)
	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
	Milli-Q water	Hydrolysis	No significant removal	Franquet-Griell et al. (2017b)
	Milli-Q water	UV	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	UV/H_2O_2	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	Solar radiation	<45	Franquet-Griell et al. (2017b)
	Milli-Q water	Electrolysis	93	Xu, Tang, Wang, Ma, & Niu (2020)
	Milli-Q water	Electrolysis	85	Barışçı et al. (2018)
	Milli-Q water	Electrolysis	>98	Tang et al. (2020)
	Milli-Q water	UV/H_2O_2	>99	Tang et al. (2020)
	Milli-Q water	O_3	>99	Chen et al. (2019)
	Milli-Q water	O_3	>98.4	Tang et al. (2020)
	Milli-Q water	Electron beam irradiation	100	Huo, Wang, Shao, Wang, & Xu (2020)
	Milli-Q water	UV	>99	Guo, Zheng, & Chen (2015)
	Milli-Q water	Biological	No significant removal	Guo et al. (2015)
	Milli-Q water	UV + biological	50	Guo et al. (2015)
Cisplatin	Milli-Q water	Electrolysis	81.5	Hirose et al. (2005)
	Milli-Q water	O_3	99.6	Hernández et al. (2008)
Cyclophosphamide	Hospital and WWTP effluent	Biological	29	Česen et al. (2015)
	Hospital and WWTP effluent	$UV/O_3/H_2O_2$	71	Česen et al. (2015)
	Hospital and WWTP effluent	Biological + $UV/O_3/H_2O_2$	>99	Česen et al. (2015)
	Hospital effluent	MBR	60	Seira, Sablayrolles, Montréjaud-Vignoles, Albasi, & Joannis-Cassan (2016)
	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
	Hospital wastewater	O_3	57	Kovalova et al. (2013)
	Hospital wastewater	O_3/H_2O_2	No significant improvement	Kovalova et al. (2013)
	Hospital wastewater	Activated carbon	>73	Kovalova et al. (2013)
	Hospital wastewater	UV	No significant removal	Kovalova et al. (2013)
	Hospital wastewater	$UV\text{-}TiO_2$	No significant improvement	Kovalova et al. (2013)
	Laboratory grade water	Nanofiltration	59.3−86.2	Cristóvão et al. (2019)
	Milli-Q water	Electrolysis	>99	Siedlecka et al. (2018)
	Milli-Q water	Electrolysis	>95	Fabiańska, Ofiarska, Fiszka-Borzyszkowska, Stepnowski, & Siedlecka (2015)
	Milli-Q water	NaOCl	>98	Hansel et al. (1996)
	Milli-Q water	H_2O_2	>98	Hansel et al. (1996)
	Milli-Q water	Fenton's reagent	>98	Hansel et al. (1996)
	Milli-Q water	O_3	<85	Fernández et al. (2010)
	Milli-Q water	O_3/H_2O_2	<95	Fernández et al. (2010)

Table 3.4 Remediation strategies used in the treatment of cytostatics with indication of the drug, the matrix tested, the treatment employed, and the removal efficiency (%). *na*, information not available; *WWTP*, wastewater treatment plant. *Continued*

Cytostatic	Matrix	Treatment employed	Removal %	Reference
	Milli-Q water	UV	No significant removal	Zhang et al. (2017b)
	Milli-Q water	UV/H_2O_2	86	Zhang et al. (2017b)
	Milli-Q water	UV/chlorine	<99	Lee, Lee, Kim, Choi, & Zoh (2021)
	Milli-Q water	UV/Fenton's reagent	>95	Emídio et al. (2020)
	Milli-Q water	UV/H_2O_2	75	Lutterbeck, Machado, & Kümmerer (2015b)
	Milli-Q water	UV/Fenton's reagent/H_2O_2	85	Lutterbeck et al. (2015b)
	Milli-Q water	UV/TiO_2	90	Lutterbeck et al. (2015b)
	Milli-Q water	UV/persulfate	>99	Akbari and Adibzadeh, (2020)
	Milli-Q water	UV/TiO_2	>99.9	Lin & Lin (2014)
	Milli-Q water	UV/TiO_2	>99	Borzyszkowska et al. (2016)
	Milli-Q water	UV/Ag-TiO_2	99	Cristea Ionut, Arcadie, Constantin Lucian, Constantin Mirela, & Nitoi (2020)
	Milli-Q water	UV, UV/H_2O_2, UV/O_3, O_3, and H_2O_2/O_3	na	Lester, Avisar, Gozlan, & Mamane (2011)
	Milli-Q water	UV/BiOClBr	<80	Wilczewska et al. (2019)
	Milli-Q water + WWTP effluent	Electrolysis	>95	Pieczyńska et al. (2019)
	Milli-Q water and WWTP effluent	UV/Ru-TNW	>99	Osawa et al. (2019)
	Hospital and pharmacy wastewater effluent	UV/TiO_2	>99	Lai, Lin, & Lin (2015)
	Municipal wastewater	MBR	80	Delgado et al. (2011)
	Municipal wastewater	Nanofiltration	60	Wang et al. (2009)
	Municipal wastewater	O_3	>70	Li, Nanaboina, Chen, & Korshin (2016)
	Pharmaceutical wastewater and hospital effluent	O_3	>99	Lin et al. (2015)
	River	O_3	>96	Garcia-Ac et al. (2010)
	Stock solution (ethanol)	Biological	<40	Castellet-Rovira et al. (2018)
	Stock solution (*Trametes hirsuta* medium)	Biological	No significant removal	Haroune, Saibi, Bellenger, & Cabana (2014)
	Surface water	Nanofiltration	>90	Verliefde et al. (2007)
	Synthetic domestic wastewater	MBR	95.6	Wang, Zhang, Chang, She, & Tang (2018)
	Synthetic urine	Nanofiltration	81.1–96.6	Cristóvão et al. (2019)
	Synthetic wastewater	Electrolysis	100	Barzan et al. (2019)
	Synthetic wastewater	Biological	No significant removal	Ferrando-Climent et al. (2015)
	Treated water, wastewater secondary effluent	UV	No significant removal	Zhang et al. (2017a)
	Treated water, wastewater secondary effluent	UV/H_2O_2	64	Zhang et al. (2017a)
	Wastewater influent and effluent	UV	80	Buerge, Buser, Poiger, & Müller (2006)
	Wastewater influent and effluent	Biological	No significant removal	Buerge et al. (2006)
	WWTP effluent	Nanofiltration	45.3–90.4	Cristóvão et al. (2019)

