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Drugs used in COVID-19 therapy and their effects on the environment

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ABSTRACT

The SARS-CoV-2 virus responsible for causing the COVID-19 disease was first identified in Wuhan in December 2019. Due to its easy transmission from person to person, it has become a global health threat, causing a pandemic that was declared by the WHO in March 2020. The therapeutic strategy for its treatment was based on commercially available drugs that were dedicated to the treatment of other diseases (e.g., votive fever, bacterial infections, other viral diseases). Currently, three antiviral drugs are approved as official drugs in COVID-19 therapy, however, other drugs are still being used to support the treatment of this disease, depending on the intensity of its symptoms. The need to treat patients infected with SARS-CoV-2 results in an increased demand for drugs supporting the treatment of COVID-19, and thus their greater consumption. Consequently, this group of drugs is very often released into the environment mainly through treated sewage. And as is observed with other micropollutants, drugs used to treat COVID-19, along with metabolites, will certainly become a new group of anthropogenic micropollutants in the environment, posing a potential threat to living organisms. Therefore, the aim of the study is a literature review on the occurrence of drugs used to treat COVID-19 in the environment and to estimate the potential threat resulting from this presence. The work will focus mainly on antiviral, antiparasitic and antimalarial drugs used in COVID-19 treatment. From the point of view of human health, the real problem with drugs used to treat COVID-19 is the potential formation of resistant strains of microorganisms through chronic exposure of organisms to drugs used in COVID-19 therapies. This phenomenon is analogous to the phenomenon of drug resistance to antibiotics in various microorganisms, including pathogenic ones.

Keywords: Drugs; COVID-19; Wastewater; Advanced oxidation processes (AOPs); Biodegradable; Risks and removal

1. Introduction

The first case of COVID-19, that is, infection caused by new virus SARS-CoV-2, was reported in December 2019 in Wuhan, China, the capital city of Hubei province. On January 30th, 2020, WHO declared it an international public emergency. Later, on March 11th, 2020, this outbreak was declared a pandemic [1]. According to the WHO report, globally, almost 494 million confirmed cases and over 6.1 million fatalities have occurred [2]. A new variation in the genomic structure of coronavirus has been reported, which causes acute respiratory infections such as SARS-CoV-2 (COVID-19), the variant of concern (Omicron) [3]. Up to date, several FDA-approved and non-approved drugs have been used in SARS-CoV-2 therapy. The release of these anti-viral drugs into wastewater and natural water is considered a big challenge for the potential fate of the aquatic environment [4].

The unpropitious effects of drugs used in COVID-19 on the aquatic environment are alarming. They are given to the population in the long term to treat the infection. Moreover, the COVID-19 outbreak results in the emission of drug residue into the environment [5]. From December 2019 to up-till now, the consumption of drugs for the treatment of

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COVID-19 has increased tenfold. The release of drugs into the water bodies, from the feces of COVID-19's patients and hospital garbage, is a serious concern [6]. The toxicity of these drugs towards aquatic organisms such as fishes and algae has far less documented, as these drugs can enter into the environment from different modes and cause harmful effects to the food chain, hinder the growth of the living organism and interfere with its natural body system [7]. Drugs can be escapable easily during wastewater treatment because of their refractory nature [8]. After the drug is administered to the patients, it will be moderately metabolized and released through the urine and feces of patients into the wastewater treatment plants (WWTPs) and intermix with the other constituents of sewage water [9].

Medicines are detected in rivers and streams at much lower quantities than the regularly prescribed doses, but there is concern that persistent exposure to several compounds could create major health problems, and that compounds can operate synergistically to cause harmful health consequences. Depending on the type of drug, its environmental effects may be different, however, antiviral drugs can cause similar resistance to their effects, as is observed in antibacterial drugs. Whether these substances are present in such concentrations in the rivers to influence human health is a serious worry that is being researched [10].

