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Review

Pharmaceutical compounds used in the COVID-19 pandemic: A review of their presence in water and treatment techniques for their elimination

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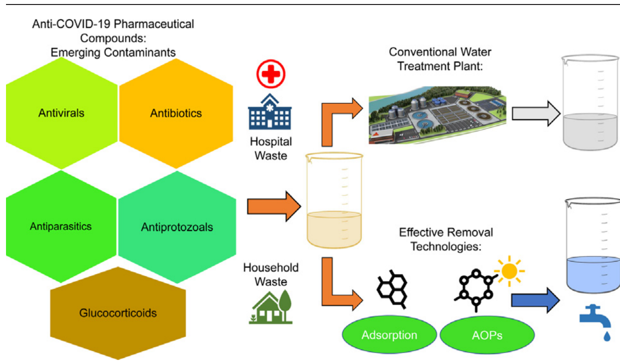
HIGHLIGHTS

- The presence and elimination of anti-COVID-19 drugs in water are summarized.
- Drug concentrations before and during the pandemic are contrasted.
- Several anti-COVID-19 drugs are not eliminated in water treatment plants.
- AOPs and adsorption removed more than 80% of anti-COVID-19 drugs.
- New trends focus on low-cost materials, energy optimization, and hybrid systems.

GRAPHICAL ABSTRACT



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ABSTRACT

During the COVID-19 pandemic, high consumption of antivirals, antibiotics, antiparasitics, antiprotozoals, and glucocorticoids used in the treatment of this virus has been reported. Conventional treatment systems fail to efficiently remove these contaminants from water, becoming an emerging concern from the environmental field. Therefore, the objective of the present work is to address the current state of the literature on the presence and removal processes of these drugs from water bodies. It was found that the concentration of most of the drugs used in the treatment of COVID-19 increased during the pandemic in water bodies. Before the pandemic, Azithromycin concentrations in surface waters were reported to be in the order of 4.3 ng L^{-1}, and during the pandemic, they increased up to 935 ng L^{-1}. Laboratory scale studies conclude that adsorption and advanced oxidation processes (AOPs) can be effective in the removal of these drugs. Up to more than 80% removal of Azithromycin, Chloroquine, Ivermectin, and Dexamethasone in aqueous solutions have been reported using these processes. Pilot-scale tests achieved 100% removal of Azithromycin from hospital wastewater by adsorption with powdered activated carbon. At full scale, treatment plants supplemented with ozonation and artificial wetlands removed all Favipiravir and Azithromycin, respectively. It should be noted that hybrid technologies can improve removal rates, process kinetics, and treatment cost. Consequently, the development of new materials that can act synergistically in technically and economically sustainable treatments is required.

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Contents

1. Introduction

The presence of pharmaceutical compounds and their metabolites in water has been defined as an environmental problem for several years (Kümmerer, 2009; Rivera-Utrilla et al., 2013; Tijani et al., 2016). However, the massive consumption of some drugs during the COVID-19 pandemic has increased the discharge of pharmacological residues in different aqueous matrices (Saadat et al., 2020). In this sense, antiviral drugs, show increases higher than 70% of their concentration in urban wastewater compared before (Ibáñez et al., 2017) and during the pandemic (Kuroda et al., 2021). Likewise, the concentration of Azithromycin (antibiotic) in domestic wastewater during the pandemic (Chen et al., 2021) is predicted to be 217 times higher than that detected in previous years (Zhou et al., 2019). Scientific interest in this type of emerging contaminants is focused on advancing analytical methods for their detection at concentrations in the $\mu g\ L^{-1}$ range (Kanakaraju et al., 2018; Majumder et al., 2021).

Quadra et al. (2017) and Klemeš et al. (2020) expose that the presence of these pharmaceuticals in water bodies is since wastewater treatment plants (WWTPs) do not remove them efficiently. Moreover, these pollutants are persistent and exhibit low levels of biodegradation (Mirzaei et al., 2018; Xiang et al., 2018). Therefore, the implementation of technologies that guarantee the removal of these pollutants with a focus on technical, economic, and environmental sustainability is required (Verlicchi et al., 2012; Svendsen et al., 2020). The technologies that have been evaluated for drug degradation include biological, physical, and chemical processes. Nanofiltration has been reported to be employed in the removal of anti-inflammatory drugs with yields above 85% (Radjenović et al., 2008). Whereas Naproxen and Diclofenac were removed from drinking water (>95%) by reverse osmosis (Heberer, 2002).

In the case of anti-COVID-19 drugs, it has been found that moving bed biofilm reactors (MBR) removed 100% of azithromycin present in WWTP effluents (Tang et al., 2021). Adsorption applying clay removed Ivermectin from aqueous solutions (>80%) (Olu-Owolabi et al., 2021). On the other hand, advanced oxidation processes (AOPs) have been studied in the removal of these pollutants in aqueous solutions at a laboratory scale. For example, electro-Fenton oxidation degraded 100% of Chloroquine (Midassi et al., 2020). Photocatalysis with TiO_2 degraded 98% of Ivermectin (Rath et al., 2016). Oxidation with Fe(VI) degraded 100% of Azithromycin (Talaiekhozani et al., 2020). These reports demonstrate that AOPs offer high yields in the remediation of these drugs. However, their main disadvantages are the costs associated with energy consumption and the acquisition of inputs for their implementation. Therefore, hybrid systems are a promising alternative in the removal of these drugs (Azuma et al., 2017; Racar et al., 2020). This is because they present high performances (100%), lower operation times, and overcome the technical-economic limitations of each technology (Ahmed et al., 2021; Patel et al., 2019). The development of low-cost nanomaterials, which have demonstrated multifunctional behavior in drug degradation, is also highlighted (Bolan et al., 2021; Kumar et al., 2020b; Nasrollahzadeh et al., 2021; Zhao et al., 2018).

It is evident from the peer-reviewed literature databases that there are many studies evaluating the occurrence and removal of pharmaceuticals in water and wastewater. However, there is no comprehensive review covering the occurrence of anti-COVID-19 drugs in water and wastewater before/during the pandemic, and also comparing the technical and economic aspects of the technologies for their removal. Therefore, the objective of the present work is to address the current state of the literature concerning the presence and removal of these drugs in water bodies. It also discusses the efficiency of the proposed technologies, their operating parameters, the cost of treatment, the combination of traditional technologies with advanced processes, and future perspectives.

2. Methodology

The selection of literature consulted was made through the Scopus database. Information was also obtained on policies for monitoring water quality proposed by the European Commission and pharmacological recommendations for patients with COVID-19 from the World Health Organization (WHO).

According to information from the main scientific literature database (Scopus, 2021), as of November 2021, more than 1800 papers have been published that analyzed the presence and elimination of drugs in aqueous matrices. However, the present literature review focused on papers focused on drugs used by SARS-CoV-2 patients. The selection of drugs was developed through information disseminated by the WHO and studies that addressed the pharmacological treatment of COVID-19. Accordingly, the search included the keywords: COVID-19, SARS-CoV-2, Drugs, Antivirals, Antibiotics, Antiparasitics, Antiprotozoals, Glucocorticoids, Favipiravir, Lopinavir, Ribavirin, Remdesivir, Azithromycin, Ivermectin, Chloroquine, Hydroxychloroquine, Dexamethasone, Water, Wastewater, Presence, Occurrence, Degradation, Elimination, Removal, and Treatment. Individual searches were performed for each selected drug.

Finally, all papers not related to the focus and objectives of the review were excluded. For this purpose, the titles, abstracts, and keywords were reviewed. This made it possible to verify whether the papers obtained covered the presence of the drugs in aquatic environments or their elimination by water and wastewater treatment techniques. In total, 171 peer-reviewed scientific papers were cited, of which 168 were published in journals indexed in Scopus.

3. Presence of drugs used in the treatment of COVID-19 in hydric matrices

In accordance with the recommendations proposed by the WHO and organizations governing state health systems, the drugs mostly used in the treatment of COVID-19 are Favipiravir (Lou et al., 2021; Pilkington et al., 2020), Remdesivir (Antinori et al., 2020; Wang et al., 2020b), Lopinavir-ritonavir (Cao et al., 2020; Choy et al., 2020), Ribavirin (Khalili et al., 2020; Tong et al., 2020), Hydroxychloroquine (Cortegiani et al., 2020; Liu et al., 2020), Chloroquine (Cortegiani et al., 2020; Wang et al., 2020b), Ivermectin (Caly et al., 2020; Venkatasubbaiah et al., 2020), Azithromycin (Gautret et al., 2020; Million et al., 2020) and Dexamethasone (Sharun et al., 2020; Villar et al., 2020). The latter two are those most frequently addressed in terms of their presence in water bodies and their impact on the environment, as shown in Table 1. Concerning the other drugs, there is little literature on their persistence in aqueous effluents. Despite this, it is known that conventional treatments are not capable of eliminating these drugs from wastewater and, consequently, they are discharged into aquatic currents.

Fig. 1 demonstrates the presence of the main drugs used in COVID-19 drug therapy in both surface water and domestic wastewater. It shows that the concentration of these contaminants varies substantially depending on the type of water and the period in which the detection was performed (before and during the COVID-19 pandemic). In any case, it is important to discuss the changes that have occurred as a result of the pandemic in the identification of these drugs in aquatic environments.

3.1. Antivirals

Antivirals have been used as therapeutic agents in the treatment of COVID-19 owing to their ability to decrease the viral load of several diseases (Abd El-Aziz and Stockand, 2020; Saha et al., 2020; Serafin et al., 2020).

Kuroda et al. (2021) evaluated the presence of such drugs in waters. The authors estimated the fate, presence, and risk of these therapeutics using mathematical structure-activity relationship models. They concluded that water treated through urban WWTP could contain high concentrations of these drugs and their metabolites (4231 ng L^{-1} of Favipiravir, 730 ng L^{-1} of Lopinavir, 7402 ng L^{-1} of Ribavirin, 319 ng L^{-1} of Remdesivir). Ecotoxicological risk in surface waters was also predicted, with reports of high risks for Favipiravir, Lopinavir, and Ritonavir, and medium-range for Remdesivir and Ribavirin.

3.1.1. Favipiravir

3.1.1.1. Surface water. Favipiravir is an antiviral drug used to combat influenza owing to its influenza virus RNA polymerase inhibitory properties (Madelain et al., 2020; Tarbet et al., 2012). Therefore, their consumption potentially increases in those seasons in which climatic conditions promote the development of these diseases. Azuma et al. (2013, 2017) reported that this drug has been detected in surface water (Japan) during the influenza season. The highest peaks of influenza cases throughout the year were detected during February and March (2016). The concentration of this drug consequently went from being undetectable in the previous months to concentrations in the range of 40–60 ng L^{-1} for the influenza period.

