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# Technology Development for the Removal of Covid-19 Pharmaceutical Active Compounds from Water and Wastewater: A Review

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**ABSTRACT.** The novel coronavirus (SARS-CoV-2) outbreak has given rise to an inevitable worldwide application of a wide variety of drugs. Some of these pharmaceutical active compounds excreted from the human body pass through water and wastewater treatment processes and appear in treated water, wastewater and biosolids. These have posed potential risks to the water quality of aquatic ecosystems and public health. As a result, the failure to lessen coronavirus drugs' negative environmental impacts is the subject of criticism. Hence, there is an urgent need for water utilities to upgrade their existing water and wastewater treatment processes to increase the removal efficiencies of these emerging micropollutants from coronavirus drugs, especially endocrine disruptor compounds. This review paper will present different treatment technologies, including physical, chemical, and biological, used in water and wastewater treatment plants to further remove pharmaceutical micropollutants from coronavirus drugs. Also, different classes of these drugs, their occurrence, and risks to aquatic ecosystems and human health have been discussed in the current study.

*Keywords:* Covid-19, coronavirus, aquatic ecosystems, environmental risk, health risk, occurrence, pharmaceutical active compound, removal processes, water and wastewater

## 1. Introduction

Over the recent decades, the increase in the consumption of drugs, endocrine disruptive compounds, and personal care products has caused an increase in the amount of micropollutants (MPs) in wastewater effluent and then freshwater supplies throughout the world (Khanzada et al., 2020). Although the amount of micropollutants is diminished during water and wastewater treatment plants, they cannot be totally removed. This demands water utilities to utilize advanced water and wastewater treatment processes to further remove the micropollutants (Nieto-Sandoval et al., 2019).

Micropollutants can be divided into four groups, including pharmaceutical active compounds (PhACs), pesticides, industrial products, and personal care products (PCPs), based on their features and consumption purposes. Recently, a number of PhACs have been globally detected in the aquatic environment (Khanzada et al., 2020). In spite of their low concentration, they may have potential risks to aquatic organisms and human bodies (Huerta et al., 2016; Praveena et al., 2018; Kumari and Kumar, 2022). More precisely, PhACs are designed to spend a particular period of time in the body for therapeutic approaches. This may be followed by excreting a great amount of PhACs, which tend to persist unchangeably, in the environments (Huerta et al., 2016). It is also reported that these substances, depending on the dose and time of exposure, may cause human diseases such as breast, testicular and prostate cancer, polycystic ovaries, and decreased male fertility (de Oliveira et al., 2020).

Since 2019, with the widespread incidence of the novel coronavirus (SARS-CoV-2), many drugs have been employed to manage and treat it in the worldwide. Since majority of these drugs, such as anti-inflammatory agents, antivirals, and anticoagulants, have already been consumed to cure other common diseases (Stasi et al., 2020; Parasher, 2021; Verma et al., 2021), they have been detected in different water sources over the years. The occurrence of these drugs in the environment has already been reported in the literature, before and during the pandemic (Santos et al., 2013; Golovko et al., 2014; Praveena et al., 2018; Gago-Ferrero et al., 2020; Madikizela et al., 2020; Mhuka et al., 2020; Rebelo et al., 2021). With regard to this point and a dramatic increase in their current consumption due to coronavirus treatment, the examination of their potential risk to the ecosystem and removal methods from water bodies are of great importance.

This review paper has been focused on the identification of different classes of coronavirus drugs, their potential risks to aquatic ecosystems and human health, their occurrence in the aquatic environment and their removal processes from water and wastewater.

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## 2. Classification of Coronavirus Drugs

Various groups of existing drugs have been used to treat SARS-CoV-2. The most commonly consumed repurposing drugs are as follow; immunomodulatory drugs: chloroquine, hydroxychloroquine, tocilizumab (Stasi et al., 2020; Parasher, 2021), baricitinib, anakinra (Stasi et al., 2020), antiviral drugs: remdesivir, lopinavir, ritonavir, favipiravir (Parasher, 2021; Verma et al., 2021), darunavir, atazanavir (Stasi et al., 2020), anticoagulants: low molecular weight heparin (Stasi et al., 2020; Wiersinga et al., 2020), and anti-inflammatory agents: dexamethasone (Stasi et al., 2020; Wiersinga et al., 2020; Parasher, 2021; Verma et al., 2021) and statins, such as rosuvastatin, simvastatin, atorvastatin, pravastatin, lovastatin and fluvastatin (Wiersinga et al., 2020). Some physicochemical features of the aforementioned drugs have been shown in Table 1.