Antivirals typically excrete to a large extent in the bioactive form of the parent dose. The amount of antiviral medications that are released into the environment is significantly influenced by their metabolism in the human body. The excreted and washed-off therapeutic drugs and their active metabolites degrade further in the environment in the presence of sunlight, air, microbes, soil, and water. There is enough information to suggest that many antiviral medications may be subject to photolysis, hydrolysis, sorption, and biodegradation, even though only a small number of articles are focused on their destiny in the environment [11]. A substantial amount of remdesivir, (GS-5734) an active ingredient of Vuklury® injections, used in the treatment of COVID-19 therapy, excreted by humans during this pandemic, entered into the WTPs in biological active forms. Remdesivir is considered an emerging pollutant because of its increasing use and subsequent environmental discharge during the COVID-19 pandemic [12]. Apart from remdesivir, the presence of other drugs used in COVID-19 treatment, their biodegradation efficiency, and the impact of their toxicity on the aquatic environment have received far less attention to date. In addition, there is a lack of available knowledge about the total usage of drugs using in COVID-19 therapy across the world. Information on new antiviral drugs approved for the treatment of this disease is mostly lacking, but information on other drugs supporting the treatment of this disease is also very limited. Therefore, it is imperative to investigate the fate, effects, and impact of these drugs on the environment. This review paper is written to provide information on the presence of drugs used in COVID-19 treatment, their toxicity in the aquatic environment, and strategies to prevent them.

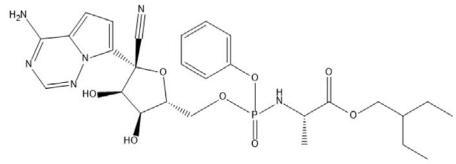
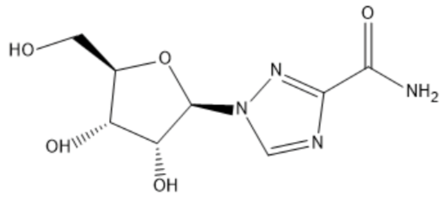
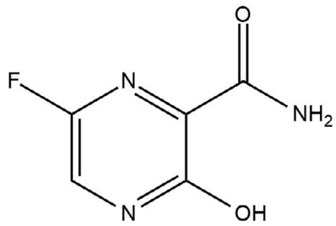
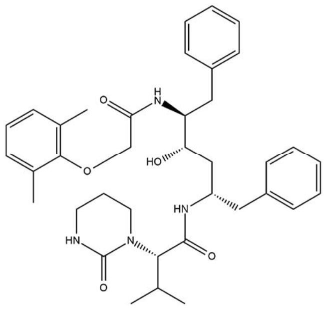
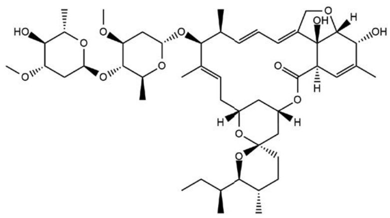
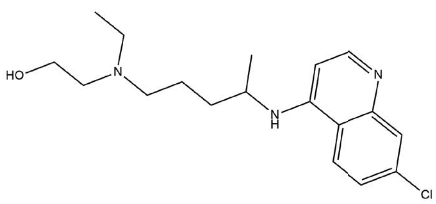
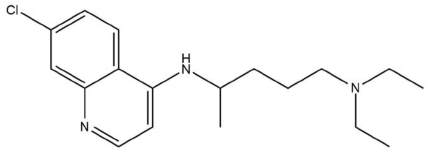
In this review paper, we have focused on selected pharmaceuticals such as antiviral drugs (remdesivir, ribavirin, lopinavir, and favipiravir), antiparasitic drugs such as ivermectin, and antimalarial drugs (chloroquine and hydroxychloroquine) used to treat COVID-19. In Table 1 are presented basic information on the selected drugs used in COVID-19 treatment.

2. Impact of drugs used in COVID-19 on aquatic environment

The drugs have been found in several types of water including wastewater, groundwater, surface water, and wastewater treatment plants (WWTP) [13]. When these compounds enter the water, they create structural alterations in the biotic and abiotic effluent treatment processes [14]. Organic and inorganic pollutants present in wastewater may react with the parent molecules, become persistent, and are difficult to remove from wastewater [15]. The formation of such tenacious molecules after the release of drugs, metabolite their byproduct into the water bodies is a serious environmental problem. These drugs enter in the wastewater treatment plants (WWTP) from different routes, as shown in Fig. 1, and may enter into the environment at different ranking levels and may eventually enters in to drinking water resources [16] . The mechanism of action and transmission of COVID-19 virus are still being studied. Drinking water is a major source of pollution exposure for humans. Therefore, this aspect of study discusses some significant contaminants in drinking water that are known to be immunotoxin, investigating sources and drinking water routes and emphasizing known mechanisms of action that may compromise humans' ability to mount an effective immune response, especially when COVID-19 virus exposure is involved [17].