(*Continued*)

Table 3.4 Remediation strategies used in the treatment of cytostatics with indication of the drug, the matrix tested, the treatment employed, and the removal efficiency (%). *na*, information not available; *WWTP*, wastewater treatment plant. *Continued*

Cytostatic	Matrix	Treatment employed	Removal %	Reference
Doxorubicin	Hospital and WWTP effluent	Biological	>99	Franquet-Griell et al. (2017b)
	Hospital effluent	Biological	>90	Mahnik et al. (2007)
	Hospital effluent	MBR	>99	Mahnik et al. (2007)
	Milli-Q water	Hydrolysis	>85	Franquet-Griell et al. (2017b)
	Milli-Q water	UV	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	UV/H_2O_2	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	Solar radiation	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	Biological	>99	Kelbert et al. (2020)
	Milli-Q water	Electrolysis	>99	Crisnic et al. (2020)
	Milli-Q water	Electrolysis	99.9	Garcia et al. (2020)
	Milli-Q water	Nanoparticles (Fe_3O_4)	80.2	Weng et al. (2018)
	Milli-Q water	O_3	40	Somensi, Simionatto, Dalmarco, Gaspareto, & Radetski (2012)
	Milli-Q water	O_3/ultrasound	47.5	Somensi et al. (2012)
	Milli-Q water	UV	No significant removal	Zhang et al. (2017b)
	Milli-Q water	UV/H_2O_2	96.6	Zhang et al. (2017b)
	Synthetic domestic wastewater	MBR	100	Wang et al. (2018)
	WWTP Influent	Nanoparticles (Fe_3O_4)	73.6	Weng et al. (2018)
Epirubicin	Milli-Q water	Electrolysis	>99	Hirose et al. (2005)
	Synthetic domestic wastewater	MBR	100	Wang et al. (2018)
Erlotinib	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
Etoposide	Milli-Q water	UV	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	Solar radiation	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	UV/H_2O_2	>99	Franquet-Griell et al. (2017b)
	Hospital and WWTP effluent	Biological	No significant removal	Franquet-Griell et al. (2017b)
	Milli-Q water	Hydrolysis	No significant removal	Franquet-Griell et al. (2017b)
	Hospital effluent	Biological	100	Ferrando-Climent et al. (2015)
	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
	Laboratory grade water	Nanofiltration	93.1−97.7	Cristóvão et al. (2019)
	Municipal wastewater	UV	100	Janssens et al. (2019)
	Municipal wastewater	UV/TiO_2	100	Janssens et al. (2019)
	Municipal wastewater	UV/H_2O_2	100	Janssens et al. (2019)
	Synthetic urine	Nanofiltration	>95	Cristóvão et al. (2019)
	Synthetic urine + Milli-Q water	UV	<99	Janssens et al. (2019)
	WWTP effluent	Nanofiltration	91.0−98.7	Cristóvão et al. (2019)

Table 3.4 Remediation strategies used in the treatment of cytostatics with indication of the drug, the matrix tested, the treatment employed, and the removal efficiency (%). *na*, information not available; *WWTP*, wastewater treatment plant. *Continued*