## 3. Potential Risk Assessment of Coronavirus PhACs

Among physicochemical parameters of drugs shown in Table 1, Log $K_{ow}$ is a factor indicating the tendency of chemicals to accumulate in the aquatic species. Thus, Log $K_{ow}$ measurement of chemicals is a kind of bioaccumulation test (Kuroda et al., 2021). In terms of chloroquine and hydroxychloroquine, their transmission to the environment could result in water and wastewater, air, and soil pollution. In fact, this may be because of the antiviral and antibacterial features of the drugs. It has been found that the high risks of chloroquine and hydroxychloroquine contamination are attributed to bioaccumulation and the persistence of living organisms. Few studies in the literature focused on the fate and degradation of chloroquine and hydroxychloroquine in water (Bensalah et al., 2020; Midassi et al., 2020).

Ritonavir is one of the most toxic antiretroviral drugs towards aquatic organism such as fish (Bayati et al., 2021). Ritonavir and lopinavir are highly hydrophobic and tend to bioaccumulate to aquatic organisms and humans due to their Log $K_{ow}$ greater than 3.9. The higher hydrophobicity, the higher ecotoxicological risk (Race et al., 2020; Kuroda et al., 2021). Some antiviral drugs, such as favipiravir, can be considered almost non-biodegradable (Majumder et al., 2021).

Statins and some of their breakdown products are selected as model contaminants in aquatic ecosystems due to their bioactivity, toxicity, high Log $K_{ow}$, and environmental persistence (Martín et al., 2011). Synthesis and aquatic organisms like fish rely on triglycerides for their primary energy storage; therefore, exposure to different concentrations of statins (as lowering the cholesterol compounds) has led to increasing concerns about aquatic organisms (Bennett et al., 2007). Studies have demonstrated different detrimental effects of these micropollutants, such as endocrine dysfunctions in fish, bleeding in wild-type larvae, and cytotoxicity to primary rainbow trout (Shi et al., 2020).

Long-term exposure to dexamethasone may affect the fresh water crustaceans' growth due to converting dexamethasone into more hazardous derivatives in freshwater through photochemical processes (Guo et al., 2017). The associated environmental risk of remdesivir, such as environmental degradability and ecotoxicity, is still unknown (Race et al., 2020).

**Table 1.** Physicochemical Properties of Coronavirus Drugs

| Compound | Chemical formula | Molecular weight (g/mol) | Log $K_{OW}$[1] | $pK_a$[2] | Reference |
|---|---|---|---|---|---|
| Dexamethasone | $C_{22}H_{29}FO_5$ | 392.46 | 1.83 | $pK_1 = 3.3$<br>$pK_2 = 12.42$ | (Dolar et al., 2011; Kebede et al., 2020; Serpone et al., 2017) |
| Atorvastatin | $C_{33}H_{35}FN_2O_5$ | 558.64 | 4.46 | 4.5 | (Martín et al., 2011) |
| Pravastatin | $C_{23}H_{36}O_7$ | 424.53 | 3.10 | 4.6 | (Martín et al., 2011) |
| Simvastatin | $C_{25}H_{38}O_5$ | 418.56 | 4.68 | 13.2 | (Martín et al., 2011) |
| Rosuvastatin | $C_{22}H_{28}FN_3O_6S$ | 481.54 | 2.05 | 4.4 | (Martín et al., 2011) |
| Lovastatin | $C_{24}H_{36}O_5$ | 404.54 | 4.26 | 13.5 | (Martín et al., 2011) |
| Fluvastatin | $C_{24}H_{26}FNO_4$ | 411.46 | 4.85 | 4.1 | (Martín et al., 2011) |
| Ritonavir | $C_{37}H_{48}N_6O_5S_2$ | 720.94 | 6.27 | $pK_1 = 2.84$<br>$pK_2 = 13.6$ | (Abafe et al., 2018; Aminot et al., 2018) |
| Atazanavir | $C_{38}H_{52}N_6O_7$ | 704.90 | - | - | (Abafe et al., 2018) |
| Darunavir | $C_{27}H_{37}N_3O_7S$ | 547.70 | - | - | (Abafe et al., 2018) |
| Lopinavir | $C_{37}H_{48}N_4O_5$ | 628.80 | 6.26<br>5.94 | - | (Abafe et al., 2018; Madikizela et al., 2017; Wood et al., 2015) |
| Favipiravir | $C_5H_4FN_3O_2$ | 157.10 | 0.72 | - | (Thi et al., 2021) |
| Chloroquine | $C_{18}H_{26}ClN_3$ | 319.87 | 4.63 | 8.5 | (Midassi et al., 2020; Olaitan et al., 2014) |
| Hydroxylchloroquine | $C_{18}H_{26}CIN_3O$ | 335.88 | 3.03 | - | (Bensalah et al., 2020) |
| Remdesivir | $C_{27}H_{35}N_6O_8P$ | 602.59 | 1.74 | - | (Thi et al., 2021) |
| Baricitinib | $C_{16}H_{17}N_7O_2S$ | 371.42 | - | - | (Thi et al., 2021) |
| Anakinra | $C_{20}H_{23}N_5O_7S_2$ | 509.60 | - | - | (PubChem, 2021) |