In general, it has been discovered that patients can excrete up to 60% of an administered dose of antiviral medication [18]. But the amount of the parent medications used to treat human illnesses varies between nature of the illness, for example, the antiviral drug remdesivir, used to treat COVID-19, its average recommended dose is reported as 110 mg/d. Another antiviral drug, ribavirin, used in COVID-19 therapy, the average daily dose is reported as 2473 mg. These COVID-19 drugs, and their metabolites such as metabolite of ribavirin ($TCONH_2$) and the metabolite of remdesivir (GS-441524), are excreted into municipal wastewater and on-site sanitation systems via urine and feces with reported concentration of 5,440 and 2,120 $ng{\cdot}L^{-1}$, respectively [19]. Around 30%–90% of medications are not metabolized, and their byproducts wind up in wastewater treatment facilities. These metabolites can be returned to their parent substance by microbes when present in surface water. Additionally, drug transformation and breakdown during API transport through sewage pipes and drug treatment in WWTPs might release drug residues and result in their presence in the environment [10]. Up to 90% of medication taken orally are eliminated into wastewater as active component in urine and feces. According to study, the removal effectiveness of these active compounds ranges from 0% to 97%. This implies that pharmaceutical or their metabolites can enter the water cycle and released into aquatic ecosystem through effluents. Pharmaceutical concentrations in surface waters, groundwater, and partially treated water are normally less than 100 $ng{\cdot}L^{-1}$, while concentrations in treated water are typically below 50 $ng{\cdot}L^{-1}$, according to research that are currently available [20]. Drugs

Table 1
Basic information on selected drugs used in COVID-19 therapy

Drug name	Chemical formula	Structure	Molecular weight (g/mol)
Remdesivir	$C_{27}H_{35}N_6O_8P$		602.58
Ribavirin	$C_8H_{12}N_4O_5$		244.20
Favipiravir	$C_5H_4FN_3O_2$		157.10
Lopinavir	$C_{37}H_{48}N_4O_5$		628.80
Ivermectin	$C_{48}H_{74}O_{14}$		875.09
Hydroxychloroquine	$C_{18}H_{26}ClN_3O$		335.18
Chloroquine	$C_{18}H_{26}ClN_3$		319.87

and their metabolites in wastewater effluents are eventually discharged into surface and groundwater systems through runoff, direct discharge, unintentional spillages, infiltration, recharge, and surface water-groundwater interactions [7]. In Germany, for example, numerous pharmaceutical medicines such as antibiotics were identified in concentrations of up to mg·L^{-1} in groundwater [21]. The quantities observed in groundwater systems, however, are affected by a number of variables, including attenuation in the underlying soils. COVID-19 medicines may be unable to reach groundwater wells if the unsaturated zone is thick (i.e., 30–40 m) since penetration of polluted effluents is generally slow-moving and time-consuming [22]. As a result, municipal wastewater is one of the primary final destinations for these medicines and their metabolites, which are then dispersed into aquatic systems. Aside from surface and groundwater contamination, various actions may contribute to the spread of COVID-19 medicines and metabolites. This includes using untreated or processed wastewater for irrigation, recreation, and groundwater recharge. Humans may be exposed to COVID-19 medicines and their metabolites by oral intake of polluted waters. The usage and release of COVID-19 pharmaceuticals into the environment is depicted in Fig. 2. COVID-19 medicines and its metabolites provide