3.1.1.2. Domestic wastewater. The use of this drug has been promoted during the COVID-19 pandemic to mitigate the high mortality rates caused by the virus. The Favipiravir has been associated with the clinical improvement of patients hospitalized as a result of COVID-19 and a 30% decrease in mortality (Hassanipour et al., 2021). During the current pandemic, the average dose is 1600 mg day^{-1} and the predicted environmental concentration of this drug is 64 ng L^{-1} and that of its main metabolite (T705M1) is 4248 ng L^{-1} in domestic wastewater. Therefore, it is estimated that this contaminant will exceed the concentrations reported in previous periods and cause a high ecotoxicological risk in water (Kuroda et al., 2021).

3.1.2. Lopinavir

3.1.2.1. Surface water. Lopinavir is an antiretroviral with a protease inhibitory capacity and is used as a subtherapeutic along with the drugs Ritonavir and Lamivudine in antiretroviral therapies. For example, HIV-infected patients and currently in the treatment of patients with COVID-19 (Choy et al., 2020). Concerning its presence in water bodies, Wood et al. (2015) determined a maximum concentration of 305 ng L^{-1} in surface waters.

3.1.2.2. Domestic wastewater. The presence of Lopinavir was also detected in domestic wastewater (South Africa), specifically in the range of 1200–1400 ng L^{-1} (Abafe et al., 2018). Although there is evidence of the consumption of this drug as a therapeutic agent against COVID-19, higher consumption of Lopinavir and other antivirals used in the combination treatment of HIV is reported in countries with high HIV-positive rates. In countries such as South Africa, it is estimated that 326 tons of these drugs enter urban WWTPs per year (Abafe et al., 2018).

Additionally, the average dose received by coronavirus patients is currently 800 mg day^{-1}, which generates an expected environmental concentration of 880 ng L^{-1} of the parent compound and 2840 ng L^{-1} of its major metabolites in domestic wastewater (Kuroda et al., 2021).

3.1.3. Ribavirin

3.1.3.1. Surface water. Ribavirin is another pharmacological agent suggested in the treatment of patients with COVID-19 (Elfiky, 2020; Frediansyah et al., 2021). It is a nucleoside analog used in the treatment of viral infections that can, in combination with Lopinavir and Ritonavir, reduce the mortality rate of patients with SARS-CoV (Yousefi et al., 2020). Chen et al. (2021) established that the frequency of detection and

Table 1
Presence of anti-COVID-19 drugs in aqueous matrices before and during the pandemic.

Therapeutic agents	Pharmaceutical compounds	Before the pandemic			During the pandemic		
		Concentration	Type of water	Reference	Concentration	Type of water	Reference
Antivirals	Favipiravir	40–60 ng L^{-1}	Surface water-Japan	Azuma et al. (2017)	64 ng L^{-1a}	Domestic wastewater	Kuroda et al. (2021)
	Lopinavir	305 ng L^{-1}	Surface water-South Africa	Wood et al. (2015)	880 ng L^{-1a}	Domestic wastewater	Kuroda et al. (2021)
		1200–1400 ng L^{-1}	Domestic wastewater-South Africa	Abafe et al. (2018)			
	Ribavirin	ND	Domestic wastewater-Germany	Prasse et al. (2010)	52.2 ng L^{-1}	Surface water-China	Chen et al. (2021)
		ND	Domestic wastewater-China	Peng et al. (2014)	2102 ng L^{-1a}	Domestic wastewater	Kuroda et al. (2021)
	Remdesivir	–	–	–	55 ng L^{-1a}	Domestic wastewater	Kuroda et al. (2021)
Antibiotics	Azithromycin	24 ng g^{-1}	Surface water sediment-Spain	Osorio et al. (2016)	935 ng L^{-1}	Surface water-China	Chen et al. (2021)
		3 ng L^{-1}	Surface water-Spain	Prieto-Rodríguez et al. (2012)			
		4.3 ng L^{-1}	Surface water-China	Zhou et al. (2019)			
		257 ng L^{-1}	Groundwater-Spain	López-Serna et al. (2013)			
		18.3 μg L^{-1}	Domestic wastewater-United States	Bhandari et al. (2008)			
		3.25 μg L^{-1}	Treated water through urban WWTP-United States	Bhandari et al. (2008)			
		163 μg L^{-1}	Hospital wastewater-Turkey	Aydin et al. (2019)			
Antiparasitics	Ivermectin	93 ng L^{-1}	Surface water-Spain	Rodriguez-Gil et al. (2013)	1500 ng L^{-1a}	Treated water through urban WWTP	Tarazona et al. (2021)
		5–20 ng L^{-1}	Treated water through DWTP-France	Charuaud et al. (2019)			
Antiprotozoals	Chloroquine	110 ng L^{-1}	Surface water-Nigeria	Olatunde et al. (2014)	32 ng L^{-1a}	Surface water	Kuroda et al. (2021)
		5000 ng L^{-1}	Groundwater-Nigeria	Olatunde et al. (2014)	857 ng L^{-1a}	Domestic wastewater	Kuroda et al. (2021)
	Hydroxychloroquine	–	–	–	78.3 ng L^{-1a}	Surface water	Kuroda et al. (2021)
					833 ng L^{-1a}	Domestic wastewater	Kuroda et al. (2021)
Glucocorticoids	Dexamethasone	0.07 ng L^{-1}	Surface water-Hungary	Tölgyesi et al. (2010)	55.6 ng L^{-1a}	Surface water	Desgens-Martin and Keller (2021)
		0.73 ng L^{-1}	Surface water-Malaysia	Praveena et al. (2018)	0.29 ng L^{-1a}	Surface water	Kuroda et al. (2021)
		0.11 ng L^{-1}	Surface water-China	Chang et al. (2007)	3 ng L^{-1a}	Domestic Wastewater	Kuroda et al. (2021)
		0.33 ng L^{-1}	Surface water-China	Gong et al. (2019)			
		ND	Surface water-United States	Sengupta et al. (2014)			
		0.02–0.09 ng L^{-1}	Treated water through urban WWTP-China	Chang et al. (2007)			
		390 ng L^{-1}	Treated water through urban WWTP-China	Chang et al. (2009)			

ND: not detected.
DWTP: drinking water treatment plant.
WWTP: wastewater treatment plant.
[a] Data obtained from predictions with mathematical models.

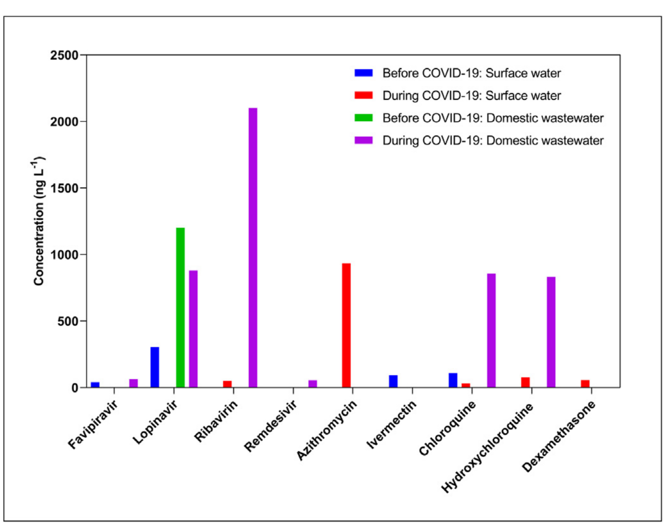

Fig. 1. Concentration of major anti-COVID-19 drugs in surface water and domestic wastewater before and during the pandemic.

concentration of Ribavirin in surface waters (China) increased during the COVID-19 pandemic. In June 2020, the concentration of this drug reached 52.2 ng L^{-1} in the surface water, this being an increase as regards historical reports of this contaminant.

3.1.3.2. Domestic wastewater. The concentration of Ribavirin remained below quantification limits in domestic wastewater from countries such as China and Germany (Peng et al., 2014; Prasse et al., 2010). This suggests that this drug may be found even in relatively low concentrations in urban wastewater, regardless of the region where the study was conducted.

In addition, Kuroda et al. (2021) have estimated a predicted environmental concentration of 2102 ng L^{-1} in domestic wastewater during the pandemic. Based on the average dose of Ribavirin recommended for COVID-19 patients (2473 mg day^{-1}), the concentration of the most representative metabolite of Ribavirin ($TCONH_2$) in wastewater is estimated to be 5440 ng L^{-1}.

3.1.4. Remdesivir

3.1.4.1. Surface water. Remdesivir is a broad-spectrum antiviral that can inhibit viral RNA polymerase (Eastman et al., 2020). The stability of this anti-

COVID-19 drug against natural photodegradation in surface waters (Nippes et al., 2021), signifies that its most representative metabolites may be present in various water sources. E.g., concentrations ranging from 430 to 2120 ng L^{-1} have been estimated in surface waters (Kumar et al., 2020a).

3.1.4.2. Domestic wastewater. Concerning its occurrence in water bodies, it has been reported that a concentration of 55 ng L^{-1} is expected in domestic wastewater as a result of its consumption during the pandemic, with an average recommended dose of 110 mg day^{-1} (Kuroda et al., 2021).

3.2. Antibiotics

Some clinical studies have shown that antibiotics with antibacterial properties can combat the severe respiratory syndrome that occurs in patients infected with COVID-19 (Oldenburg and Doan, 2020). Within this group, that which has been reported to the greatest extent is Azithromycin owing to the anti-inflammatory characteristics that allow it to act favorably against the inflammation caused by bacterial lipopolysaccharides in pneumonia (Mirtaleb et al., 2021; Stellari et al., 2014).

While the COVID-19 pandemic led to an increase in Azithromycin consumption, this drug had already been widely detected in water samples from various sources in previous years. The European Union has consequently established two watch lists of substances for water monitoring (Decision (EU) 2015/495 and Decision (EU) 2018/840) (European Commission, 2015), among which Azithromycin was included (Ivanová et al., 2018; Petrie et al., 2016).

3.2.1. Azithromycin

3.2.1.1. Surface water. Azithromycin is a broad-spectrum antibiotic belonging to the macrolide group that acts against several Gram-positive and Gram-negative bacteria, which has promoted its use in the treatment of several respiratory diseases (Oldenburg and Doan, 2020). Azithromycin is a drug that, in addition to its antibacterial activity, has proven to have antiviral and immunomodulatory activities that are of interest in viral infections (Parnham et al., 2014), including COVID-19 (Echeverría-Esnal et al., 2021). However, its presence has been detected in environmental matrices, reflecting the need to develop treatment alternatives that will allow its removal from water (Cano et al., 2020).

In a study conducted by Osorio et al. (2016), surface water sediment (Spain) was analyzed, and it was determined that Azithromycin is among the most widespread and highly concentrated pharmaceutical compounds. It ranks first in the characterization of the samples, with a concentration of 24 ng g^{-1}, followed by Ibuprofen (13 ng g^{-1}), Codeine (12 ng g^{-1}), and Tetracycline (6 ng g^{-1}).