1. Octanol-water partition coefficient
2. Acid dissociation constant

In addition to the above, the risk quotient (RQ) or hazard quotient (HQ) is an evaluation factor representing the possible risks of a targeted pharmaceutical to aquatic ecosystems, depending on the dilution of the recipient stream (Praveena et al., 2018). The HQ or RQ establishes the ratio between predicted environmental concentration (PEC) or measured environmental Concentration (MEC) in surface water, which the latter leads to a more realistic scenario, and predicted no-effect concentration (PNEC) of pharmaceuticals as shown in Equation (1) (Santos et al., 2013; Archana et al., 2017). This factor indicates the toxicity of pharmaceuticals towards different aquatic organisms, such as fish, green algae, and daphnids:

$$HQ \sim RQ = MEC / PNEC \quad (1)$$

With regard to Equation 1, RQ value ≤ 0.01, negligible; 0.01 < RQ value < 0.1, low; 0.1 < RQ value < 1, moderate, and RQ value ≥ 1, high possible risk to the environment is expected (Bischel et al., 2015; Kuroda et al., 2021). It should be noted that the presence of a mixture of various pharmaceutical compounds in water bodies, even at lower concentrations, alongside their transformation products might be more toxic than individual ones and pose more serious threats to the environment. Therefore, the synergic effect of a group of compounds should be taken into account to evaluate a more realistic environmental risk assessment (Santos et al., 2013).

Regarding the potential human health risk of PhACs, it was discovered that trace levels of active pharmaceutical ingredients or their metabolites in drinking water, particularly statins, have an effect on human embryonic kidney cells and human blood cells (Razavi et al., 2011). Although no acute effects on human health are predicted, the long-term effects of these chemicals can be detrimental as much as acute exposure, thus their discharge into the environment should be avoided (Margot et al., 2013).

As it is discussed above, fish is sensitive to most of coronavirus PhACs and their metabolites in the aquatic environment. As a result, the health risk posed by human exposure through the consumption of contaminated foods, such as fish, should also be considered. More recently, it has been reported that among all coronavirus drugs, ritonavir followed by rapamycin and lopinavir have the greatest impacts on risk exposure to the contaminated food consumption, fish, whilst the rest of the drugs pose negligible risk to human health (Kumari and Kumar, 2022).

In terms of human health risk evaluation, there is a factor, namely the hazard quotient of human health risk $HQ_{HH}$, which can be estimated according to Equation 2. Also, Drinking Water Equivalent Level (DWEL) can be calculated based on Equation 3:

$$HQ_{HH} = Cs / DWEL \quad (2)$$

$$DWEL = (ADI \times BW \times HQ) / (WDI \times AB \times FOE) \quad (3)$$

where surface water concentration of pharmaceutical compounds are referred to as Cs, ADI refers to the Acceptable Daily Intake (mg/kg day), BW is body weight for distinct age groups (kg), HQ is the Hazard Quotient supposed to be one, AB shows the gastrointestinal absorption rate, DWI is the Drinking Water Intake (L/day), and FOE indicates the Frequency of Exposure (de Jesus Gaffney et al., 2015; Praveena et al., 2018).

It is worth mentioning that $HQ_{HH}$ values less than 1 represent a negligible risk to human health, whereas $HQ_{HH}$ values over 1 demonstrate a potential risk to human health, both children and adults. Praveena and co-workers calculated the $HQ_{HH}$ value for dexamethasone in three rivers in Malaysia. The findings indicated that the presence of dexamethasone in the rivers poses a potential risk to both children and adults, particularly children because of their lower body weight (Praveena et al., 2018).

## 4. Occurrence of Coronavirus PhACs in the Aquatic Environment

According to the articles published from 2012 to 2021, the occurrence of coronavirus drugs in different water sources, the HQ and $HQ_{HH}$ measured by some researchers have been summarized in Table 2. As shown in Table 2, the presence of many coronavirus drugs had already been detected in the aquatic environment prior to the pandemic. Considering the current occurrence of different coronavirus PhACs, the increase in their consumption, and their possible risks to human health and the aquatic environment, there is an urgent need to adopt solid policies for the removal of the most dangerous PhACs from the aquatic environment.

## 5. Technology Development for the Removal of Coronavirus Drugs from Water and Wastewater

Several studies have revealed that conventional wastewater treatment plants are incapable of completely removing PhACs (Chatzimpaloglou et al., 2021). Hence, various methods have been developed to boost the efficiency of PhACs removal. This study has reviewed existing technologies in the literature for Covid-19 pharmaceutical micropollutants removal to help engineers develop novel technologies that can be used for the process upgrade. They have been summarized in Figure 1 and discussed in the following sections of physical, chemical and biological treatment processes.