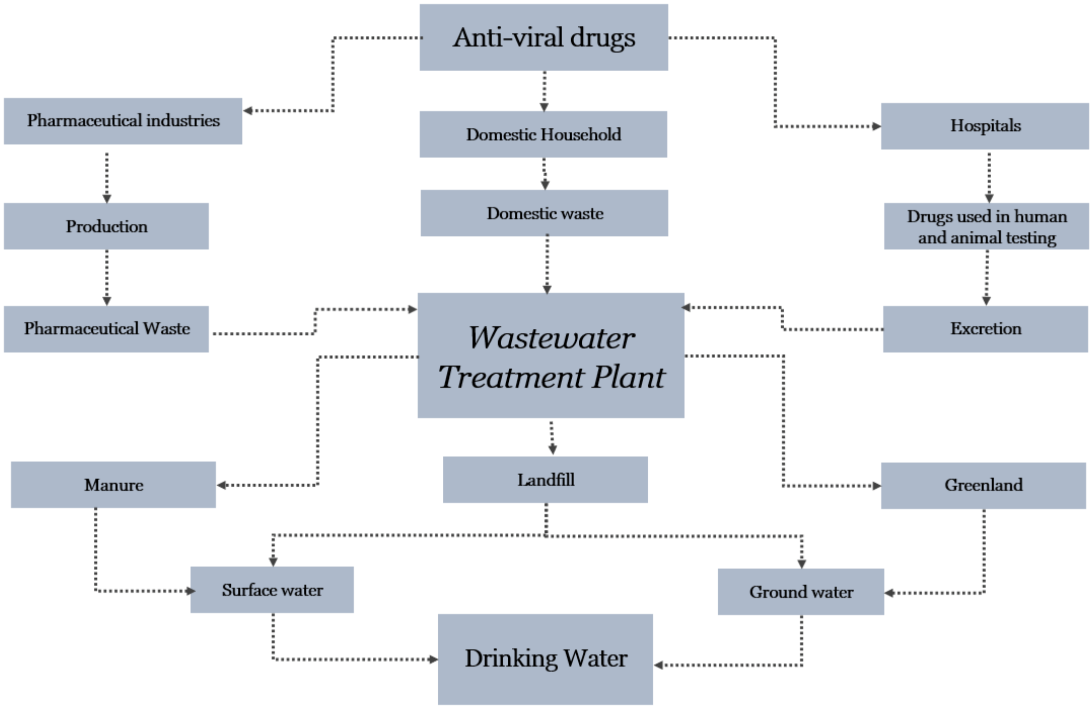


Fig. 1. Routes of antiviral drugs into wastewater treatment plants.

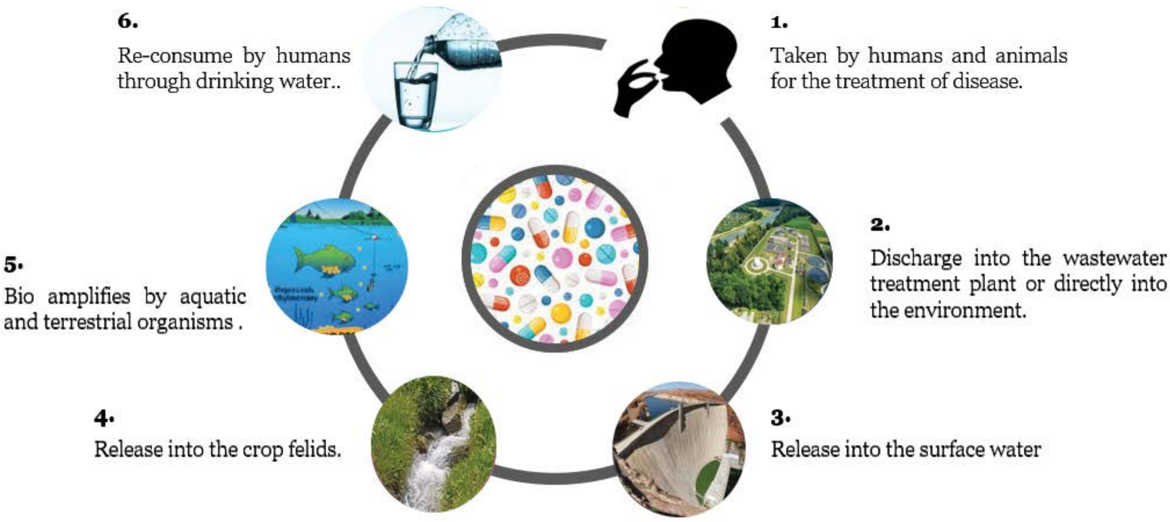


Fig. 2. Consumption and release of anti-COVID drugs in the environment.

a particularly significant risk of water contamination in low-income nations. This is due to the fact that low-income nations rely on traditional wastewater treatment systems based on primary and secondary treatment procedures, with no sophisticated treatment alternatives such as tertiary treatment [23]. The traditional methods of wastewater treatment such as coagulation–flocculation, precipitation, biodegradation, filtration. Adsorption can remove large particles of organic matter and many undesirable organic matter still remains in the treated water [24,25]. In order to remove micropollutants, modern techniques such as advanced oxidation processes (AOPs), UV in combination with oxidation (photolysis/photocatalysis), nanotechnology, and automatic variable filtration are used to remove challenging pollutants from wastewater [26]. Additionally, in low-income nations, there are no efficient legislative and regulatory structures for reducing water pollution.