Moreover, the surface water of Spain has been evaluated using samples taken between 2017 and 2019. Quantification frequencies of 91% were identified for Azithromycin, 82% for Imidacloprid, 80% for Clarithromycin, and 78% for Diclofenac (Solaun et al., 2021). Likewise, López-Serna et al. (2011) and Prieto-Rodríguez et al. (2012) evaluated the quality of Spanish surface waters and obtained similar reports on the detection of this contaminant. The results reflect a concentration of 3 ng L^{-1}, respectively.

There has been a significant increase in the consumption of this drug in the context of the current COVID-19 pandemic and, consequently, an increased presence in water effluents. Zhou et al. (2019) report in a study conducted in surface water in Wuhan (China) before the pandemic, a maximum Azithromycin concentration of 4.3 ng L^{-1} and detection frequency of 11.9%. Comparing these results with those reported by Chen et al. (2021) during June 2020, where they reached values of 935 ng L^{-1} with a detection frequency of 94.7%, an 80-fold increase in the concentration of this drug in the surface water is evident. Coinciding with the highest peak of infection and consequently higher consumption.

3.2.1.2. Groundwater. Azithromycin has also been detected in groundwater (Spain) in the order of 257 ng L^{-1} in studies reported by López-Serna et al. (2013). Pharmacological contamination of these water bodies may be related to the transfer of chemical waste from surface water and domestic wastewater with high levels of contamination.

3.2.1.3. Domestic wastewater. Bhandari et al. (2008) concluded that the concentration of Azithromycin in domestic wastewater from the United States is in the order of 18.3 μg L^{-1}, while in water treated through urban WWTPs of the same locality it is 3.25 μg L^{-1}. It is shown that some urban WWTPs can partially reduce the concentration of Azithromycin in domestic wastewater. However, the results are insufficient to guarantee that these residues will not affect water quality in the long term.

3.2.1.4. Hospital wastewater. In the case of hospital wastewater, Azithromycin concentrations equivalent to 163 μg L^{-1} have been detected (Aydin et al., 2019). Hospitals generate clinical waste that can easily enter urban wastewater discharge systems. Therefore, this wastewater should be comprehensively managed before it is mixed with other wastes of lesser environmental impact.

3.3. Antiparasitics

It has been reported that some antiparasitic drugs with anthelmintic activity can inhibit the replication of SARS-CoV-2 (Chaccour et al., 2020). One of the drugs in this group is Ivermectin, which is a macrocyclic lactone that has been used in the treatment of human and animal parasites such as scabies and ticks since the 1980s (Olu-Owolabi et al., 2021). Moreover, this drug is tolerated by humans and animals as regards a wide spectrum of pathologies, but recent studies suggest that it could be used as an anticancer and antiviral, especially against COVID-19 respiratory syndrome (Heidary and Gharebaghi, 2020; Rizzo, 2020).

3.3.1. Ivermectin

3.3.1.1. Surface water. This is a widely used drug that can persist in aqueous environments, soil, and food (Bai and Ogbourne, 2016; Jensen and Scott-Fordsmand, 2012). This is because, it does not undergo metabolic transformation processes in the organisms that consume it and is generally excreted without changes in its chemical composition, thus giving it stability in the environment. Its environmental effects have, therefore, been more extensively investigated than those of other drugs. Studies on the environmental fate of Ivermectin have shown that this drug can persist in sediments, in addition to accumulating in various aquatic organisms, thus leading to considerable levels of toxicity (Mesa et al., 2017, 2020). Before the coronavirus pandemic, Ivermectin had already been detected in several aquatic environments. In surface waters of Spain, the presence of this drug was counted in 0.093 μg L^{-1} (Rodriguez-Gil et al., 2013).

3.3.1.2. Treated water through DWTP. Charuaud et al. (2019) investigated the environmental impact of pharmaceutical waste in water resources, determining that treated water through DWTPs in France may contain concentrations of Ivermectin ranging from 5 to 20 ng L^{-1}.

3.3.1.3. Treated water through urban WWTP. The pandemic had an impact on the consumption of this drug and this has led to a consequent concern about the accumulation of Ivermectin in water. Essid et al. (2020) conclude that there has been a high discharge of Ivermectin into the WWTPs as a result of the consumption of this drug in three countries that have become epicenters of the pandemic: Spain, Italy, and France.

Similarly, Tarazona et al. (2021) estimate a concentration of 1500 ng L^{-1} of Ivermectin in the treated water through urban WWTP. A greater presence of this contaminant in aqueous matrices is, therefore, expected, constituting an environmental problem of high ecological risk that has increased owing to the high consumption registered during the pandemic.

3.4. Antiprotozoals

Some of the drugs that have been most commonly used to treat SARS-CoV-2 are Chloroquine and Hydroxychloroquine (Liu et al., 2020). These antiprotozoal agents have been described as persistent, bioaccumulative, and hazardous to aquatic organisms (Daughton, 2014; Ramesh et al., 2018; Zurita et al., 2005). It is estimated that large amounts of wastewater contaminated with these drugs will be discharged in the coming years owing to the licensed use of these drugs in patients infected with COVID-19. However, little research reports the disposal and elimination of Chloroquine in water. Most studies on Hydroxychloroquine, meanwhile, focus on the stability of the compound and its metabolites in water (Coelho et al., 2017; Ahmad et al., 2016). This means that the literature concerning its presence and occurrence in aqueous matrices is still incipient.

3.4.1. Chloroquine

3.4.1.1. Surface water. The presence of Chloroquine in surface water samples in Nigeria was evaluated before the pandemic by Olatunde et al. (2014). A concentration of 110 ng L^{-1} is reported in the study performed by high-performance liquid chromatography. A model proposed by Kuroda et al. (2021) shows that the predicted concentration of this contaminant during the pandemic of COVID-19 in the surface water is on the order of 32 ng L^{-1}. Kuroda et al. (2021) reported that concentrations during the pandemic could be lower than those recorded in previous periods. However, it should be noted that this is because Kuroda's estimate predicts that Chloroquine removal in WWTPs will be very effective.

3.4.1.2. Groundwater. Chloroquine concentration of 5000 ng L^{-1} was reported in groundwater from an urbanized area in Nigeria (Olatunde et al., 2014). The water samples collected in this study were located near an industrial complex. Therefore, the high content of this drug in groundwater may be closely related to the high rate of untreated industrial waste discharged into the environment.

3.4.1.3. Domestic wastewater. The model developed by Kuroda et al. (2021) also predicts a significant increase in the environmental concentration of Chloroquine in domestic wastewater. Predicting a Chloroquine concentration in domestic wastewater of 857 ng L^{-1} due to the effect of consumption of this drug during the COVID-19 pandemic.

3.4.2. Hydroxychloroquine

3.4.2.1. Surface water. According to Romano et al. (2021), one of the drugs for which the highest growth rate was recorded as regards sales during 2020, in contrast to the same period in 2019, is Hydroxychloroquine. This is associated with the high consumption of the drug during the highest peaks of the pandemic, and the maximum consumption value was attained in countries such as Portugal at the end of March 2021. The same approach was employed by Kuroda et al. (2021) to estimate that, concentrations of 78.3 ng L^{-1} will be reached in surface water, as the result of increased consumption of Hydroxychloroquine during the pandemic.

3.4.2.2. Domestic wastewater. On the other hand, Kuroda et al. (2021) estimate that domestic wastewater will present a high increase in the concentration of Hydroxychloroquine. As a result, they concluded that the concentration of this anti-COVID-19 drug in domestic wastewater will be 833 ng L^{-1}.

3.5. Glucocorticoids

Clinical research has shown that glucocorticoids can counteract excessive cytokine generation in pulmonary inflammation and also enhance the immune response to the complications that can be generated by COVID-19 (Águas et al., 2021). Dexamethasone is, in particular, a synthetic hormone that has anti-inflammatory and immunosuppressive activity (Villar et al., 2020; Wu et al., 2020). Its pharmacokinetic characteristics have led to its use in mitigating the effects of COVID-19, and it is more effective in patients suffering from a severe condition than those with mild symptomatology. According to a WHO (2020) report, this drug can reduce approximately 33% of the mortality of patients connected to ventilators and 20% of that of patients who require only an oxygen supply.

Its consumption has, therefore, increased during the current COVID-19 pandemic, leading to an important impact on the environment. This drug and its metabolites are excreted through urine and feces (Desgens-Martin and Keller, 2021) and can thus enter water bodies and increase biological toxicity in water sources.

3.5.1. Dexamethasone

3.5.1.1. Surface water. Dexamethasone has been detected in surface waters in different concentration ranges. The results vary depending on the place where the water samples were obtained since each country has different levels of environmental pollution and drug use in the population. Tölgyesi et al. (2010) reported a concentration of Dexamethasone in Hungarian surface waters of 0.07 ng L^{-1}. Praveena et al. (2018) reflected a concentration of 0.73 ng L^{-1} in Malaysian surface waters. Chang et al. (2007) and Gong et al. (2019) detected concentrations of 0.11 and 0.33 ng L^{-1} in surface waters of China, respectively.

Desgens-Martin and Keller (2021) conducted a study of the environmental risk posed by therapeutic agents used in the treatment of COVID-19. Predicting that, in January 2021, the concentration of Dexamethasone could reach a maximum peak of 55.6 ng L^{-1} in surface waters (United States), where this drug had not previously been detected (Sengupta et al., 2014).

Additionally, Kuroda et al. (2021) estimate that due to the effect of increased consumption of this drug during the pandemic, the concentration of Dexamethasone in surface waters could reach 0.29 ng L^{-1}.

3.5.1.2. Domestic wastewater. Kuroda et al. (2021) estimated that the environmental concentration of Dexamethasone in domestic wastewater may reach 3 ng L^{-1}, during the COVID-19 pandemic. The concentration of Dexamethasone is expected to be lower than that of other drugs used in the treatment of COVID-19 in water bodies receiving these wastes (Tarazona et al., 2021). Such a result may be associated with the low recommended dose of Dexamethasone (6 mg day^{-1}) for COVID-19 patients.

3.5.1.3. Treated water through urban WWTP. Several studies have investigated the presence of Dexamethasone in water. It has been shown that in countries such as China, water treated through urban WWTPs is discharged into the environment at concentrations of between 0.02 and 0.09 ng L^{-1} of this pollutant (Chang et al., 2007). Moreover, the presence of Dexamethasone was established in the order of 390 ng L^{-1} in water treated through urban WWTP (China) (Chang et al., 2009).

4. Removal of pharmaceutical compounds from aqueous matrices

Scientific literature evidences the application of treatment technologies to remove this type of emerging contaminants from aqueous effluents (Fijalkowski, 2019). The principal technologies employed to remove the pharmaceutical compounds used in the treatment of patients with COVID-19 are explained below.