### 5.1. Physical Processes

Among the physical processes, membrane filtration is a growing technology used in treatment of municipal drinking water and wastewater (Zhou et al., 2020). Ceramics and polymers are mainly used to fabricate membranes. Although ceramic membranes have apparent upsides of high stability, high flux, low fouling, lengthy lifetime, their relatively high fabrication cost, limited material types, complex preparation, and modification restrict the industrial application of this type of membranes. Consequently, polymeric membranes have established their position in water and wastewater treatment and desalina-

**Table 2.** Occurrence and Concentration of Coronavirus Drugs in Aquatic Environment

| Therapeutic Group | Drug | Country | Source | Concentration range | Concentration mean | Risk or hazard quotient (RQ or HQ) | Reference |
|---|---|---|---|---|---|---|---|
| Synthetic glucocorticoid anti-inflammatory drugs | Dexamethasone | Portugal | WWTP influent | n.d.[1] ~ < MQL[2] | < MQL | - | (Santos et al., 2013) |
| | | | WWTP effluent | < MDL[3] ~ < MQL | < MQL | $HQ = \frac{MEC}{PNEC} < 1$ for fish and Daphnid | |
| | | | University Hospital | 72.4 ~ 352 (ng/L) | 127 ± 87 (ng/L) | $HQ = \frac{MEC}{PNEC} > 1$ for fish < 1 for Daphnid | |
| | | | General Hospital | < MQL ~ 61.8 (ng/L) | 28.4 ± 19.5 (ng/L) | $HQ = \frac{MEC}{PNEC} < 1$ for fish and Daphnid | |
| | | | Pediatric Hospital | n.d. ~ 31.0 (ng/L) | <MQL | | |
| | | | Maternity Hospital | < MDL ~ 278 (ng/L) | 66.9 ± 98.9 (ng/L) | $HQ = \frac{MEC}{PNEC} = 1$ for fish < 1 for Daphnid | |
| | | Malaysia | Surface Water (Lui River) | n.d. ~ 0.11 (ng/L) | 0.02 (ng/L) | - | (Praveena et al., 2018) |
| | | | Surface water (Gombak River) | 1.75 ~ 8.78 (ng/L) | 6.31(ng/L) | $HQ_{HH}$ value > 1 in both adults and children | |
| | | | Surface Water (Selangor River) | n.d. ~ 2.21 (ng/L) | 0.73 (ng/L) | | |
| | | France | Ground Water/Surface Water | n.d. | n.d. | - | (Charuaud et al., 2019) |
| | | Spain | Piggery Wastewater (PWW) | n.d. | n.d. | - | (López-Serna et al., 2019) |
| | | Malaysia | Surface Water (Langat River) | 0.40 ~ 1.96 (ng/L) | 1.13 ± 0.71 (ng/L) | $RQ = \frac{MEC}{PNEC} > 1$ under acute and chronic exposure: high risk | (Wee et al., 2019) |
| | | South Africa | WWTP influent | < ILOD[4] | - | - | (Mhuka et al., 2020) |
| | | | WWTP effluent | < ILOD ~ 0.92 (ng/L) | 0.08 (ng/L) | | |
| Antiretroviral | Ritonavir | Switzerland | WWTP influent | - | 110 (±14) (ng/L) | - | (Margot et al., 2013) |
| | | | WWTP effluent | - | 90 (ng/L) | - | |
| | Ritonavir | France | WWTP influent | 53 ~ 155 (ng/L) | - | - | (Aminot et al., 2015) |
| | Lopinavir | South Africa | Hartebeesfontein WWTW Outflow | - | 130 (ng/L) | - | (Wood et al., 2015) |
| | | | Hartbeespoort Dam, Meerhof (2011) | - | 283 (ng/L) | - | |
| | | | Hartbeespoort Dam, Meerhof (2014) | - | 305 (ng/L) | - | |
| | Lopinavir | South Africa | WWTP effluents | > 3800 (ng/L) | - | - | (Ncube et al., 2018) |
| | Ritonavir | South Africa | WWTP | 0.787 ~ 20.0 (ng/L) | - | - | (Mosekiemang et al., 2019) |
| | Ritonavir | South Africa | WWTP influent | 1.6 ~ 3.2 (µg/L) | - | - | (Madikizela et al., 2020) |
| | | | WWTP effluent | 0.46 ~ 1.5(µg/L) | - | - | |
| | Darunavir | | WWTP influent | 0.069 ~ 43 (µg/L) | - | - | |
| | | | WWTP effluent | 0.13 ~ 17 (µg/L) | - | - | |
| | Lopinavir | | WWTP influent | 1.2 ~ 2.5 (µg/L) | - | - | |