As per WHO recommendations and health care institutions, the drugs used in the treatment of COVID-19 are remdesivir [27], molnupiravir [28–30], bebtelovimab [31,32], Paxlovid™-nirmatrelvir/ritonavir [33,34], favipiravir [35,36], ribavirin [37,38], ivermectin [39,40], lopinavir/ritonavir [41,42], hydroxychloroquine [43,44], chloroquine [45,46], azithromycin [47,48], baricitinib [49,50], isoprinosine (inosine pranobex) [51,52] and dexamethasone [43,44]. As seen in Table 2, some of them are the most commonly addressed in terms of their existence in bodies of water and their influence on the ecosystem. There is minimal information on the persistence of the other medications in watery effluents. Despite this, standard treatments such as ozonation, photolysis, electrochemical advanced oxidation process, photocatalysis, adsorption, activated sludge process, and membrane bioreactor. These methods effectively remove antiviral medications from the water supply, but they come with a number of disadvantages, such as high equipment costs, high energy consumption, secondary pollution, and the production of extra toxic byproducts [18]. However, modern techniques, such as liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) [53], high-performance liquid chromatography (HPLC) [54], ultra-performance liquid chromatography with positive electrospray ionization tandem spectrometry (UPLC-MS/MS), and (ultraviolet) UV-Vis spectrophotometer are known to determine antiviral drugs from aqueous samples [55].

3. Ecotoxicity of anti-COVID drugs on aquatic creatures

Many therapeutic medications used to treat COVID-19 and associated human health disorder has been reported previously, such as anti-parasitic (e.g., ivermectin and niclosamide), anti-malarial and DMARDs (e.g., chloroquine and hydroxychloroquine), antivirals and antiretrovirals (e.g., remdesivir, lopinavir, ritonavir, favipiravir, ribavirin, and oseltamivir) [60] . It is worth noting that, in addition to those mentioned above, the number of therapies now being utilized for COVID-19 and associated human health disorders is relatively diverse. Apart from the above-mentioned drugs, the other therapies are being used to cure COVID-19 such as analgesic, anti-inflammatory, and recently developed vaccines [7]. Till now, a variety of aquatic creatures, as well as freshwater and terrestrial organisms, have been employed to research the ecotoxicology of medicinal medications. Ivermectin and niclosamide have comparatively well-documented aquatic ecotoxicology when compared to other COVID-19 treatment drugs. Hepditch et al. [61] reported that 0.11 $mg\cdot L^{-1}$ of niclosamide, an anthelmintic drug, has an exposure EC_{50} for rainbow trout (*Oncorhynchus mykiss*). It is reported that favipiravir shown the ecotoxicological activities in mice and rats (2,000 $mg\cdot kg^{-1}$), and 1,000 $mg\cdot kg^{-1}$ in dogs respectively (PubChem 2021 [62]). Another study reported that the predicted non-observed effect concentration (NOEC) of lopinavir for algae was found to be 0.05 $\mu g\cdot L^{-1}$ which was below predicted effluent concentration (0.26 $\mu g\cdot L^{-1}$) [63]. For algae, ribavirin has shown the non-observed effect concentration for growth inhibition of less than 100 $mg\cdot L^{-1}$ [7]. Embryos of zebrafish treated with 100 μM remdesivir experienced delayed epiboly and poor convergent movement during gastrulation, as well as dose-dependent increases in mortality and deformity [64]. The COVID-19 epidemic has the overall impact of increasing the prevalence and concentrations of these medicines and their metabolites in the aquatic environment because, at the beginning of the pandemic, the therapeutic drugs that had been consumed globally were either experimentally approved or unapproved. Pharmaceuticals such as antivirals (remdesivir, lopinavir, ritonavir, favipiravir, ribavirin, oseltamivir, and umifenovir), antimalarials (chloroquine and hydroxychloroquine), and antiprotozoals (ivermectin) were used to treat flu and fever, which are the main symptoms of COVID-19. These