The presence of pharmaceutical compounds in water has aroused considerable interest in the scientific community in recent years. This has led to a steady increase in the number of publications related to the elimination of these pollutants. The growing interest in this type of contaminants is since conventional water treatment systems are not able to remove them effectively. Fig. 2 shows the evolution of scientific publications on the elimination of pharmaceutical compounds in water. A total of 1641 documents indexed in the Scopus database are reported.

During water treatment in DWTP and WWTP, pharmaceutical compounds can be removed from the aqueous phase through either physical

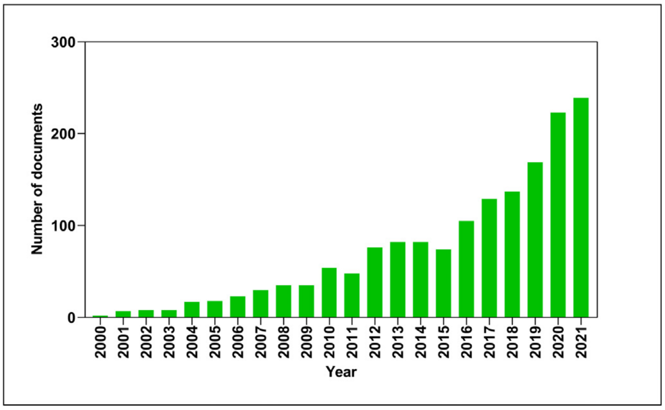

Fig. 2. Evolution of publications on the elimination of pharmaceutical compounds from aqueous effluents, retrieved from Scopus database, 04/12/2021. Subject article title, abstract, keywords: "aqueous pharmaceuticals compounds" or "pharmaceuticals compounds" or "pharmaceuticals products" or "pharmaceuticals pollution" or "pharmaceuticals contaminants" and "water" or "wastewater" and "degradation" or "elimination" or "removal" or "treatment".

(Andrade et al., 2020; Hu et al., 2016; Mailler et al., 2016), chemical (Díaz-Rodríguez et al., 2020; do Nascimento et al., 2020; Sciscenko et al., 2021) or biological degradation (Bernal-Romero del Hombre Bueno, 2020; Radjenović et al., 2009) processes. The most common mechanisms traditionally reported for the elimination of emerging compounds of a pharmaceutical origin are biological processes (45%), followed by adsorption (33%) and ultraviolet radiation (22%). However, it is essential to discern between the effectiveness of the processes, the economic feasibility of the treatments, and the availability of the materials required to implement these technologies. New treatment processes, and even their combinations that allow better removal of pollutants, are currently being implemented (Alfred et al., 2020; Bernal-Romero del Hombre Bueno et al., 2019; Bogunović et al., 2021; Cataldo et al., 2016). Consequently, there is ample updated information on the removal of pharmaceutical compounds from water bodies.

5. Elimination of pharmaceutical compounds used in pharmacological therapies to combat COVID-19

Table 2 presents the main treatments employed to remove the pharmaceutical compounds used in drug therapies with patients infected with SARS-CoV-2. The drug concentrations, process characteristics, and results of the main treatments reported in the literature for the removal of these emerging contaminants are described. Subsequently, the effectiveness of the proposed technologies is discussed according to the scale of the process (laboratory, pilot, real) and the type of water evaluated in the treatment.

5.1. Antivirals

5.1.1. Favipiravir

5.1.1.1. Laboratory scale: aqueous solution. The study by Azuma et al. (2017) made it possible to evaluate the behavior of antiviral drugs when treated employing photodegradation, biodegradation, and adsorption in aqueous solution. While the vast majority of antivirals are resistant to natural photodegradation and have marked persistence, the authors of the study state that Favipiravir can be removed by using spontaneous photodegradation. Suggesting that this pharmaceutical compound can be removed from water bodies employing solar action. Favipiravir in aqueous solution decreased to 60% of its initial concentration after exposure for 1 h and was reduced to a level of below 1% within 7 h. In contrast to the reported high effectiveness of spontaneous photodegradation of Favipiravir, it was observed that this contaminant is resistant to other natural degradation mechanisms, such as biodegradation.

5.1.1.2. Real scale: treated water through urban WWTP. The presence of this emerging contaminant was not detected in the treated water through urban WWTP (Japan). This WWTP uses a sludge system combined with ozonation (Azuma et al., 2016). In contrast, effluents from an activated sludge and chlorination system that were treated had a concentration of Favipiravir of over 600 ng L^{-1} in the months of the highest prevalence of influenza. Antoniou et al. (2013) found that ozonation is highly efficient as regards the removal of difficult-to-remove drugs. However, it is necessary to analyze the formation of by-products, such as nitrosodimethylamine and bromate. It is for this reason that Von Gunten (2018) suggests the application of an additional treatment based on a biologically activated sand filter, which will allow the removal of such by-products.

5.2. Antibiotics

5.2.1. Azithromycin

5.2.1.1. Laboratory scale: aqueous solution. Multiple investigations have evaluated the capability of current technologies in the remediation of Azithromycin in aqueous matrices. On a laboratory scale, the feasibility of adsorption, advanced oxidation processes, and biological treatments in the removal of Azithromycin from aqueous solutions has been determined.

Talaiekhozani et al. (2020) analyzed the removal of Azithromycin from synthetic wastewater through the use of ZnO nanoparticles. Obtaining a degradation of 99.9% for an optimal acidic pH of around 2, a temperature of 25 °C, and an adsorbent concentration/initial adsorbate concentration ratio of 0.00009. The thermodynamic data were adjusted to the Langmuir isotherm. In accordance with the above, it is evident that nanoparticles could provide important benefits as regards the adsorption of pharmaceutical compounds that are difficult to treat. In this respect, synthetic and functionalized nanomaterials are a potential alternative that may optimize the adsorption capacity, operation time, and selectivity for a certain group of contaminants, such as those discussed in this review.

Furthermore, several AOPs have been applied to eliminate concentrations of Azithromycin in aqueous solutions. Accordingly, Cano et al. (2020) succeeded in completely degrading this antibiotic by applying H_2O_2 and simulated solar radiation, starting from an initial concentration of 1000 μg L^{-1} of Azithromycin. The kinetic study revealed that this process can be described through the use of pseudo-first-order kinetics. In their study, Sayadi et al. (2019) succeeded in degrading 90% of the concentration of Azithromycin in aqueous solution through the use of a photocatalytic reactor with nanocomposite reinforced graphene oxide. The degradation kinetics of the drug was adjusted to the first-order model. This type of catalyst can improve the operational conditions of different treatments, and photocatalytic degradation, in particular, achieves better yields, higher stability, and selectivity as regards the removal of drugs.

Likewise, Jaramillo-Baquero et al. (2020) corroborated that at an acidic pH (3), a $FeSO_4$ concentration of 7.5 mg L^{-1} and an H_2O_2 concentration of 27.5 mg L^{-1}, the Fenton process with simulated sunlight provides favorable yields in the degradation of Azithromycin. Removal efficiencies of 92% of the initial concentration of Azithromycin in aqueous solution were obtained in a relatively low reaction time (30 min).

Wang et al. (2020a) carried out oxidation tests with H_2O_2 and Fe (II) regenerated from ferric sludge derived from a Fenton process. They obtained an Azithromycin removal efficiency in the order of 90%. Optimal operating conditions were defined at neutral pH, Fe(II) concentration of 15 mg L^{-1}, and H_2O_2 concentration of 5 mg L^{-1}. In contrast, Talaiekhozani et al. (2020) state that oxidation with Fe (VI) makes it possible to obtain 100% elimination efficiencies for Azithromycin. The optimal operating conditions for this are an acid pH, a temperature of 60 °C, and a ferrate concentration of 5 mg L^{-1}. It is important to note that ferrate is a chemical substance that can be implemented in oxidation, coagulation, and disinfection processes (Talaiekhozani et al., 2017). However, its application in treatment plants has not taken place on a large scale owing to the lack of experimental studies confirming its effectiveness and determining the operational, thermodynamic, and kinetic parameters.

Table 2
Effectiveness and characteristics of reported treatments in the elimination of pharmaceutical compounds used in pharmacological therapies to combat COVID-19.

Therapeutic agents	Pharmaceutical compounds	Treatment used	Drug concentration	Type of water	Characteristics of the process	Results obtained	References
Antivirals	Favipiravir	Photodegradation	100 μg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Experiments were carried out during the influenza season. Intensity of sunlight: 0.8 mW cm^{-2}. UV range: 315–380 nm. Temperature: 8.2 ± 3.2 °C. pH: 7.	Elimination efficiency: 40% (1 h of exposure). >99% (7 h of exposure).	Azuma et al. (2017)
		Active sludge system + ozonation	Not reported	Treated water through urban WWTP.	Scale: real scale tests. Ozone concentration: 8.6 mg L^{-1}.	Elimination efficiency: 100%.	Azuma et al. (2016); Azuma et al. (2017)
Antibiotics	Azithromycin	Adsorption with ZnO nanoparticles	110 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum ZnO concentration: 0.05 g L^{-1}. Optimum pH: 2. Optimum temperature: 25 °C. Optimum HRT: 15 min. Exothermic process.	Elimination efficiency: 99.9%.	Talaiekhozani et al. (2020)
		Photodegradation with UV/H_2O_2	1000 μg L^{-1}	Aqueous solution[a].	Scale: laboratory scale tests (batch mode). pH: 3–6-9. Initial H_2O_2 concentration: 240–480-720 mg L^{-1}.	Elimination efficiency: 100%. Acid pH and higher doses of H_2O_2 affect photocatalytic treatment.	Cano et al. (2020).
		Photocatalytic degradation with nanocomposite: Fe_3O_4/ZnO/SnO_2	30 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Reactor volume: 1 L. Optimum pH: 3. Catalyst concentration: 1 g L^{-1}. Radiation: 3 UV-C lamps of 6 W.	Elimination efficiency: 90% (2 h of exposure).	Sayadi et al. (2019)
		Photo-Fenton degradation with simulated solar irradiation	1–3 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum initial $FeSO_4$ concentration: 7.5 mg L^{-1}. Optimum initial H_2O_2 concentration: 27.5 mg L^{-1}. UV power: 50 mW cm^{-2}. Wavelength: 290–800 nm. pH: 3.	Elimination efficiency: 92% (30 min of exposure).	Jaramillo-Baquero et al. (2020)
		Degradation by oxidation with Fe(II)/H_2O_2	31.2 ± 1.3 μg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum Fe(II) concentration: 15 mg L^{-1}. Optimum H_2O_2 concentration: 5 mg L^{-1}. Optimum pH: 7.	Elimination efficiency: 90%.	Wang et al. (2020a)
		Degradation by oxidation with Fe(VI)	110 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum Fe (VI) concentration: 5 mg L^{-1}. Optimum pH: 2. Optimum temperature: 60 °C. HRT: 20 min.	Elimination efficiency: 100%.	Talaiekhozani et al. (2020)
		UV photodegradation	110 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum pH: 2–11. Optimum UV power: 163 mW cm^{-2}. Optimum temperature: 65 °C.	Elimination efficiency: 73% (50 min of exposure).	Talaiekhozani et al. (2020)