Table 2 continued

| Therapeutic Group | Drug | Country | Source | Concentration range | Concentration mean | Risk or hazard quotient (RQ or HQ) | Reference |
|---|---|---|---|---|---|---|---|
| Antiretroviral | Lopinavir | South Africa | WWTP effluent | 1.9 ~ 3.8 (µg/L) | - | - | (Madikizela et al., 2020) |
| | Atazanavir | | WWTP influent | 0.064 ~ 6.4 (µg/L) | - | - | |
| | | | WWTP effluent | 0.078 ~ 7.4 (µg/L) | - | - | |
| | Atazanavir | Greece | WWTP influent | - | 0.02 (µg/L) | - | (Gago-Ferrero et al., 2020) |
| | | | WWTP effluent | - | 0.02 (µg/L) | - | |
| | Darunavir | | WWTP influent | - | 0.15 (µg/L) | - | |
| | | | WWTP effluent | - | 0.10 (µg/L) | - | |
| | Ritonavir | | WWTP influent | - | 0.03 (µg/L) | - | |
| | | | WWTP effluent | - | 0.025 (µg/L) | - | |
| | Atazanavir | South Africa | WWTP influent (Pretoria) | < ILOD | - | - | (Mhuka et al., 2020) |
| | | | WWTP effluent (Pretoria) | < ILOD ~ 308.2 (ng/L) | 75.12 (ng/L) | - | |
| | Ritonavir | | WWTP influent (Pretoria) | 4.08 - 393.90 (ng/L) | 72.77 (ng/L) | - | |
| | | | WWTP effluent (Pretoria) | 14.43 ~ 675.90 (ng/L) | 128.5 (ng/L) | - | |
| | Ritonavir | South Africa | Upstream of the Daspoort WWTW effluent discharge point (Apies River) | < ILOD ~ 58.84 (ng/L) | 25.54 (ng/L) | - | (Mhuka et al., 2020) |
| | | | Downstream of the Daspoort WWTW effluent discharge point (Apies River) | 5.0 ~ 52.57 (ng/L) | 35.04 (ng/L) | - | |
| | Darunavir | | WWTP influent | ≤ 920 (ng/L) | - | - | (Nannou et al., 2020) |
| | | | WWTP effluent | ≤ 350 (ng/L) | - | - | |
| | Lopinavir | | Surface water | n.d. ~ 305 (ng/L) | 239 (ng/L) | - | |
| | | | Ground waters | < LOQ ~ 0.02 (ng/L) | - | - | |
| Cholesterol-lowering (reducing) agent = Lipid regulating agents | Atorvastatin | Spain | WWTP influent | 70 ~ 90 (ng/L) | 80 (ng/L) | RQ = $\frac{MEC}{PNEC}$ = 1 for Daphnia magna | (Jelic et al., 2012) |
| | | | WWTP effluent | 40 ~ 60 (ng/L) | 50 (ng/L) | RQ = $\frac{MEC}{PNEC}$ < 1 for Daphnia magna | |
| | Atorvastatin | South-eastern USA | WWTP influent | 1560 ± 390 (ng/L) | - | - | (Ottmar et al., 2012) |
| | | | WWTP effluent | 2100 ± 50 (ng/L) | | | |
| | Simvastatin | South-eastern USA | WWTP influent | 1230 ± 210 (ng/L) | - | - | (Ottmar et al., 2012) |
| | | | WWTP effluent | 90 ± 20 (ng/L) | | | |
| | Atorvastatin | Spain | Urban wastewater Influent | - | 0.1 (µg/L) | - | (Ibáñez et al., 2013) |
| | Atorvastatin | Czech Republic | WWTP influent | 70 ~ 750 (ng/L) | 300 (ng/L) | - | (Golovko et al., 2014) |
| | | | WWTP effluent | 4 ~ 240 (ng/L) | 13 (ng/L) | | |
| | Rosuvastatin | | WWTP influent | 62 ~ 460 (ng/L) | 190 (ng/L) | | |
| | | | WWTP effluent | 8 ~ 320 (ng/L) | 54 (ng/L) | | |
| | Simvastatin | Greece: Ioannina City | WWTP influent | n.d. ~ 52.7 (ng/L) | 24.9 (ng/L) | - | (Kosma et al., 2014) |
| | | Ioannina hospital | | n.d. ~ 62 (ng/L) | 26.9 (ng/L) | | |
| | | Arta | | n.d. ~ 53.3 (ng/L) | 25.7 (ng/L) | | |
| | | Preveza | | n.d. ~ 39.8 (ng/L) | 17.9 (ng/L) | | |
| | | Agrinio | | n.d. | n.d. | | |
| | | Grevena | | n.d. ~ 59.4 (ng/L) | 26.2 (ng/L) | | |
| | | Kozani | | n.d. ~ 91.2 (ng/L) | 39.6 (ng/L) | | |
| | | Veroia | | n.d. | n.d. | | |