Table 2
Presence of anti-COVID-19 drugs in aquatic environment

Compound	Water matrix	Country	Concentration	References
Remdesivir	Effluent (conventional WWTPs)	–	319 $ng\cdot L^{-1}$	[56]
	Effluents WWTPs	–	54–270 $ng\cdot L^{-1}$	[57]
Ribavirin	Effluents (conventional WWTPs)	–	7,402 $ng\cdot L^{-1}$	[56]
Favipiravir	Effluents (conventional WWTPs)	–	4,231 $ng\cdot L^{-1}$	[56]
Lopinavir	Effluents (conventional WWTPs)	–	730 $ng\cdot L^{-1}$	[56]
Ivermectin	Tap water	France	5–20 $ng\cdot L^{-1}$	[58]
	Urban river	China	52 $ng\cdot L^{-1}$	[45]
Hydroxychloroquine	River water	Brazil	26.7 $mg\cdot L^{-1}$	[59]
Chloroquine	Domestic water	–	857 $ng\cdot L^{-1}$	[56]
	Surface water	–	78.3 $ng\cdot L^{-1}$	

therapeutic drugs are predominantly overused in residential areas. Additionally, the misconception about using antiparasitic or antiprotozoal drugs contributed to self-medication. As a result, concentrations within anthropogenic sources, including aquatic systems, may rise over the ecotoxicological thresholds (e.g., NOEC, EC_{50}) necessary to cause deleterious effects in land and marine animals. According to Groffman et al. [65], 'an ecological threshold is the point at which there is abrupt change in an ecosystem quality, property or phenomenon, or where small changes in environmental drivers can lead to the dramatic changes to the ecosystem'.

To better comprehend the issue at hand, a table was created that included the effects of the medications investigated in the environmental matrices, as described in the literature. Table 3 summarizes the consequences of these medications' presence in the environmental matrices.

4. Environmental risk and preventive measures of main drugs used in COVID-19 therapy

The effects of pharmaceuticals on the environment are numerous. Large-scale carbon emissions, water scarcity, pollution, and biodiversity loss are the effects. For all species on Earth, each of these consequences has enormous, short- and long-term impacts. It is indeed important to recognize and comprehend the effects. During the COVID-19 pandemic, the consumption of pharmaceuticals has been increases by tenfold and they ended up into the environment. The primary medications clinically investigated to treat COVID-19, as well as their occurrence and risk in environmental matrices, are given below:

4.1. Antiviral drugs

Antiviral drugs are class of drugs used to treat viral infections only such as HIV, herpes virus, influenza, hepatitis viruses. The drug residue and metabolite are discharged into the environment via wastewater, resulting in antiviral drug peaks in wastewater and aquatic waterways. Even in a small concentration, antiviral causes toxicity to the aquatic organism such as algae, fish and crustaceans.

4.1.1. Remdesivir and favipiravir

Remdesivir, brand name Veklury, and more specifically its active metabolite (GS-5734) shows broad antiviral activity *in vitro* against a diverse panel of RNA viruses, including the Ebola virus, MERS-CoV, and SARS-CoV [28]. Another broad-spectrum antiviral favipiravir, brand name Avigan, and in principle its active metabolite (T-705) can be potentially used against RNA viruses (*in vitro*), such as influenza H1N1/A, H1N1/pdm09, H5N1, and Avian Virus A (H7N9). Remdesivir has been approved by FDA and EMA to treat COVID-19, whereas favipiravir has been authorized for treating COVID-19 in several countries including Japan, Russia, Serbia, Turkey, India, and Thailand, under emergency provisions [35]. The ecotoxicity, degradability, and environmental risk of both drugs have been far less well documented. However, they can react with organic or inorganic matter during wastewater treatment. Furthermore, the consumption of these drugs during a pandemic will increase their presence in surface water effluents and may pose a high environmental risk because both are poorly soluble in water, and there is less information on the *n*-octanol/water partition coefficient has been published [70]. This coefficient is a key factor in the assessment of the environmental risk of the medicine for human use, according to the European Medicines Agency (EMA), making experimental investigations aimed at obtaining the value of *n*-octanol/water partition coefficient extremely important [71]. Unfortunately, data on the concentrations of remdesivir and favipiravir in the environment are currently limited. An early estimate of the amounts of favipiravir and remdesivir that rivers and lakes receive was found to be 430–2,120 $ng \cdot L^{-1}$ and 54–270 $ng \cdot L^{-1}$, respectively [57].