Table 2 (*continued*)

Therapeutic agents	Pharmaceutical compounds	Treatment used	Drug concentration	Type of water	Characteristics of the process	Results obtained	References
		Photo-assisted electrochemical oxidation	200 μg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Electrodes: TiO_2RuO_2-Ti (anode) & TiO_2-Ti (cathode).	Elimination efficiency: 52%.	da Silva et al. (2018).
		UV photodegradation	10 μg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum pH: 7 Optimum UV power: 76.5 mW cm^{-2}. Wavelength: 300–800 nm. Temperature: 40 °C. Reactor volume: 2 L. Current density: 10 mA cm^{-2}. UV lamp power: 250 W. Treatment time: 360 min. UV radiation exposure time: 144 min.	Elimination efficiency: 90% (7 days of exposure).	Mathon et al. (2021)
		Low-frequency ultrasound degradation	1 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Ultrasound frequency: 40 kHz. Power: 0–50 W. Exposure time: 1 h. Reactor volume: 0.3 L. pH: 3–7-9.	Elimination efficiency: 46%. The best yields were obtained at basic pH (9).	Muñoz-Calderón et al. (2020)
		Microalgae treatment	20–50-100 μg L^{-1}	Synthetic wastewater.	Scale: laboratory-scale tests (batch mode). Incubation temperature: 25 °C. Fluorescent light cycle: light (12 h)-dark (12 h). Incubation time: 40 days.	Elimination efficiency: 78%. *H. pluvialis* provided the best drug elimination performances.	Kiki et al. (2020)
		Heterogeneous photocatalysis: UV and TiO_2	227.1 ng L^{-1} (controlled photocatalysis) 250 ng L^{-1} (solar photocatalysis)	Domestic wastewater.	Scale: laboratory-scale tests (batch mode). TiO_2 P25 immobilized in two configurations: thin films and sandwich films. Cumulative UV dose: controlled photocatalysis (55 Wh m^{-2}) and solar photocatalysis (33 Wh m^{-2}).	Elimination efficiency: 51.8% (controlled radiation photocatalysis). 87.2% (solar photocatalysis).	Rueda-Márquez et al. (2020)
		UV-LED photocatalytic degradation with $BiVO_4$ doped with Gd^{3+}	892 ± 186.8 ng L^{-1}	Domestic wastewater.	Scale: laboratory-scale tests (batch mode). Catalyst concentration: 0.25–2 g L^{-1}. UV-LED power: 4.65 mW cm^{-2}. Wavelength: 370 nm.	Elimination efficiency: 62.9% (3 h of exposure).	Orona-Návar et al. (2020)
		Membrane biological reactor + nanofiltration/reverse osmosis	92.54 μg L^{-1}	Domestic wastewater.	Scale: laboratory-scale tests (batch mode). Number of bioreactors: 2. Hydraulic volume of bioreactors: 5 L. HRT in bioreactors: 4.4–8.7 h. Membranes: NF90, NF270, RO XLE. Monitoring: 6 months.	Elimination efficiency: 80.08% (NF270 membranes). >99.9% (NF90 and RO XLE membranes).	Racar et al. (2020)
		Anaerobic digestion in ASBR	69 ± 7.5 mg L^{-1}	Wastewater from the pharmaceutical industry.	Scale: laboratory-scale tests (batch mode). Reactor volume: 1.7 L. Temperature: 35 °C. OLR: 3.1 g COD L day^{-1}. HRT: 1.2 days. Operating time: 27 days.	Elimination efficiency: 30%. The presence of Azithromycin decreased the clearance of COD.	Liu et al. (2018)
		Moving-bed biofilm reactors	20–50 μg L^{-1}	Treated water through urban WWTP.	Scale: laboratory-scale tests (batch mode). 7 sets of reactors. Reactor volume: 3 L.	Elimination efficiencies: 20–100% (24 h). Increasing the COD and NH_4-N loading improved	Tang et al. (2021)

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Table 2 (*continued*)

Therapeutic agents	Pharmaceutical compounds	Treatment used	Drug concentration	Type of water	Characteristics of the process	Results obtained	References
					Monitoring: 6 months.	performance.	
		Photo-Fenton degradation with sunlight	25 ng L^{-1}	Treated water through urban WWTP.	Scale: laboratory-scale tests (batch mode). Type of reactors: Raceway Pond Reactor (RPR). Number of reactors: 2. Reactor volume: 15 L. H_2O_2 concentration: 50 mg L^{-1}. Fe^{2+} concentration: 20 mg L^{-1}. pH: 7. Solar UV power: 2.65 ± 0.68 mW cm^{-2}.	Elimination efficiency: 24% (180 min of exposure).	Fiorentino et al. (2019)
		Adsorption with powdered activated carbon (PAC)	0.11 ± 0.18 μg L^{-1}	Hospital wastewater (pretreated in an MBR).	Scale: pilot-scale tests. System capacity: 180 L. Industrial PAC (Norit SAE Super). Surface area: 1300 m^2 g^{-1}. Particle size: 15 μm. Optimum adsorbent dose: 23 mg L^{-1}.	Elimination efficiency: 100%. Equilibrium was reached in 2 days.	Kovalova et al. (2013)
		Hydrothermal liquefaction	30.6 μg kg^{-1}	Domestic wastewater (sludge).	Scale: pilot-scale tests. Reactor volume: 19 L. Volume of sludge fed: 4000 L. Operating time: 15 h. Temperature: 300, 325 and 350 °C.	Elimination efficiency: 99.8%.	Silva Thomsen et al. (2020)
		Granular activated carbon (GAC) biological filter + ultrafiltration	0.1 μg L^{-1}	Treated water through urban WWTP.	Scale: pilot-scale tests. Feed flow: 48 m^3 day^{-1}. Monitoring: 12 months.	Elimination efficiency: 63%. The biofilter contributed to the elimination of 32% of the drug.	Sbardella et al. (2018)
		Artificial wetlands	709 ± 544 ng L^{-1}	Treated water through urban WWTP.	Scale: real scale tests. Consists of 4 units. Cultivation of *Typha latifolia* L. on land, height of 15 cm. Total area: 53 ha. HRT: 3.7 days.	Elimination efficiency: 97%. Adsorption appears to be the predominant mechanism of drug elimination.	Bayati et al. (2021)
Antiparasitic	Ivermectin	Adsorption: clay + biomaterial	100–600 μg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Operating time: 15–1440 min. pH: 3–11. Temperature: 19.5–39.5 °C.	Adsorption capacity: clay + papaya seeds (105.3 μg g^{-1}); clay + pine cones (115.8 μg g^{-1}). Final adsorbate concentrations: ≤20 μg L^{-1}.	Olu-Owolabi et al. (2021)
		Heterogeneous photocatalysis: UV and TiO_2	0.5 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum initial TiO_2 concentration: 10 mg L^{-1}. Wavelength: 254 nm. pH: 4.7; 7; 8.5. Temperature: 25 °C.	Elimination efficiency: 98% (10 min of exposure). pH had no effect.	Rath et al. (2016)
		Heterogeneous photocatalysis: UV and TiO_2	10 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum initial TiO_2 concentration: 2000 mg L^{-1}. UV light wavelength: 366 nm. pH: 3, 5, 7, 9. Temperature: 25 °C.	Elimination efficiency: 90% (4 h of exposure). The pH did not affect the treatment.	Havlíková et al. (2016)
		Degradation by oxidation with Fe(VI)	100 μg L^{-1}	Tap water.	Scale: laboratory-scale tests (batch mode). Mixing phases: fast (maximum rpm, 2 min), slow (40 rpm, 20 min), and sedimentation (60 min). Optimum pH: 9. Optimum Fe(II)	Elimination efficiency: 25%.	Patibandla et al. (2018)

Table 2 (*continued*)

Therapeutic agents	Pharmaceutical compounds	Treatment used	Drug concentration	Type of water	Characteristics of the process	Results obtained	References
					concentration: 3 mg L^{-1}.		
Antiprotozoal	Chloroquine	Electro-Fenton oxidation	125 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Electrodes: Silver and boron-doped diamond. Optimum pH: 3. Temperature: 25 °C. Agitation: 300 rpm.	Elimination efficiency: 100%. Degradation leads to the formation of aromatic intermediates and carboxylic acids.	Midassi et al. (2020)
		Adsorption with biomass and melanin + membrane bioreactor	51.6 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (continuous mode). Reactor volume: 1.5 L. Biomass concentration: 10 g L^{-1} (*E. coli*). pH: 7.5.	Elimination efficiency: 98.2%.	Lindroos et al. (2019)
	Hydroxychloroquine	Adsorption with natural kaolin	5–50 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Optimum kaolin dosage: 150 mg L^{-1}. Optimum pH: 7.	Adsorption capacity: 51 mg g^{-1}. Adsorption of this drug is stable and exothermic.	Bendjeffal et al. (2021)
		Photo-assisted electrochemical oxidation	250 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Electrodes: boron-doped diamond (anode) and AISI 304 stainless steel (cathode). Initial pH: 7.1. Current density: 20 mA cm^{-2}. Wavelength: 254 nm. UV lamp power: 15 W.	Elimination efficiency: 100% (60 min of exposure). The combination of electrochemical oxidation with UV radiation improved the efficiency of the process.	Bensalah et al. (2020)
		Photodegradation with simulated solar radiation	3×10^{-5} mol L^{-1}	Surface water.	Scale: laboratory-scale tests (batch mode). Wavelength: 300–800 nm. UV power: 50 mW cm^{-2}. pH (river water): 7.54. pH (spring water): 6.87.	Elimination efficiency: 99% (river water). 100% (spring water).	Dabić et al. (2019)
Glucocorticoids	Dexamethasone	Adsorption with carbon nanotubes and activated carbon	8–14 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Adsorbent dosage: carbon nanotubes (5 mg) and activated carbon (5 mg). Temperature: 25 ± 2 °C.	Adsorption capacity: carbon nanotubes (0.67 mg g^{-1}) and activated carbon (0.62 mg g^{-1})-(10 min of exposure).	Vadi et al. (2013)
		Adsorption with zeolite	5–40 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). Temperature: 25 °C. pH: 4–7–9. Adsorbent dose: 2–6–10 g L^{-1}. Specific surface area: 43.91 cm^2 g^{-1}. Agitation: 180 rpm.	Elimination efficiency: 78% (60 min of exposure).	Mohseni et al. (2016)
		Photocatalytic degradation	5–30 mg L^{-1}	Aqueous solution[a].	Scale: laboratory-scale tests (batch mode). UV lamp photoreactor. Ag/TiO_2 dose: 0.75–2.5 g L^{-1}. H_2O_2 dose: 10–20 mg L^{-1}. Average particle size: 23 nm. BET surface: 50 m^2 g^{-1}. Reactor volume: 1 L UV lamp power: 20 W. pH: 3–11. Temperature: 30–80 °C.	Elimination efficiency: 82.3% (240 min of exposure).	Pazoki et al. (2016)
		Electrocoagulation	100 μg L^{-1}	Hospital wastewater (fortified with dexamethasone).	Scale: laboratory-scale tests (batch mode). Aluminum electrodes. Effective electrode area: 61 cm^2. Electrolyte concentration: 250–1250 mg L^{-1}.	Elimination efficiency: ~38% (45 min of exposure).	Arsand et al. (2013)

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Table 2 (*continued*)

Therapeutic agents	Pharmaceutical compounds	Treatment used	Drug concentration	Type of water	Characteristics of the process	Results obtained	References
					Reactor volume: 1 L. Temperature: 20–25 °C. pH: 6.5–8.5. Agitation: 120–150 rpm. Applied current: 100–500 mA.		