Table 2 continued

| Therapeutic Group | Drug | Country | Source | Concentration range | Concentration mean | Risk or hazard quotient (RQ or HQ) | Reference |
|---|---|---|---|---|---|---|---|
| Cholesterol-lowering (reducing) agent = Lipid regulating agents | Atorvastatin | Canada (Nova Scotia and New Brunswick) | WWTP influent | 85 ~ 280 (ng/L) | 240 (ng/L) | - | (Greenham et al., 2019) |
| | Simvastatin | Brazil | Wastewater treatment station (WWTS) | - | 50 (µg/L) | - | (da Silva et al., 2020) |
| | | India | 7 hospital wastewater treatment plants (WWTPs) | Hospital 1:625 (ng/L)<br>Hospital 2:250<br>Hospital 3:500<br>Hospital 4:250<br>Hospital 5:625<br>Hospital 6:185<br>Hospital 7:625 | - | RQ = $\frac{MEC}{PNEC}$ in wastewater effluent for the aquatic environment: high | (Khan et al., 2020) |
| | | South Africa | WWTP influents<br>WWTP effluents | - | 11.7 ± 3.2 (µg/L)<br>2.65 ± 0.8 (µg/L) | - | (Rebelo et al., 2021) |
| | | Portugal | Apies River WWTP | | 1.585 ± 0.3 (µg/L)<br>0.37 (µg/L) | | |
| Cholesterol-lowering (reducing) agent | Pravastatin | Colombia | CCWT[5] influent<br>CCWT effluent | 600 ~ 1234 (ng/L)<br>- | 917 (ng/L)<br>- | 0.1 < RQ = $\frac{MEC}{PNEC}$ <1 medium risk | (Bayati et al., 2021) |
| Immunomodulatory drugs | Chloroquine | Nigeria | Surface water<br>Underground water | n.d. ~ 0.11 (µg/L)<br>- | -<br>5.014 (µg/L) | - | (Olaitan et al., 2014) |

1. Not detected
2. < MQL: below method quantification limit
3. < MDL: below method detection limit
4. Instrument limit of detection
5. Constructed wetlands treatment system

tion. Their availability, pore size range, low relative cost, and ease of processing are some of their benefits (Galiano et al., 2018; He et al., 2019; Qing et al., 2019).

According to the membrane pore size, the pressure-driven membrane processes can be divided into microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO) (He et al., 2019). Note that RO, NF, and UF are more promising membrane processes for the totally and near-totally removal of many types of micropollutants from wastewater and water. Furthermore, researchers pay attention to non-pressure-driven membranes, including forward osmosis (FO) and membrane distillation (MD) systems, as possible implementation candidates in the future due to their high-quality performance and low operating expenditures (Khanzada et al., 2020).

Despite the benefits of membrane filtration processes, including simple operation and maintenance, less required space, low sludge production, and fewer chemical storage tanks and supply systems, they have some drawbacks. Membrane fouling (resulting in low permeation) and incomplete removal of soluble contaminants are critical issues in the membrane filtration processes (Esfahani et al., 2019). As a result, cleaning must be executed periodically to prevent membrane fouling (Li et al., 2019). These phenomena reduce the productivity and lifetime of the system.

In 2011, Davor Dolar and co-workers examined the performance of six high-pressure membranes, including two RO membranes (LFC-1 and XLE) and four NF membranes (NF90, NF 270, NF, and HL) for the removal of dexamethasone and four other pharmaceutical compounds from different types of water samples. Based on this research, a higher rejection of five pharmaceutical compounds, particularly dexamethasone, was achieved with both RO and NF90 membranes. It was reported that size exclusion was the main mechanism, whilst physicochemical interactions between solutes and membrane and charge exclusion were the main separation mechanism in other NF membranes. Considering the effective diameter of dexamethasone in water ($d_c$), which is bigger than the pore sizes of LFC-1, XLE, and NF90 membranes, and its molecular weight higher than the molecular weight cut-off of the membranes, this compound was removed completely with the mentioned membranes in all water samples (Dolar et al., 2011).