Cytostatic	Matrix	Treatment employed	Removal %	Reference
Gemcitabine	Milli-Q water	Hydrolysis	No significant removal	Franquet-Griell et al. (2017b)
	Milli-Q water	Solar radiation	No significant removal	Franquet-Griell et al. (2017b)
	Milli-Q water	UV/H_2O_2	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	UV	>90	Franquet-Griell et al. (2017b)
	Hospital and WWTP effluent	Biological	>99	Franquet-Griell et al. (2017b)
Ifosfamide	Hospital and WWTP effluent	Biological	32	Česen et al. (2015)
	Hospital and WWTP effluent	UV/O_3/H_2O_2	68	Česen et al. (2015)
	Hospital and WWTP effluent	Biological + UV/O_3/H_2O_2	>99	Česen et al. (2015)
	Hospital effluent	Biological	61	Ferrando-Climent et al. (2015)
	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
	Hospital wastewater	Activated carbon	>60	Kovalova et al. (2013)
	Hospital wastewater	O_3	20–62	Kovalova et al. (2013)
	Hospital wastewater	O_3/H_2O_2	No significant improvement	Kovalova et al. (2013)
	Hospital wastewater	UV-TiO_2	No significant improvement	Kovalova et al. (2013)
	Laboratory grade water	Nanofiltration	61.8–84.8	Cristóvão et al. (2019)
	Milli-Q water	Electrolysis	>99	Fabiańska et al. (2015)
	Milli-Q water	Electrolysis	>95	Siedlecka et al. (2018)
	Milli-Q water	UV-TiO_2	>99	Borzyszkowska et al. (2016)
	Milli-Q water	UV-TiO_2	>99	Ofiarska, Pieczyńska, Fiszka Borzyszkowska, Stepnowski, & Siedlecka (2016)
	Milli-Q water	NaOCl	>99	Hansel et al. (1996)
	Milli-Q water	H_2O_2	>99	Hansel et al. (1996)
	Milli-Q water	Fenton's reagent	>99	Hansel et al. (1996)
	Milli-Q water + WWTP effluent	Electrolysis	>95	Pieczyńska et al. (2019)
	Milli-Q water and WWTP effluent	UV/Ru-TNW	>99	Osawa et al. (2019)
	Hospital and pharmacy wastewater effluent	UV/TiO_2	>99	Lai et al. (2015)
	Municipal wastewater	O_3	75	Li et al. (2016)
	Pharmaceutical wastewater and hospital effluent	O_3	>99	Lin et al. (2015)
	Stock solution (ethanol)	Biological	<40	Castellet-Rovira et al. (2018)
	Stock solution (*Trametes hirsuta* medium)	Biological	<35	Haroune et al. (2014)
	Synthetic urine	Nanofiltration	82.5–96.3	Cristóvão et al. (2019)
	Synthetic wastewater	Biological	No significant removal	Ferrando-Climent et al. (2015)
	Wastewater influent and effluent	Biological	No significant removal	Buerge et al. (2006)
	Wastewater influent and effluent	UV	60	Buerge et al. (2006)
	WWTP effluent	Nanofiltration	43.8–88.8	Cristóvão et al. (2019)

(*Continued*)

Table 3.4 Remediation strategies used in the treatment of cytostatics with indication of the drug, the matrix tested, the treatment employed, and the removal efficiency (%). *na*, information not available; *WWTP*, wastewater treatment plant. *Continued*

Cytostatic	Matrix	Treatment employed	Removal %	Reference
Imatinib	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
	Milli-Q water	Electrolysis	>99	Siedlecka et al. (2018)
	Milli-Q water	UV/BiOClnBrm	>99	Wilczewska et al. (2021)
	Milli-Q water	UV/BiOClBr	>99	Wilczewska et al. (2019)
	Milli-Q water	UV-TiO_2	>99	Borzyszkowska et al. (2016)
	Milli-Q water	UV-TiO_2	>99	Ofiarska et al. (2016)
Irinotecan	Hospital and WWTP effluent	Biological	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	Hydrolysis	85	Franquet-Griell et al. (2017b)
	Milli-Q water	UV	>85	Franquet-Griell et al. (2017b)
	Milli-Q water	UV/H_2O_2	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	Solar radiation	90	Franquet-Griell et al. (2017b)
	Milli-Q water	Electrolysis	72.1	Hirose et al. (2005)
	Milli-Q water	UV/TiO_2	99	Chatzimpaloglou et al. (2021)
Methotrexate	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
	Milli-Q water	Electrolysis	98	Hirose et al. (2005)
	Milli-Q water	Electrolysis	>99	Siedlecka et al. (2018)
	Milli-Q water	Electrolysis	>99	Barışçı et al. (2018)
	Milli-Q water	O_3, O_3/US	80	Somensi et al. (2012)
	Milli-Q water	UV/Fenton's reagent/H_2O_2	<75	Lutterbeck, Baginska, Machado, & Kümmerer (2015a)
	Milli-Q water	UV/H_2O_2	<60	Lutterbeck et al. (2015a)
	Milli-Q water	UV/TiO_2	<70	Lutterbeck et al. (2015a)
	Milli-Q water	UV	20	González-Burciaga, García-Prieto, Núñez-Núñez, García-Roig, & Proal-Nájera (2020)
	Milli-Q water	$UV/TiO_2/H_2O_2$	55	González-Burciaga et al. (2020)
	Milli-Q water	UV/H_2O_2	82	González-Burciaga et al. (2020)
	Milli-Q water	UV	No significant removal	Zhang et al. (2017b)
	Milli-Q water	UV/H_2O_2	88.3	Zhang et al. (2017b)
	Municipal wastewater	O_3	>95	Li et al. (2016)
	River	O_3	>99	Garcia-Ac et al. (2010)
	Urine	Electrolysis	>99	Kobayashi et al. (2012)
Paclitaxel	Laboratory grade water	Nanofiltration	>95	Cristóvão et al. (2019)
	Milli-Q water	Electrolysis	99.5	Hirose et al. (2005)
	Municipal wastewater	UV	100	Janssens et al. (2019)
	Municipal wastewater	UV/TiO_2	100	Janssens et al. (2019)
	Municipal wastewater	UV/H_2O_2	100	Janssens et al. (2019)
	Synthetic urine	Nanofiltration	>95	Cristóvão et al. (2019)
	Synthetic urine + Milli-Q water	UV	<99	Janssens et al. (2019)
	WWTP effluent	Nanofiltration	>99	Cristóvão et al. (2019)