COD: chemical oxygen demand; NH_4-N: ammonium; L: liters; ng: nanograms; μg: micrograms; mg: milligrams; Kg: kilograms; nm: nanometers; μm: micrometers; cm: centimeters; A: Amperes; kHz: kilohertz; W: Watts; h: hours; Fe: iron; Fe(VI): ferrate; ZnO: Zinc oxide; $BiVO_4$: bismuth vanadate; Gd^{3+}: gadolinium; Fe_3O_4/ZnO/SnO_2: ferrous-ferric oxide/zinc oxide/tin dioxide; H_2O_2: hydrogen peroxide; TiO_2: titanium oxide; UV: ultraviolet radiation; rpm: revolutions per minute; OLR: organic loading rate; HRT: hydraulic retention time; MBR: membrane bioreactor; ASBR: anaerobic sequencing batch reactor; Ha: hectares; BET: Brunauer, Emmett and Teller; PAC: powdered activated carbon.

[a] Aqueous solutions of drugs are prepared in the laboratory.

The degradation of this drug employing UV photodegradation was also evaluated by Talaiekhozani et al. (2020). In this study, they obtained lower removal efficiencies lower than those found for other AOPs and detected that temperature was the only parameter that managed to increase the removal efficiency. An efficiency of 73% was achieved at 65 °C in 50 min of exposure. Although it is possible to increase the efficiency of UV photodegradation to levels higher than those shown in this research, very long exposure times are required. This conclusion was confirmed by Mathon et al. (2021), who required 7 days of exposure to UV radiation to attain an elimination of at least 90% of the initial concentration of Azithromycin.

Water and wastewater may contain a mixture of several emerging contaminants, and current trends, therefore, suggest that the capacity of treatments should be evaluated in laboratory-scale tests that assess such mixtures. One option that has recently been analyzed is the application of hybrid treatments with two or more remediation technologies, in which AOPs could be coupled with other processes efficiently and sustainably.

For example, da Silva et al. (2018) analyzed the capability of a hybrid technology based on photoassisted electrochemical oxidation. A 52% efficiency in terms of mineralization of Azithromycin present in an aqueous solution containing two other antibiotics was demonstrated. In this research, it was concluded that Azithromycin had a lower degradation efficiency than those obtained for the mineralization of the other drugs. This is presumably owing to the absence of chromophore groups in the saturated aliphatic rings of Azithromycin, which can absorb UV radiation. The combination of ultrasound with Fenton reagents has similarly been evaluated. In the latter case, Muñoz-Calderón et al. (2020) demonstrated that elimination levels of approximately 50% can be achieved in batch scale reactors and in an exposure time of 60 min. Concerning the operational parameters, a pH of 9, the presence of UV light, and a power of 50 W led to the best performances. Chemical compounds such as H_2O_2 and Fe^{2+} have an inhibitory effect on the elimination of Azithromycin when low-frequency ultrasound is employed.

Although these hybrid technologies have not been able to exceed the yields reported for other treatments, please note that the combination of electrochemical oxidation, along with the application of ultrasound, can remove percentages of Azithromycin higher than 50%. However, their main advantage is that they can have a synergistic effect on the degradation of two or more drugs present in the same aqueous solution, as in the case of electrochemical oxidation.

5.2.1.2. Laboratory scale: synthetic wastewater. It has been reported that most macrolides, including Azithromycin, are barely biodegradable when using conventional treatments (Dolar et al., 2012; Ternes et al., 2017). WWTPs frequently apply biological processes during the removal of organic pollutants (Bernal-Romero del Hombre Bueno, 2020). However, the broad spectrum of antimicrobial activity of macrolides could affect the efficiency of biological treatments, which favors the dissemination of these micropollutants into other water bodies (Čizmić et al., 2019). Despite the above, there are reports of laboratory-scale studies showing that certain biological treatments may favor the degradation of this drug.

Kiki et al. (2020) analyzed the capacity of a laboratory-scale microalgae treatment with which they removed 78% of the Azithromycin present in pre-sterilized synthetic wastewater during a 40-days incubation period. The best performance was provided by *Haematococcus pluvialis*, which adjusted favorably to the pseudo-first-order kinetics.

5.2.1.3. Laboratory scale: domestic wastewater. The literature shows that titanium dioxide is a catalyst that can, in the presence of UV light, degrade high rates of aqueous micropollutants in domestic wastewater. However, its effectiveness may depend on the dose and type of UV radiation, as pointed out by Rueda-Márquez et al. (2020). In this work, Azithromycin removal was on the order of 87.2% and 51.8% for natural solar photocatalysis and controlled radiation photocatalysis, respectively. Moreover, the coating of the catalyst, which was carried out using the sandwich approach (anatase-TiO_2-anatase), produced the best performances in this oxidative technology. In this case, the degradation with solar radiation led to more significant results than the simulated radiation. This demonstrates that photocatalytic degradation with solar radiation may be an effective method for the degradation of Azithromycin in domestic wastewater under certain experimental conditions. It is also important to highlight the decrease in the cost of this treatment concerning the implementation and maintenance of UV lamps.

From the same perspective of AOPs, Orona-Návar et al. (2020) removed 69.2% of Azithromycin present in domestic wastewater by employing UV-LED photocatalysis with gadolinium-doped bismuth vanadate as a catalyst. However, the low level of contaminant removal in this process may be associated with the use of real wastewater. These effluents may contain micropollutants or trace elements in their composition, which could somehow slow down or limit the capacity of the oxidative technologies.

In their work, Racar et al. (2020) used a hybrid system in which MBR and nanofiltration/reverse osmosis technologies were coupled to improve the quality of domestic wastewater for its reuse in irrigation activities. While the MBR decreased the concentration of Azithromycin in the range of 23.2–52.6%. The nanofiltration (NF90) and reverse osmosis (RO XLE) membranes optimized the capacity of the hybrid treatment because they were able to remove percentages higher than 99.9%. In this case, the combination of biological treatment with nanofiltration membranes and reverse osmosis led to high removal rates of Azithromycin and other drugs present in wastewater.

5.2.1.4. Laboratory scale: wastewater from a pharmaceutical industry. Under the approach of biological treatments, anaerobic digestion in an ASBR has been found to remove 30% of the Azithromycin present in the wastewater from the pharmaceutical industry. The anaerobic granular sludge proved to be more efficient than the flocculent sludge for an organic load of 3.1 g COD L day^{-1} and a hydraulic retention time of 1.2 days (Liu et al., 2018). The low effectiveness obtained could be related to two factors: the low hydraulic retention time and the high concentration of the drug

(69 mg L^{-1}), because this pollutant could have an inhibitory effect on the biochemical phases of the anaerobic digestion.

5.2.1.5. Laboratory scale: treated water through urban WWTP. Tang et al. (2021) reported the effectiveness of a system of 7 moving bed biofilm reactors (MBBR) as a refining biotreatment with which to remove Azithromycin and other micropollutants from treated water through urban WWTP. The removal capacity varied considerably depending on the ratio of the WWTP influent and effluent supplied to the MBBRs. Similarly, intermittent addition of primary wastewater with high COD and NH_4-N loading improved the removal effectiveness of Azithromycin to levels approaching 100%.

In addition, Fiorentino et al. (2019) analyzed the capacity of the photo-Fenton process with natural sunlight at laboratory scale on treated water through urban WWTP. A degradation of Azithromycin of 24% in 180 min was evidenced. In this study, the Fenton technology was applied at a neutral pH, H_2O_2, and Fe^{2+} concentration of 50 and 20 mg L^{-1}, respectively. The low effectiveness reported may be associated with the pH, since neutral pH is less efficient than acid pH for the removal of antibiotics using Fenton degradation.

Concerning this issue, it can be concluded that the high degree of contamination caused by Azithromycin in aqueous matrices has given rise to studies that on a laboratory scale have demonstrated the effectiveness of technologies for the removal of the contaminant. Various biological, physical, and chemical treatments, along with their combinations, show that it is possible to eliminate the occurrence of this drug in water bodies. However, some treatments may require long contact times to achieve the expected efficiency. In this respect, AOPs are technologies with very high removal levels (100%) and relatively low operation times. Also, the combination of AOPs with traditional treatments (adsorption) can provide economic and environmental advantages through the application of nanoparticles that can act in parallel as highly selective catalysts and adsorbents.

5.2.1.6. Pilot-scale: hospital wastewater. Although there have been conclusive reports on the efficacy of Azithromycin water treatment technologies, the vast majority of these studies have been conducted at the laboratory scale. Importantly, pilot-scale studies that will accelerate the application of these technologies on a large scale. In this regard, the work of Kovalova et al. (2013) evaluated the removal of Azithromycin from hospital wastewater through a pilot-scale adsorption process. This study determined 100% efficiency in the removal of Azithromycin by adsorption with PAC when used with hospital wastewater previously treated in an MBR. Although three doses of adsorbent (8–23-43 mg L^{-1}) were evaluated, the intermediate dose (23 mg L^{-1}) provided the best performance.

5.2.1.7. Pilot-scale: domestic wastewater. One of the disadvantages of some biological treatments is the generation of sludge. To address this problem, Silva Thomsen et al. (2020) evaluated the capacity of a hydrothermal liquefaction system when used with domestic sewage sludge. They concluded that the use of a reactor of a 19 L capacity in an operation time of 15 h and at different temperatures makes it possible to eliminate 99.8% of the Azithromycin present in sewage sludge. This shows that the liquefaction could be adapted to treatments that generate large amounts of sludge since it is well known that these wastes contain pollutants that need to be eliminated to comply with environmental regulations.