In addition to membrane filtration, adsorption processes using nanoparticles, carbon nanotubes, nanocomposites, and nanofibers are other physical methods for PhACs removal. In spite of the large surface area of nanoparticles suspensions, some of their downsides have made them unattractive for wastewater treatment. Their tendency towards aggregation and the cost and complexity of removing them in a post-treatment step, with the exception of magnetic nanoparticles, are their demerits. In terms of nanofibers, their advantages have made them technically feasible for water treatment. Nanofibers benefit from larger surface area to volume ratio properties in comparison to nanoparticles. Moreover, polymer-based nanofibers have shown excellent mechanical features, easy to reuse, and high interfacial reactivity. It should be highlighted that the majority of nanomaterials have failed to be used in industry. More recently, Kebede et al. (2020)

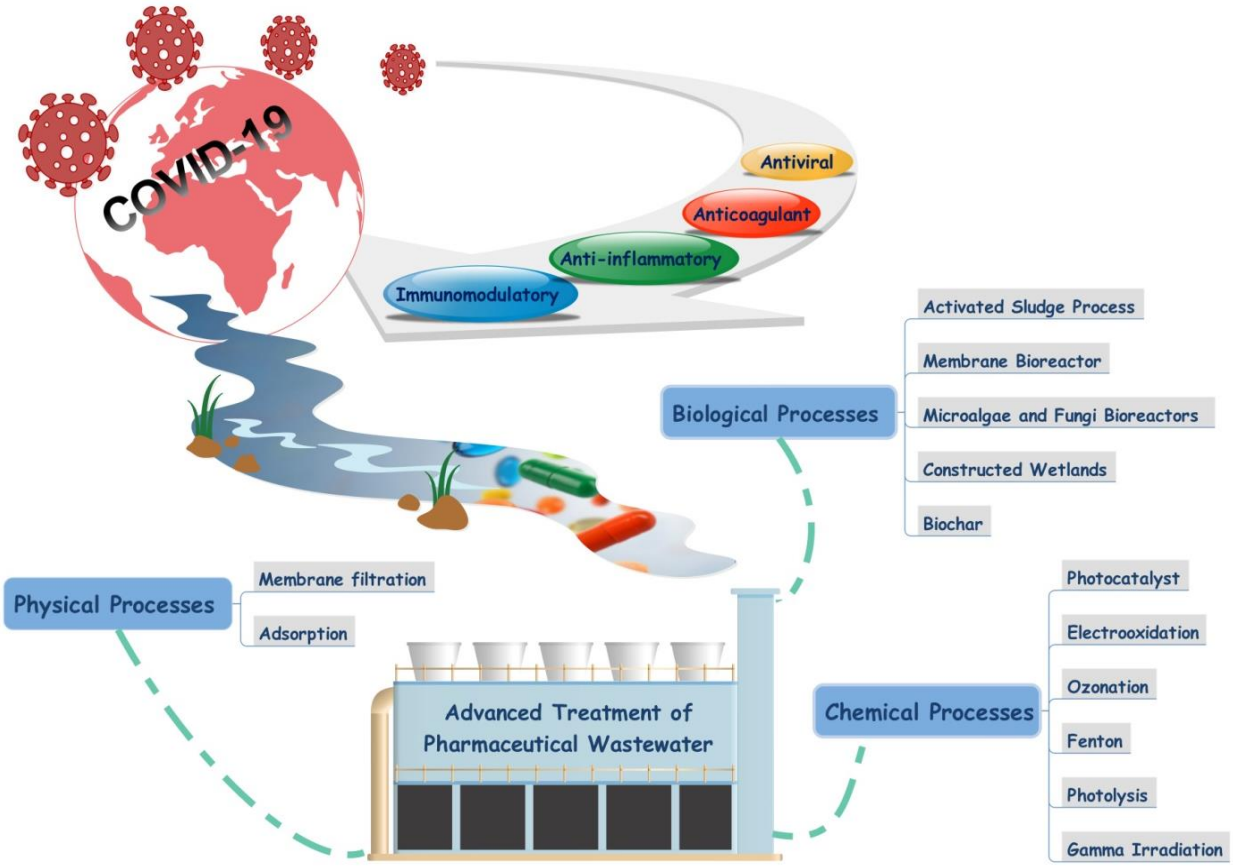


**Figure 1.** Coronavirus drugs removal methods from water and wastewater.

have fabricated nanofibers from *Mondia whitei* root to remove 13 antiretroviral and related drugs from wastewater streams. On the basis of the results, 75 ~ 320 mg/g was gained as the maximum adsorption capacity of the nanofibers for a mixture of the mentioned drugs.

Jonas Margot and colleagues conducted one-year experiments to compare the removal efficiencies of 70 pharmaceutical micropollutants treated using a conventional WWTP, which was upgraded by two different tertiary treatment processes separately. These two tertiary treatment processes were a large-scale combination of ozonation and sand filtration, and a large-scale combination of adsorption by powdered activated carbon and UF membrane. Although 25% of ritonavir removal was reported for the conventional WWTP, more than 78 and 56% were reported for ritonavir removal using a conventional WWTP followed by the tertiary treatment processes in the order mentioned above. Also, these data were measured more than 70%, and 65% for simvastatin removal when 5.9 mg/L of ozone and 12 mg/L of powdered activated carbon were considered average doses (Margot et al., 2013).