Table 3.4 Remediation strategies used in the treatment of cytostatics with indication of the drug, the matrix tested, the treatment employed, and the removal efficiency (%). *na*, information not available; *WWTP*, wastewater treatment plant. *Continued*

Cytostatic	Matrix	Treatment employed	Removal %	Reference
Tamoxifen	Hospital effluent	O_3	>99	Ferre-Aracil et al. (2016)
	Hospital effluent	O_3/H_2O_2	>99	Ferre-Aracil et al. (2016)
	Hospital effluent 1	Biological	91	Ferrando-Climent et al. (2015)
	Hospital effluent 2	Biological	48	Ferrando-Climent et al. (2015)
	Milli-Q water	O_3	>99	Ferrando-Climent et al. (2017)
	Milli-Q water	O_3/UV	>99	Ferrando-Climent et al. (2017)
	Milli-Q water	O_3/H_2O_2	>99	Ferrando-Climent et al. (2017)
	Milli-Q water	UV	<90	Ferrando-Climent et al. (2017)
	Milli-Q water	UV/H_2O_2	<92	Ferrando-Climent et al. (2017)
	Municipal wastewater	O_3	>99	Li et al. (2016)
	Synthetic domestic wastewater	MBR	100	Wang et al. (2018)
	Synthetic wastewater	Biological	99	Ferrando-Climent et al. (2015)
Vincristine	Hospital and WWTP effluent	Biological	95	Franquet-Griell et al. (2017b)
	Milli-Q water	Electrolysis	99.8	Hirose et al. (2005)
	Milli-Q water	Hydrolysis	>85	Franquet-Griell et al. (2017b)
	Milli-Q water	UV	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	UV/H_2O_2	>99	Franquet-Griell et al. (2017b)
	Milli-Q water	Solar radiation	>99	Franquet-Griell et al. (2017b)

WWTP, *wastewater treatment plants.*

were not successful for all cytostatics tested. Franquet-Griell et al. (2017a) reported the rapid absorption of *megestrol* to sludge, also *gemcitabine* was rapidly biodegraded within 15 min and only 5% of *etoposide* was detected after 48 h. Nevertheless, *cyclophosphamide* and *ifosfamide* remained almost unchanged, with 85% of the initial concentration still present after 24 h, which demonstrates their recalcitrance to biodegradation. Moreover, considering that a WWTP activated sludge has a retention time between 2 and 8 h (which is much lower than the conditions used by the authors at the lab scale, i.e., 48 h), several compounds including *capecitabine*, *ifosfamide*, *cyclophosphamide*, *etoposide*, and *mycophenolic acid* will remain in concentrations between 10% and 80% of their initial concentrations, which demonstrates the need for further treatments (Franquet-Griell et al., 2017a). Also, in another study, activated sludge failed to efficiently eliminate *cyclophosphamide* and *ifosfamide*, with removal efficiencies of 59% and 35%, respectively (Česen et al., 2015). Further, no biodegradation was detected for the same cytostatic drugs under laboratory conditions with 24 h incubation (Buerge et al., 2006). *5-Fluouracil* and *doxorubicin* present in hospital wastewater when incubated with activated sludge failed to be eliminated, with removal efficiencies of <99% and >90%, respectively (Mahnik et al., 2007).

Biological treatments can also be performed by the release of a microorganism's enzymes into an extracellular medium such as laccase, lignin peroxidase, or manganese peroxidase, or through the intracellular enzymatic complexes, for example, cytochrome P450 (Castellet-Rovira et al., 2018; Ferrando-Climent et al., 2015; Haroune et al., 2014; Pereira et al., 2020; Singh, Saharan, Kumar, Gulati, & Kapoor, 2018; Yadav et al., 2021). The fungus *Trametes versicolor*, is one of the

most widely used microorganisms. Laccase released from *T. versicolor* efficiently removes *etoposide* (100% removal efficiency) from nonsterilized hospital wastewater (Ferrando-Climent et al., 2015). The cytostatic *doxorubicin* is also completely degraded by *T. versicolor* (Kelbert et al., 2020), which also showed efficiency in the removal of *tamoxifen* (99% removal efficiency) from a synthetic solution. On the other hand, *cyclophosphamide* and *ifosfamide* were resistant to biodegradation by *T. versicolor* (Ferrando-Climent et al., 2015). Moreover, further testing with *T. versicolor*, *T. hirsuta*, *Ganoderma lucidum*, *Irpex lacteus*, *Stropharia rugosoannulata*, *Gymnopilus luteofolius*, and *Agrocybe erebia* showed that none of the organisms were able to achieve removal efficiencies greater than 45% and 35%, respectively (Castellet-Rovira et al., 2018; Haroune et al., 2014).