4.1.2. Lopinavir

Lopinavir boosted ritonavir, commonly sold under the brand name Kaletra was also approved by FDA to treat mild symptoms of COVID-19. Formally, this antiretroviral drug used to treat HIV/AIDS in a fixed dose. It is a protease

Table 3
Effect of selected drugs used for COVID-19 treatment in the environment

Drugs	Medicinal class	Effects in the environment	References
Remdesivir	Antiviral	Persistence in the environment due to stability to biodegradation. It can disrupt early embryonic development, blood flow, and behavior in aquatic creatures.	[64]
Ribavirin	Antiviral	It suppressed infectious pancreatic necrosis virus replication in fish cell cultures in a reversible manner.	[66]
Favipiravir	Antiviral	It caused environmental toxicity. Even at low concentrations, their metabolites and transformation products are more persistent in the environment.	[67]
Lopinavir	Antiretroviral	Low degradation properties result in the possibility of chronic exposure to the organism and cause harmful effects.	[68]
Ivermectin	Antiparasitic	It accumulates in plant roots and leaves, inhibits antioxidant functions and stresses aquatic plants; it is harmful to herbivorous invertebrates and has a negative impact on the ecology.	[69]
Hydroxychloroquine Chloroquine	Antimicrobial Antimicrobial	It has the potential for persistence and bioaccumulation. They have a high solubility and a low biodegradability.	[45]

inhibitor. Lopinavir/ritonavir suppresses the HIV protease enzyme by generating an inhibitor-enzyme complex, blocking gag-pol polyprotein cleavage. Domingo-Echaburu et al. [72] discovered a concentration of 0.033 $g \cdot L^{-1}$ of the antiviral lopinavir in effluent WWTPs (Spain) and they consider that the ecotoxicity of lopinavir has far less documented. According to the Swedish Pharmaceutical Environmental Categorization, "lopinavir has a high potential for bioaccumulation" ($\log D_{ow}$ = 4.7, which is greater than 4). The NOEC of lopinavir in green algae was found to be 1.914 $mg \cdot L^{-1}$ [73].

4.2. Antiparasitic drug – ivermectin

Ivermectin is an antiparasitic drug licensed by FDA that is prescribed to treat variety of chronic tropical diseases such as onchocerciasis, helminthiases, and scabies. The FDA has not approved ivermectin for the treatment of any viral infection. However, according to National Institute of Health in US, the cell cultures shows that ivermectin has the tendency to inhibit the replication of virus SARS-CoV-2 [74]. Furthermore, ivermectin docking may affect SARS-CoV-2 spike protein interaction to the human cell membrane. Some studies have also shown potential anti-inflammatory qualities, which may be beneficial in persons with COVID-19 [75]. At the beginning of the pandemic, due to the misconception, this drug widely overused domestically, to treat the COVID-19 thus it is found to be in water environment in high concentration. According to the Schweitzer et al. [76], the direct discharge of feces containing modest levels of ivermectin in water bodies was harmful for the species *Daphnia magna* and *Chironomus riparius*, having detrimental consequences for the survival, growth, and abundance of the aquatic organism. The widespread discharge of ivermectin in the Mediterranean Sea's maritime zones, which have three COVID-19 European epicenters (Italy, Spain and France). The scientists found that when ivermectin is present in large levels in an environment, it significantly reduces the abundance of nematodes and lowers biodiversity in deep sea. Because of its bio accumulative power, it is important to closely monitor all seafood, even those intended for human consumption, particularly if it is obtained close to the coast of nations that are severely affected by COVID-19 [77].

4.3. Anti-malarial drugs

4.3.1. Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine are both used to treat malaria, rheumatoid arthritis, lupus, and prophylaxis and are thus considered broad-spectrum antiviral agents. They belong to the aminoquinoline group. During the pandemic, some healthcare organizations allowed these two drugs in order to treat COVID-19 patients in combination with azithromycin in isolation. Thus, the emergency use of this drug caused a high consumption rate among the people affected by COVID-19. Hence, these drugs ended up in the environment. The behavior and monitoring of these drugs in aquatic environments are still far less well documented. According to the previous study, the detection of chloroquine in surface and groundwater samples from a Sango Ota, Nigerian Pharmaceutical Industry Sector. The average amount of chloroquine that the researchers were able to find was 0.11 $g \cdot L^{-1}$ in surface water and 5.014 $g \cdot L^{-1}$ in groundwater. One of the primary concerns raised by the scientists is that the therapeutic benefits of the drug may be lost if it were to end up in drinking water [78].

Another study revealed that due to their antibacterial and anti-microbial properties, both drugs shows high persistence bioaccumulation thus might transfer to the organisms causes harmful effects and show toxicity towards the environment [79]. According to Coelho et al. [80], when the samples of chloroquine were subjected to the degradation using acid, alkaline, and neutral hydrolysis, oxidation, heat, and light, it was found that chloroquine is only degraded in an alkali medium and by oxidation, which results in several unknown by-products.