5.2.1.8. Pilot-scale: treated water through urban WWTP. Sbardella et al. (2018) evaluated the potential of a pilot plant designed by combining a biological treatment and adsorption with GAC for the removal of different drugs. This process permitted the removal of 63% of Azithromycin, thus demonstrating that biological processes can act synergistically in the presence of GAC. Furthermore, macrolides in DWTP underwent removal of 80–95% when using PAC (Westerhoff et al., 2005), thus demonstrating that the adsorption of Azithromycin with PAC could be more efficient.

5.2.1.9. Real scale: treated water through urban WWTP. The efficiency of artificial wetlands as regards removing Azithromycin was analyzed by Bayati et al. (2021). This technology was evaluated in a full-scale plant, demonstrating that its application can be feasible from the environmental point of view. For an initial concentration of 709 ng L^{-1} in treated water through urban WWTP, an efficiency of 97% was obtained for the removal of the contaminant, leading the authors to conclude that adsorption is the most representative remediation mechanism. However, its main limitation is the 53 ha that this treatment plant required for its operation.

In any case, more pilot and full-scale studies are required to accurately determine the applicability and feasibility of the treatment techniques addressed in the degradation of Azithromycin from water bodies.

5.3. Antiparasitics

5.3.1. Ivermectin

5.3.1.1. Laboratory scale: aqueous solution. The synergistic adsorption of low-cost kaolinite clay and two biosorbents derived from papaya and pine cone seeds has been tested as regards the removal of Ivermectin from aqueous solutions at laboratory scale (Olu-Owolabi et al., 2021). This demonstrates that biomass sources can be profiled as eco-friendly, cost-effective, and technically feasible adsorbents. In this study, Ivermectin concentrations in the range of 100–600 μg L^{-1} and at a pH ranging from 3 to 11 were analyzed, and it was determined that the application of biomaterials improved Ivermectin removal under continuous agitation. The process conformed to the Freundlich isotherm model, while the kinetic parameters reflected an affinity with the pseudo-second-order model. Some of the adsorbate-adsorbate interactions may include electrostatic, hydrogen bridge, pore-filling, and Van der Waals interactions (Altenor et al., 2009; Diagboya et al., 2020).

Furthermore, AOPs are technologies that have proven their effectiveness as regards the elimination of Ivermectin in aqueous solution. Heterogeneous photocatalysis with UV radiation and TiO_2 was, in particular, highly effective and selective. In their study, Rath et al. (2016) obtained the removal of 98% in the first 10 min of reaction and stated that the presence of H_2O_2 did not alter the performance. However, a previous experiment that was part of the same research showed that 20% of the Ivermectin concentration can be adsorbed on the surface of the catalyst. Similarly, Havlíková et al. (2016) investigated the removal of Ivermectin (10 mg L^{-1}) employing heterogeneous photocatalysis with TiO_2/UV and obtained the removal of 90% in a reaction time of 240 min. A comparison of these treatments shows that, in both cases, the pH had a weakly significant effect.

We think that the difference between the effectiveness of the studies by Rath et al., 2016 (98%) and Havlíková et al., 2016 (90%) is principally owing to the ratio of initial Ivermectin concentration/initial TiO_2 concentration. In the first case, a low range of TiO_2 (10–120 mg L^{-1}) was evaluated and it was determined that the ratio that provided the best performance was 0.05. While in the second study, concentrations ranging from 250 to 2500 mg L^{-1} were evaluated and it was established that the ratio of 0.005 allowed the attainment of better yields (Table 2). It is, therefore, concluded that the initial concentration of TiO_2 does not necessarily have a directly proportional relationship with the removal efficiency of Ivermectin. Abellán et al. (2007) obtained similar behavior in the degradation of a pharmaceutical compound and detected that there were no significant changes in the degradation at concentrations higher than 519 mg L^{-1} of TiO_2.

It should be noted that titanium dioxide is insoluble in water, and that increasing its concentration, therefore, increases the turbidity of the medium and consequently limits the penetration of UV light (Kunz et al., 2002). This is presumably the main mechanism that decreases the effectiveness of photodegradation at high concentrations of catalysts.

5.3.1.2. Laboratory scale: tap water. The research by Patibandla et al. (2018) evaluated the effectiveness of oxidative treatment with Fe(VI) in the removal of Ivermectin in aqueous solution diluted with tap water. However, the degradation of Ivermectin with ferrate did not prove to be as effective as other advanced oxidation treatments. Patibandla et al. (2018) managed to eliminate only 25% of the initial concentration of the drug. They stated that the highest yields were obtained with Fe (VI) at a concentration of 3 mg L^{-1} in a basic medium (pH 9) and that the initial concentration of the drug had no significant effect on the efficiency of the process.

The low performance recorded may be related to the use of tap water in the experimental trials. In the previous sections, it was mentioned that drinking water can carry the presence of several emerging contaminants. This includes organic and inorganic compounds that can cause the effectiveness of the treatment technology (ferrate oxidation) to decrease, as they can be a barrier to the degradation of the target contaminant.

5.4. Antiprotozoals

5.4.1. Chloroquine

5.4.1.1. Laboratory scale: aqueous solution. The electro-Fenton oxidation treatment on boron-doped diamond electrodes allowed the complete elimination of the Chloroquine concentration in a time of 180 min (Midassi et al., 2020). Laboratory tests were performed in an aqueous solution of Chloroquine (125 mg L^{-1}), in a reactor operating in batch mode at a temperature of 25 °C. A high degradation efficiency was obtained in this study, possibly owing to the high production of OH radicals from the catalytic decomposition of H_2O_2 in the presence of Fe^{2+} in solution.

On the other hand, the adsorption process developed inside a membrane bioreactor has been investigated for the elimination of Chloroquine in aqueous solution. In their study, Lindroos et al. (2019) evaluated the adsorptive capacity of melanin impregnated in a biological complex containing *Escherichia coli* cells inside a membrane bioreactor (1.5 L). This treatment, which operated in continuous mode (laboratory scale), eliminated 98.2% of Chloroquine.

5.4.2. Hydroxychloroquine

5.4.2.1. Laboratory scale: aqueous solution. Bendjeffal et al. (2021) reported that the adsorption (laboratory scale) of Hydroxychloroquine in aqueous solution (5 mg L^{-1}) with natural kaolin is a spontaneous, stable, and exothermic process. The optimum conditions that allow the attainment of a high adsorption capacity (51 mg g^{-1}) are a neutral pH and a kaolin concentration of 0.15 g L^{-1}. Concerning the kinetics, it was established that the sorption mechanism adjusts to the pseudo-second-order model, whereas the isothermal adsorption models adjust to the Langmuir model.

Furthermore, Bensalah et al. (2020) evaluated the capacity of the photoassisted electrochemical oxidation treatment in aqueous solution. Complete depletion of Hydroxychloroquine was determined within 60 min of exposure to UV light. The treatment was performed in the presence of a boron-doped diamond (anode) and AISI 304 stainless steel (cathode). The kinetics of this process was adjusted to the pseudo-first-order model. Although the boron-doped diamond led to the production of aromatic intermediates (carboxylic acids and 4-quinolinamine), these were eventually mineralized.

5.4.2.2. Laboratory scale: surface water. Hydroxychloroquine is a pharmaceutical compound that can be degraded by employing photolysis in various aquatic media. Dabić et al. (2019) performed experimental tests under conditions of simulated solar radiation with samples of surface waters (river water, spring water) and determined degradation efficiencies of over 99%. The water samples evaluated were maintained at a neutral pH. However, the pH has been found to have a significant influence on the environmental half-life of this contaminant. We also suggest that some organic and inorganic compounds that are part of the composition of surface waters promote the formation of OH radicals. Therefore, these water components, enhance the photodegradation of the Hydroxychloroquine molecule, with exceptions such as bromides, chlorides, and sulfates.

It has been demonstrated that the drugs Chloroquine and Hydroxychloroquine have been eliminated from aqueous matrices employing biochemical, physical, and chemical techniques, although there are fewer studies on other contaminants. This demonstrates the mismatch between the number of reports that have evaluated remediation technologies on these drugs and other drugs that have also been used to combat COVID-19. However, of all the treatments analyzed, the AOPs were more effective in the degradation of these contaminants in water. Complete removal of these contaminants in aqueous solutions was achieved in significant operation times: 180 min (Chloroquine) and 60 min (Hydroxychloroquine). Finally, the challenge of evaluating the effectiveness of such treatments in real aqueous matrices containing a wide variety of contaminants remains.

5.5. Glucocorticoids

5.5.1. Dexamethasone

5.5.1.1. Laboratory scale: aqueous solution. The study by Vadi et al. (2013) compared the effect of the use of two materials with an adsorption capacity on Dexamethasone in aqueous solution. It was established that, at a concentration of 14 mg L^{-1} of the drug and in a time of 10 min, the adsorption capacity of 0.67 and 0.62 mg g^{-1} could be obtained on carbon nanotubes and activated carbon, respectively. Although there was a slight difference between the performances of the adsorbents considered, it is possible to conclude that the correlation coefficient in the Langmuir isotherm model is very close to 100% for both cases. This means that there is no significant difference between the efficiency of the adsorbents compared.

However, Mohseni et al. (2016) reported effectiveness of 78% for an adsorption treatment with modified clinoptilolite zeolite that aimed to remove Dexamethasone loading in aqueous solutions. The operational conditions that yielded the maximum contaminant removal were pH 4, the highest adsorbent dose (10 g L^{-1}), and the lowest initial drug concentration. The experimental data were fitted to the Freundlich and Sips isotherm models, while the kinetics was fitted to the pseudo-second-order model. The results showed that the adsorbent concentration has a directly proportional relationship with the removal performance of Dexamethasone and an inverse relationship with the adsorption capacity. This same behavior was reported in the investigations of Bhaumik et al. (2011) and Ai et al. (2013).

AOPs have also been implemented in the removal of this pollutant. In this respect, Pazoki et al. (2016) obtained 83.2% degradation of the Dexamethasone in aqueous solutions through photocatalysis with Ag/TiO_2 and in the presence of a strong oxidant (H_2O_2) and UV radiation. The photocatalytic degradation reactions were fitted to the Langmuir-Hinshelwood kinetic model, while the ideal temperature and pH were on the order of 35 °C and 3, respectively. Furthermore, the optimum values for parameters such as pollutant concentration, catalyst loading, and H_2O_2 concentration were: 5 mg L^{-1}, 1.5 g L^{-1}, and 15 mg L^{-1}, respectively.

When comparing the treatments evaluated as regards the degradation of Dexamethasone, it is evident that the most favorable processes are adsorption and AOPs, with yields close to 80%. However, the main difference between them is the operation time, since adsorption with zeolite required 1 h (Mohseni et al., 2016) and photocatalysis with Ag/TiO_2, a total of 4 h (Pazoki et al., 2016). But it should be emphasized that to strengthen the hypothesis of the feasibility of given water and wastewater treatment, it is necessary to consider the cost of the technology employed.