Overall, the recalcitrant nature of some cytostatic drugs (such as cyclophosphamide and ifosfamide) compromises the degradation efficiency of the biological treatment (Castellet-Rovira et al., 2018; Česen et al., 2015). Furthermore, biological degradation in surface waters is not likely to occur, and elimination processes based on volatilization and sorption are irrelevant (Buerge et al., 2006). Another important limitation of the biological degradation approach is the fact that the feasibility of scaling up the processes is still unknown (Castellet-Rovira et al., 2018), which highlights the need for further research.

3.4.2 Physicochemical treatment

Physicochemical treatment comprises *membrane filtration processes* (Cristóvão et al., 2019; Verliefde et al., 2007; Wang et al., 2009) and *advanced oxidation processes (AOPs)*. The AOPS can be further subdivided into *UV-based photodegradation treatments* such as photolysis (UV) (Buerge et al., 2006; Franquet-Griell et al., 2017a; González-Burciaga et al., 2020; Governo et al., 2017; Guo et al., 2015; Janssens et al., 2019; Kovalova et al., 2013; Lin et al., 2013; Lutterbeck et al., 2016; Zhang & Lim, 2020; Zhang et al., 2017a); *photooxidation treatments* (UV-H_2O_2; UV-Cl, UV-$Na_2S_2O_8$) (Akbari & Adibzadeh, 2020; Franquet-Griell et al., 2017a; González-Burciaga et al., 2020; Janssens et al., 2019; Lee et al., 2021; Lester et al., 2011; Lutterbeck et al., 2015a; Lutterbeck et al., 2015b; Lutterbeck et al., 2015c; Tang et al., 2020; Zhang et al., 2017a; Zhang et al., 2017b) and *photocatalytic oxidation treatments* (UV-TiO_2, UV-$BiOCl_nBr_m$, UV-BiOClBr, UV-Fenton's reagent) (Borzyszkowska et al., 2016; Chatzimpaloglou et al., 2021; Cristea Ionut, Arcadie, Constantin Lucian, Constantin Mirela, & Nitoi, 2020; Governo, Santos, Alves, & Madeira, 2017; Janssens et al., 2019; Koltsakidou et al., 2017; Kovalova et al., 2013; Lai, Lin, & Lin, 2015; Lin & Lin, 2014; Lutterbeck et al., 2015c; Lutterbeck, Baginska, Machado, & Kümmerer, 2015a; Lutterbeck, Machado, & Kümmerer, 2015b; Mazierski et al., 2019; Ofiarska, Pieczyńska, Fiszka Borzyszkowska, Stepnowski, & Siedlecka, 2016; Osawa, Barrocas, Monteiro, Oliveira, & Florêncio, 2019; Wilczewska et al., 2019, 2021). AOPs also include *electron beam (EB) radiation treatments and nanoparticles* (Huo et al., 2020; Weng et al., 2018).

The *filtration processes* include the application of membranes or the combination of membranes with a bioreactor (*membrane bioreactor, MBR*). As previously mentioned, activated sludge alone is not able to remove some cytostatics effectively, namely cyclophosphamide, ifosfamide, and tamoxifen. So *MBR* emerges as an upgrade of the conventional sludge treatment for secondary wastewater (Zhang et al., 2013). An anaerobic osmotic *MBR* with 3.6 L of sludge was successfully used to remove *doxorubicin*, *epirubicin*, *methotrexate*, and *tamoxifen* from synthetic domestic wastewater with removal efficiencies of 100%. The same setup also allowed the efficient removal of *cyclophosphamide* with 95.6% of removal efficiency with a retention time of 60 days (Wang et al., 2018). Moreover, *5-fluorouracil*

and *doxorubicin* were very efficiently removed (*<99%*) from a 1000 L bioreactor filled with wastewater from the Vienna University Hospital, it having been determined that the elimination pathways of those drugs include biodegradation and adsorption, respectively (Mahnik et al., 2007). Another study reports the biodegradation of *cyclophosphamide* through *MBR* in a 20 L bioreactor filled with wastewater effluents, registering 60% removal efficiency and a sludge retention time of 20 days (Seira et al., 2016). Similarly, Delgado et al. (2011) using a 20 L MBR bioreactor registered a removal efficiency for *cyclophosphamide* of 80% with sludge retention of 50 days from domestic wastewater. Thus it seems that the longer the retention time, the better removal efficiencies are.

Nanofiltration is also able to eliminate *paclitaxel*, *etoposide*, *cyclophosphamide*, and *ifosfamide* from hospital wastewater with removal efficiencies of 99.9%, 98.7%, 90.4%, and 88.8%, respectively (Cristóvão et al., 2019). Moreover, a *cyclophosphamide* removal efficiency higher than 90% was obtained by Verliefde et al. (2007) through a nanofiltration system operating at low feed water recoveries (10%) and sampling from a WWTP intake. However, lower efficiencies for *cyclophosphamide* were also reported, namely 20%−40% from Milli-Q water and 60% from MBR effluent, while reverse osmosis reached >90% in the same water matrices (Wang et al., 2009).