Investigations like these should serve as a wake-up call to regulatory agencies, even though the global effects of high medicine consumption can cause immeasurable harm in a short period of time. In the context of the fact that the effluent and treatment plants lack sufficient procedures for the removal of developing pollutants, it is significant that the monitoring of these medications should become increasingly important [81].

Pharmaceutical environmental consequences can be reduced by removing drugs from the environment or regulating pharmaceutical discharge into the environment. Pollution remediation focuses on lowering pharmaceutical levels in environmental matrices following a pollution incident. Wastewater treatment plants are the most often utilized pollution cleanup methods. The drugs used in COVID-19 therapy has been eliminated poorly after primary and secondary treatment, but the removal efficiency can be high after tertiary treatment. For example, in South Africa at three conventional wastewater treatment plants, it was observed the removal efficiency of ritonavir (60%–95%), lopinavir (43%), and darunavir (66%), respectively [7]. However, the data are basically one of the few documented on the subject.

Anti-COVID-19 drugs are prone to both direct photodegradation by photon absorption and indirect photodegradation via reactive species such as photo-excited natural organic matter, hydroxyl radicals, and peroxyl radicals in surface water. Natural organic materials can speed up the photodegradation of photostable medications like ibuprofen and amoxicillin. Natural organic matter, on the other hand, can prevent photo-oxidation of sulfonamide antibiotics by inhibiting the triplet-induced photodegradation transformation or by competing for photons, particularly when the drug's photodegradation products have a high quantum yield [82].

Recently, improved oxidation/reduction methods have emerged as alternatives to natural photodegradation, which is slow and ineffective. TiO_2 and ZnO are photocatalysts that generate reactive species that help photodegrade drugs in aquatic environments. TiO_2 and ZnO are highly photoreactive, affordable, plentiful, and efficient photocatalysts. They frequently need UV irradiation for activation due to their enormous bandgap energies [83]. However, heterogeneous catalysts are vulnerable to inactivation over time and have a short contact duration. Furthermore, carbon compounds are frequently utilized as doping materials (e.g., carbon nanotubes, carbon quantum dots, or biochar) or as supports (e.g., as electrodes) in advanced oxidation/reduction processes because they boost photoactivity by improving electron-transfer interactions [84].

To improve drugs removal in wastewater, hybrid wastewater treatment has proposed, which combines conventional configurations (primary and secondary treatment) and/or membrane bioreactors with advanced post-treatment methods such as advanced oxidation processes (ozonation, Fenton oxidation, photocatalysis, and electrochemical oxidation) and adsorption (e.g., activated carbon and nanoparticles) [85].

5. Conclusion

This review article discussed the presence of pharmaceutical used in COVID-19 therapies in the environment, their routes of entry, their impact on the water environment, the ecotoxicity of drugs on aquatic creatures, as well as preventive measures such as wastewater treatment methods. These drugs include antivirals such as remdesivir, favipiravir, lopinavir, ribavirin, antiparasitic such as ivermectin, and, antimalarial such as chloroquine, and hydroxychloroquine. The review of publications on the detection of the foremost drugs tested in the therapies of COVID-19 allowed data to be collected demonstrating that these pharmaceuticals are already existent in environmental matrices, particularly aquatic one and that a rise in their exposure levels may occur. Possible source of these drugs is effluents from WWTPs, healthcare units such as quarantine centers, and hospitals, pharmaceutical industries, and households. A particular amount of parent dose and their metabolites are administrated to treat COVID-19, their metabolites are excreted through urine and feces and enters in municipal wastewater system. Furthermore, the enter in the surface water as well as ground water through run off, direct discharge, accidental spillages, and infiltration and thus contaminate drinking water.

In addition, these drugs may cause a possible ecotoxic effects, including acute and chronic toxicity. However, information on the effects of aquatic animals on ecosystem processes and trophic interactions is currently scarce. Up until now, there has been little information available on the hazards to human health posed by exposure to COVID-19 medicinal medications through drinking water and aquatic foods.

Physicochemical mechanisms such photodegradation, and removal via wastewater treatment procedures, as well as bio uptake, bioaccumulation, and biotransformation in aquatic animals were also discussed in the paper. However, the mechanism of degradation of drugs and their metabolites has been far less documented. Hence, studies to monitor the presence of these drugs used to treat COVID-19 drugs mentioned in environmental matrices, as well as studies to analyze the use of effective and financially feasible methods for removing these compounds with the possibility of being implemented into current wastewater treatment plants, are both necessary and extremely urgent.

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