5.5.1.2. Laboratory scale: hospital wastewater. In their study, Arsand et al. (2013) were able to eliminate 38% of the Dexamethasone present in fortified hospital wastewater until attaining an initial concentration of 100 μg L^{-1} of the drug. The electrocoagulation process was developed at laboratory scale for 45 min. However, the drug began to decompose from minute 15. One of the most influential factors in electrocoagulation processes is the intensity of the current applied. Thus, the best performances in this research were obtained by increasing the intensity of the current and reducing the distance between the electrodes. Aluminum electrodes led to the generation of residual aluminum, which can be counteracted by adjusting the pH (6.5) (Emamjomeh and Sivakumar, 2006).

6. Cost of treatment for elimination of therapeutic agents against COVID-19

A significant number of the treatments analyzed in this review provide high yields as regards the elimination of anti-COVID-19 pharmaceutical compounds (Table 2). However, their large-scale implementation depends on economic aspects that determine the profitability of the technology in the medium and long term. Although very few studies have evaluated the economic feasibility of anti-COVID-19 drug elimination treatments, some economic aspects that have been reported in the studies considered in the previous section are presented as follows.

Kovalova et al. (2013) reported that the treatment of hospital wastewater (318 m^3 day^{-1}) containing a significant mixture of drugs represents a cost of US $3.1 m^{-3}. This pilot-scale treatment plant employs the combination of MBR/adsorption technologies with PAC and obtains 100% effectiveness as regards the removal of Azithromycin. The work of Kovalova et al. (2013), meanwhile, determined that replacing the PAC adsorption technology with an ozonation process resulted in a decrease of US $0.3 for the total cost of treatment. However, the main disadvantage of ozonation was that its level of effectiveness as regards removing Azithromycin (91%) did not attain the levels reported for the adsorption process (100%).

Other studies have assessed the feasibility of a full-scale water treatment plant for the removal of antibiotics using photo-Fenton technology with solar radiation. This implies a cost of US $3.6 m^{-3} in a system operating under a capacity of 30 m^3 day^{-1}, attaining degradation levels of over 90% of the initial concentration of drugs (Alalm et al., 2015).

The cost of implementing treatment plants based on technologies that are highly effective as regards removing drugs used by patients with COVID-19 will depend on several factors. These include operational factors, labor, system maintenance, and the acquisition of equipment and materials. However, the cost of the materials used in the adsorption, along with the generation of intermediate compounds and the energy cost required to implement an AOPs, are the main limitations that prevent the large-scale expansion of these technologies. It is, therefore, imperative to promote, among other things:

- The research and development of new materials that are more economical and sustainable than those traditionally used in adsorption processes.
- The optimization of the energy consumption of oxidative treatments, taking advantage of the availability of solar energy. As mentioned above can, under certain experimental conditions, provide high levels of effectiveness as regards the oxidative degradation of the emerging pollutants analyzed.
- The application of hybrid treatments that generate a completely treated effluent in a shorter operation time.

7. Final considerations

Fig. 3 shows the treatments addressed above from both the traditional perspective (adsorption, membranes, biofilter) and that of new technologies (AOPs).

The combination of technologies for the removal of pharmaceutical compounds in water is an interesting option as regards solving the need for highly efficient, environmentally friendly, and economically profitable treatments. Especially considering that consolidated treatments can work synergistically with new technologies and optimize the yields obtained

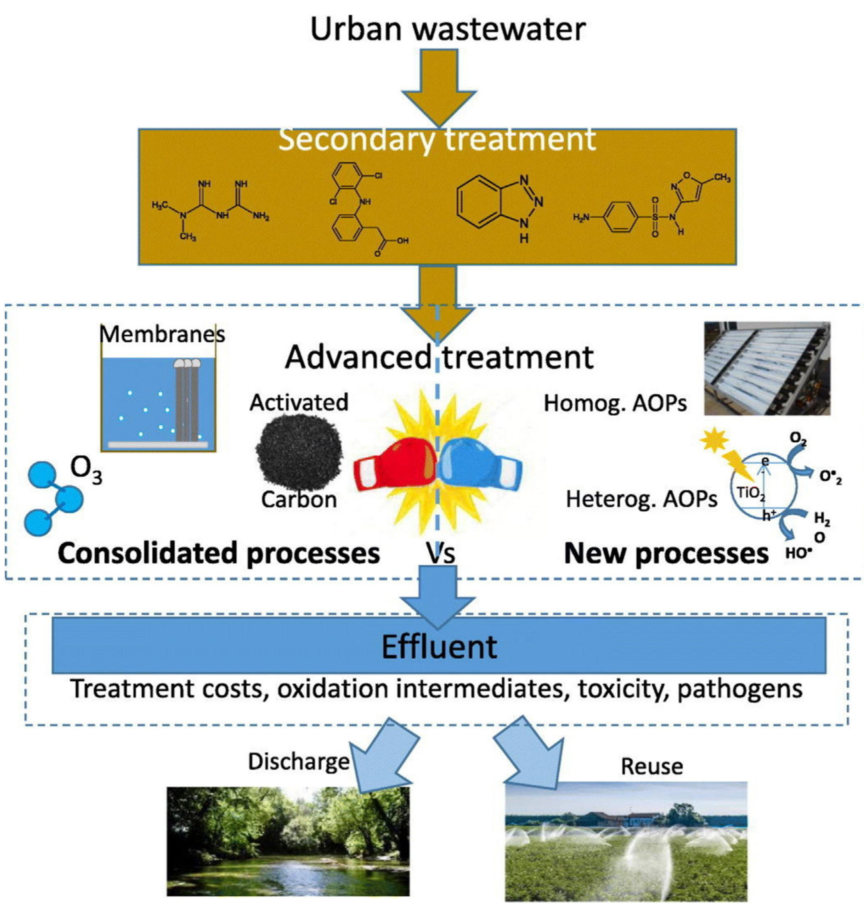

Fig. 3. Tertiary wastewater treatment: Consolidated vs. new processes.
Source: Taken from Rizzo et al. (2019).

independently. In this respect, GilPavas et al. (2019) designed an operation mechanism that combines electrocoagulation, advanced oxidation, and adsorption processes for the treatment of industrial wastewater. This hybrid technology can generate total color removal, and reduce up to 72% of the chemical oxygen demand.

The preparation of nanocomposites from natural kaolinite clay, titanium dioxide, and biomass has also been carried out. This material can remove commonly used pharmaceutical compounds such as Ampicillin, Sulfamethoxazole, and Artemether. It was established that several mechanisms may occur during treatment, one of which is exposed photodegradation with sunlight, which developed relatively fast with >90% removal in 30 min. Furthermore, it is suggested that the removal of contaminants from wastewater enriched with the pharmaceuticals may be due to retention on the surface of the nanocomposite. While the combination of adsorption and photodegradation in this treatment is highly likely, the results suggest that photodegradation alone dominates the process (Alfred et al., 2020).

On the other hand, Cataldo et al. (2016) determined at laboratory scale, that heterogeneous photocatalysis, homogeneous ozonation, and adsorption with GAC have remarkable synergistic effects in the treatment of synthetic wastewater. This combination increases the oxidation rate of the organic compounds present in wastewater with simulated characteristics. The coupling of ozonation and photocatalysis resulted in a 20% improvement in terms of reaction rate.

Hybrid systems that combine advanced technologies such as AOPs and other traditional techniques should continue to be evaluated. Currently, they are presented as an option that can be extended in the future, especially due to the decrease in treatment operating costs and the optimization of process yields.

8. Future prospects

The literature review carried out led to the discovery that there are ample opportunities for study in the framework of environmental treatments with which to remediate the contamination generated by the anti-COVID-19 drugs. It has been established that the generation of this type of waste affects the quality and sustainability of water resources. This means that wastewater will contain not only pollutants of pharmaceutical origin but also all types of substances introduced as a result of anthropogenic activities. The scientific community should, therefore, move towards the generation of proposals that evaluate the capacity of treatments with different mixtures of pharmaceuticals and other pollutants present in the same aqueous medium. This is because waters and wastewaters can present complex mixtures of contaminants of different nature, which can inhibit the effect of remediation treatments (Liu et al., 2018; Orona-Návar et al., 2020; Racar et al., 2020). In this respect, proposals based on Innovation & Development & Research principles, which are also environmentally friendly and sustainable on an economic scale, could attain large-scale implementation. They should, however, first be analyzed on a pilot scale.

The development of new materials that can replace the already-existing ones with greater feasibility, selectivity, and efficiency in the treatment of wastewater loaded with pharmaceutical compounds is required. This being case, one viable option is the development of nanoparticles that act as adsorbents and catalysts with high effectiveness and selectivity (Gerard et al., 2016; Nithya et al., 2018). Functionalized biomaterials are also presented as an alternative that can be employed with a wide spectrum of emerging pollutants through the use of abundant and low-cost raw materials (Alfred et al., 2020; Rathi and Kumar, 2021; Saxena et al., 2020). Likewise, metal-organic frameworks (MOFs) are materials that, owing to their high porosity, provide high levels of efficiency, recycling, and reuse in processes that aim to remove these types of contaminants (Ali et al., 2021; Lu et al., 2021; Su et al., 2020).

Finally, hybrid technologies are an alternative that should be addressed to a greater extent. This is based on the fact that it has been demonstrated that bio and nanomaterials can act simultaneously in several processes and operations such as adsorption, oxidation, filtration (Ren et al., 2020; Rodríguez-Narváez et al., 2017; Truong et al., 2020). It is, therefore, necessary to establish the parameters for the operation of these materials in processes that will ensure compliance with regulations for the discharge of water into water bodies and that which is for human consumption.

9. Conclusions

A significant increase in the concentration of anti-COVID-19 drugs has been detected in surface water, wastewater, and treated wastewater following the pandemic. This has generated an emerging concern about the impact that these drugs present in different aqueous matrices can have on human health and the ecosystem. Therefore, it is innovative to propose technological alternatives that allow the removal of these contaminants in an efficient and economically feasible way. At laboratory scale, adsorption techniques with bio and nanomaterials and AOPs are presented as an interesting alternative, since they removed more than 80% of some of these drugs. Likewise, pilot-scale treatment plants have been evaluated that were able to remove all of the Azithromycin employing adsorption systems with PAC. On the other hand, full-scale wastewater treatment plants degraded 100% of Azithromycin and Favipiravir.

The combination of technologies for the treatment of water and wastewater containing pharmaceutical compounds is a booming field of study. Even more so in the specific case of the drugs used in pharmacological therapies employed to mitigate COVID-19. However, hybrid systems that combine traditional and innovative technologies can generate operational, technical, and economic advantages, and thanks to the synergistic behavior of the individual processes.

CRediT authorship contribution statement

Carlos Augusto Morales-Paredes: Writing - Original Draft, Writing - Review and Editing. **Joan Manuel Rodríguez-Díaz**: Writing - Review and Editing, Supervision. **Nuria Boluda-Botella**: Writing - Review and Editing, Supervision.

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.

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