UV-based photodegradation treatments were able to remove effectively (with percentages higher than 99%) *capecitabine, doxorubicin, etoposide, vincristine, and 5-fluorouracil* from Milli-Q water, municipal wastewater, or synthetic urine (Franquet-Griell et al., 2017a; Governo et al., 2017; Guo et al., 2015; Janssens et al., 2019; Lutterbeck et al., 2016). High removal efficiencies were also attained when *gemcitabine, irinotecan*, and *cyclophosphamide* drugs were spiked into an aqueous solution (Milli-Q water) and treated with UV (namely, 90%, 85%, and 80%; Franquet-Griell et al., 2017a). However, *cyclophosphamide*, *doxorubicin*, *methotrexate*, and *5-fluorouracil* were not removed from a real wastewater matrix using the same treatment (Zhang et al., 2017a; Zhang et al., 2017b). Similar results were obtained for *5-fluorouracil* for synthetic waters and river waters (Lin et al., 2013). And in the same line, neither *ifosfamide* nor *cyclophosphamide* was degraded when exposed to UV radiation in hospital wastewater (Kovalova et al., 2013).

Photooxidation treatments assemble *UV* with H_2O_2 and this setup has been successfully used for a large number of cytostatic drugs. High removal efficiencies (>99%) were obtained with this treatment for *5-fluorouracil, capecitabine, doxorubicin, gemcitabine, irinotecan*, and *vincristine* in Milli-Q water and *etoposide* and *paclitaxel* in municipal wastewater (Franquet-Griell et al., 2017a; Governo et al., 2017; Janssens et al., 2019; Lutterbeck et al., 2015c; Tang et al., 2020). In addition, an approximate value (92%) was registered by Ferrando-Climent et al. (2017) for *tamoxifen* in Milli-Q water. On the other hand, lower values were obtained for *cyclophosphamide* (e.g., 86% and 75%) in Milli-Q water (Lutterbeck et al., 2015b; Zhang et al., 2017b). However, when tested in a WWTP effluent, the value dropped to 64% (Zhang et al., 2017a).

UV radiation and persulfate activation (UV/persulfate) were also used for cytostatics removal. Akbari and Adibzadeh (2020) achieved a removal efficiency of *cyclophosphamide* from Milli-Q water higher than 99%. Also, $UV/NaHCO_3 + NaNO_3$ allowed a phototransformation of *5-fluorouracil* with efficiencies higher than 90% from both synthetic water and river water (Lin et al., 2013).

The photocatalytic UV/Fenton's process was demonstrated to be very effective for the removal of *5-fluorouracil and cyclophosphamide* with values higher than 95% for the removal of these cytostatic drugs from aqueous solutions (Milli-Q water) (Emídio et al., 2020; Koltsakidou et al., 2017; Lutterbeck et al., 2015c). In addition, by adding H_2O_2, the *UV/Fenton's/*H_2O_2 system was able to

fully degrade *5-fluorouracil* from a Milli-Q water solution, but for *cyclophosphamide* and *methotrexate* in aqueous solutions, removal efficiencies were lower than 85% (Governo et al., 2017; Lutterbeck et al., 2015a; Lutterbeck et al., 2015b).

The *photocatalytic UV/TiO_2 treatment* was successfully used in the degradation of *5-fluorouracil, cyclophosphamide, etoposide, ifosfamide, irinotecan*, and *paclitaxel* with removal efficiencies of 99%−100% for *5-fluorouracil* in Milli-Q (Borzyszkowska et al., 2016; Koltsakidou et al., 2017; Lin & Lin, 2014; Lutterbeck et al., 2015c; Mazierski et al., 2019); >90% for *cyclophosphamide* either from Milli-Q water or hospital/pharmacy wastewater (Lai et al., 2015; Lin & Lin, 2014; Lutterbeck et al., 2015b); 100% for *etoposide* from municipal wastewater (Janssens et al., 2019); >99% for *ifosfamide* from hospital/pharmacy wastewater (Lai et al., 2015); 99% for irinotecan from Milli-Q water (Chatzimpaloglou et al., 2021), and 100% for *paclitaxel* from municipal wastewater (Janssens et al., 2019). Nevertheless, *methotrexate* could not reach values above 70%, even when combined with H_2O_2, with the removal efficiency dropping to 55% in an aqueous solution (Milli-Q water; González-Burciaga et al., 2020; Lutterbeck et al., 2015a).

UV/Ag-TiO_2 uses Ag as an additional generator of superoxide radicals to degrade pollutants, allowed a removal efficiency of 99% for *cyclophosphamide* from Milli-Q water (Cristea Ionut et al., 2020).

UV/Ru-TNW is also a photocatalytic treatment that uses ruthenium-doped titanate nanowires as photocatalysts. Through this technique, Osawa et al. (2019) were able to reach a removal efficiency higher than 99% for *cyclophosphamide* and *ifosfamide* from a WWTP effluent (Osawa et al., 2019).

UV/$BiOCl_nBr_m$ and *UV/BiOClBr* uses the *photocatalytic activity* of bismuth-based semiconductors that were prepared from ionic liquids. Both had a removal efficiency higher than 99% for *5-fluorouracil* and *imatinib* drugs from Milli-Q water (Wilczewska et al., 2019; Wilczewska et al., 2021). However, *cyclophosphamide* removal was lower than 80% (Wilczewska et al., 2019).

Electron beam (EB) radiation treatments and nanoparticles were less investigated. Nevertheless, an *EB* based on radiolytic degradation was attempted by Huo et al. (2020), which resulted in the total degradation of *capecitabine* from an aqueous solution. *Nanoparticles* (Fe_3O_4) synthesized and prepared for the removal of cytostatic drugs were used to remove *doxorubicin*. Removal efficiencies of 80.2% from aqueous solutions and 73.6% from real wastewater samples were achieved (Weng et al., 2018).

Despite the high removal efficiencies obtained, the physiochemical treatment can, in a generalized manner, produce toxic metabolites. Increased toxicity for *capecitabine* was reported even when higher values of UV were used in treatments (Guo et al., 2015). Also, *cyclophosphamide* and *ifosfamide* photocatalytic treatment (UV/TiO_2) led to higher toxicity of the treated effluent (Lai et al., 2015). Furthermore, those cytostatic drugs (cyclophosphamide and ifosfamide) presented a recalcitrant nature to UV, which makes necessary further treatment processes (AOPs) such as UV/H_2O_2 to completely remove them (Franquet-Griell et al., 2017a). Also, membranes are susceptible to fouling through the retention and adsorption of organic matter (Cristóvão et al., 2019), which compromises the removal efficiency.

3.4.3 Chemical treatment

Chemical treatments comprise oxidizing agents that generate hypochlorite (Yadav et al., 2021; Zhang & Lim, 2020). These include, for example, NaOCl, $NaMnO_4$, $KMnO_4$, H_2O_2 and Fenton's reagent, often used in electrolysis, and ozonation (Barışçı et al., 2018; Barzan et al., 2019; Chen

et al., 2019; Crisnic et al., 2020; Fabiańska et al., 2015; Ferreira Garcia et al., 2020; Garcia-Ac et al., 2010; Hansel et al., 1996; Hernández et al., 2008; Hirose et al., 2005; Kobayashi et al., 2012; Li et al., 2016; Lin et al., 2015; Ochoa-Chavez et al., 2018; Pieczyńska et al., 2019; Siedlecka et al., 2018; Xu et al., 2020).

Ozonation (O_3) treatment was successfully used for different cytostatics. Removal efficiencies around 100% for *5-Fluorouracil, capecitabine, and tamoxifen* were obtained either from Milli-Q or real effluent (WWTP, hospital or municipal). Furthermore, the removal efficiency does not drop below 98.4% (Chen et al., 2019; Ferrando-Climent et al., 2017; Ferre-Aracil et al., 2016; Li et al., 2016; Lin & Lin, 2014; Tang et al., 2020). *Cyclophosphamide* in both in Milli-Q water and real samples (hospital and municipal effluents) registered very wide removal efficiencies between 57% and 99% (Fernández et al., 2010; Ferre-Aracil et al., 2016; Kovalova et al., 2013; Li et al., 2016; Li, Dao, Nagao, & Yoshino, 2014). *Erlotinib*, *etoposide*, *ifosfamide*, and *imatinib* were degraded only from real samples such as hospital effluents, municipal and pharmacy wastewater, and rivers, with removal efficiencies higher than 99% (Ferre-Aracil et al., 2016; Lin & Lin, 2014) except two studies in which *ifosfamide* removal efficiencies ranged from 20% to 75% (Kovalova et al., 2013; Li et al., 2016). High removal efficiencies were obtained for *methotrexate* in Milli-Q water solutions, hospital and municipal wastewaters and river samples with values of 80%, >99%, >95%, and >99%, respectively (Ferre-Aracil et al., 2016; Garcia-Ac et al., 2010; Li et al., 2016; Somensi et al., 2012). However, ozonation was only able to remove *doxorubicin* from Milli-Q water with comparatively smaller removal efficiencies of 40% (Somensi et al., 2012).

The combination of *ozonation (O_3)* with *UV, H_2O_2*, or *ultrasound (US)* is possible and removal efficiencies above 99% were obtain either from *O_3/UV, O_3/H_2O_2, O_3/US, O_3/UV/H_2O_2* or even *biological/O_3/UV/H_2O_2* (Česen et al., 2015; Fernández et al., 2010; Ferrando-Climent et al., 2017; Ferre-Aracil et al., 2016) for *capecitabine, cyclophosphamide, erlotinib, etoposide, ifosfamide, imatinib, methotrexate*, and *tamoxifen*. However, despite these high efficiencies, the gain in improvement is not significant (Česen et al., 2015; Kovalova et al., 2013; Somensi et al., 2012).

Electrochemical treatment demonstrated to be effective in the removal of *5-fluorouracil*, *cyclophosphamide, doxorubicin, epirubicin, ifosfamide, methotrexate, paclitaxel*, and *vincristine* from Milli-Q water with efficiencies higher than 95% (Barışçı et al., 2018; Crisnic et al., 2020; Fabiańska et al., 2015; Ferreira Garcia et al., 2020; Hansel et al., 1996; Hirose et al., 2005; Kobayashi et al., 2012; Pieczyńska et al., 2019; Siedlecka et al., 2018; Tang et al., 2020). Siedlecka et al. (2018) used electrochemical oxidation with a boron-doped diamond (BDD) electrode and achieved degradations higher than 95% for *5-fluorouracil, ifosfamide, cyclophosphamide, imatinib*, and *methotrexate* from an aqueous solution. With the same method, a removal efficiency higher than 95% was obtained for *cyclophosphamide* and *ifosfamide* was almost fully degraded (<99%; Fabiańska et al., 2015). Also, *doxorubicin* in Milli-Q water solution registered a removal efficiency higher than 99.9% when using BDD electrochemical oxidation (Ferreira Garcia et al., 2020). However, in another study, only 77% of removal efficiency was registered for *5-fluorouracil* in Milli-Q water (Ochoa-Chavez et al., 2018). A similar efficiency was achieved for *5-fluorouracil* when a recirculating split-flow batch reactor was applied, but higher values (>95%) were registered for *cyclophosphamide* and *ifosfamide* (Pieczyńska et al., 2019). *Capecitabine* in aqueous solution (Milli-Q water) was successfully degraded (removal efficiency 93%) with a Ti/SnO_2-Sb/Ce-PbO_2 anode (Xu et al., 2020). Also, similar efficiency values were obtained by Barışçı et al. (2018) when using a Ti/IrO_2-RuO_2 electrode (85%) and by Tang et al. (2020) with a Ti/SnO_2-Sb/Ce-PbO_2 electrode (>98%), from the

same medium. The electrochemical treatment involving two platinum electrodes was able to almost fully remove *epirubicin* (<99%), *methotrexate* (98%), *paclitaxel* (99.5%), and *vincristine* (99.8%), with lower values registered for *cisplatin* (81.5%) and *irinotecan* (72.1%), all treatments from Milli-Q water (Hirose et al., 2005). Barzan et al. (2019) obtained a full degradation of *cyclophosphamide* from synthetic wastewater, building an asymmetric current density electrochemical reactor with chlorine reactive species. An asymmetric current density laboratory reactor involving chlorine-reactive species efficiently removed (<99%) *doxorubicin* from Milli-Q water (Crisnic et al., 2020). Kobayashi et al. (2012) tested the removal efficiency of a platinum-based iridium oxide composite electrode applied to *methotrexate* in urine, and the values for the tested parameter were higher than 99%.

Chemical treatment involving *sodium hypochlorite (NaOCl)* as an alkylating agent to remove *cyclophosphamide* and *ifosfamide* allowed removal efficiencies higher than 98% and 99%, respectively from Milli-Q water (Hansel et al., 1996).

Overall, the described chemical treatments present a high removal efficiency. However, they exhibit some important limitations. *UV/O_3* treatment of *tamoxifen*, for example, generated much more toxic compounds than *tamoxifen* itself (Ferrando-Climent et al., 2017). Also, the degradation of *cyclophosphamide*, *ifosfamide*, and *5-fluorouracil* by *ozonation* (O_3) increased the toxicity of the treated water to higher values than the untreated sample (Lin et al., 2015). Moreover, *ozonation* (O_3) treatment energy costs, despite being variable with treatment conditions, are generally very high and should be taken into consideration when considering scaling up this process (Ferre-Aracil et al., 2016).

3.5 Concluding remarks and future trends

The release of cytostatic drugs into the environment is an important environmental and health problem. Since the consumption of these drugs will increase in the future, the efficient management of their release into the environment is particularly important. WWTPs play a crucial role in preventing the contamination of water bodies by the retention or elimination of these compounds. However, the occurrence of cytostatic drugs in natural waters has been reported in the nanograms to micrograms per liter range, which demonstrates that the current strategies are not being effective. This reinforces the idea that, despite current treatment strategies are contributing to reducing the levels of cytostatic drugs in the environment, full degradation is not being accomplished. To achieve complete removal of those compounds, technologies that are already developed and available, some of which, such as MBR, UV/H_2O_2, UV/TiO_2, UV/Fentoń's, O_3, and O_3/H_2O_2, achieve high removal efficiencies, will have to be adopted and implemented. However, those treatments still present drawbacks, namely the production of toxic subproducts/metabolites. In addition, scale-up readiness is still not achieved, mainly due to the high costs of these technologies. Future cost-effective technologies that can easily be implemented in real WWTP are necessary.

Acknowledgments

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UIDB/50011/2020 & UIDP/50011/2020, financed by national funds through the Portuguese Foundation for Science and Technology/

MCTES and project UIDB/04923/2020 —Comprehensive Health Research Centre (CHCR) financed by the Portuguese Foundation for Science and Technology, IP. This work was financially supported by the project IonCytDevice (POCI-01−0145-FEDER-031106, PTCD/BTA-BTA/31106/2017) funded by FEDER, through COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTE).

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