### 5.2. Chemical Processes

Chemical processes used for micropollutant removal mainly include advanced oxidation processes, such as photocatalytic process, electrooxidation, ozonation, Fenton/Fenton-like processes, photolysis, and gamma irradiation. The Advanced Oxidation Processes (AOPs) are one of the attractive treatment processes which are based on hydroxyl radical (•OH) formation reactions to mineralize the micropollutants incompletely or completely (Karungamye, 2020).

A heterogeneous photocatalytic process as a member of AOPs has recently gathered significant attention. Most efforts have been dedicated to using visible light sources for its applications. In this case, da Silva et al. (2015) synthesized $TiO_2$ZN-$SiO_2$ as a UV and visible-light-driven photocatalyst of the catalyst remnant from a Ziegler-Natta catalyst petrochemical plant. This photocatalyst was used to degrade some drugs, including atorvastatin calcium, dexamethasone. The synthesized photocatalyst could degrade the mentioned drugs, 48.6% and 45.2% under UV and visible irradiation, respectively. Additionally, $TiO_2$ZN$SiO_2$ exhibited acceptable durability even after five-time reactions.

Decomposition of dexamethasone in both synthetic solution and hospital wastewater was conducted by Ghenaatgar et al. (2019). Zirconium dioxide ($ZrO_2$) and tungsten trioxide ($WO_3$) nanoparticles were used in the photocatalytic process. Regarding the effective parameters, they claimed that the maximum efficiency, equal to 100%, occurred at a pH value of 3, dexamethasone concentration of 5 mg/L, and catalyst doses of 500 and 1500 for $ZrO_2$ and $WO_3$, respectively. Moreover, they

found that the percentage of dexamethasone removal using BLB/$WO_3$ as an irradiation source is twice that of Halogen/$WO_3$. Although the mineralization of dexamethasone in the hospital effluent was lower than the synthetic solution, it was 100% removed with a contact time of 100 min using a halogen/$WO_3$ radiation source.

Piecha et al. (2010) reported their studies on the photocatalysis of synthetic wastewater consisting of cholesterol-lowering statin drugs (including simvastatin, lovastatin, and pravastatin) in the presence of $TiO_2$-based catalyst. Because of the susceptibility of statins to hydrolysis under different pH conditions (be in the lactone forms at pH = 7 and open hydroxy forms at pH = 9), the effect of the experimental medium pH (7, 9) on the efficiency of photodegradation was evaluated. It has been found that despite simvastatin and lovastatin, whose transformed forms are strongly dependent on the solution pH, hydroxyl acid forms are the only existing form of pravastatin compounds irrespective of the pH value. Besides, dissolved oxygen concentration plays an important role in photocatalytic reactions. It was found that replacing oxygen with air requires a longer degradation time. The results showed that complete removal could be achieved during 120 min regardless of the pH value, suggesting the effectiveness of the adopted mineralization method in degrading statins. However, presenting in the hydroxyl forms facilitated the degradation process resulting in a faster removal.

Pazoki et al. (2016) synthesized different concentrations of a photocatalyst ($TiO_2$/Ag) and studied the degradation mechanism of dexamethasone in water samples under both visible and UV light. In addition, an optimization of the principle operational parameters, including pH, temperature, drug concentration, and concentration of adding $H_2O_2$ oxidant, was carried out. The authors found that at a temperature of 35 °C, photocatalyst concentration of 1.5 g/L as well as pH = 3, 71.5 and 82.3% of dexamethasone could be effectively removed under visible and UV light irradiation, respectively by adding (15 mg/L) $H_2O_2$ to dexamethasone (5 mg/L).

Being among the three best-selling drugs in the United States as well as the frequent occurrence in European effluent made treating rosuvastatin (RST) a challenging issue which drew Segalin et al. (2015) attention to conduct intensive research on its photocatalytic removal by ZnO. It was revealed that about 94% removal during 15 min of reaction could be achieved in a synthetic wastewater sample containing 26 mg/L of RST, 550 mg/L of ZnO, and at pH = 7 under UV-vis irradiation.

Razavi et al. (2011) were determined to study the photochemical behavior of atorvastatin in model samples containing two different concentrations of atorvastatin (i.e., 35.8 mM and 35.8 nM, which is an environmentally representative concentration) at pH = 7 through specifying the role of hydrolysis, direct photolysis, reaction with hydroxyl radical (•OH), singlet oxygen ($^1O_2$ or $O_2$ ($^1D$)), and excited-state dissolved organic matter. It was reported that 23% of photodegradation efficiency was achieved at the high concentration of atorvastatin, reaction with singlet oxygen ($^1O_2$), while hydroxyl radical (•OH) had an insignificant role in this regard. It was concluded that the rest of the responsibility for photodecomposition (nearly 77%) was taken by the excited state of dissolved organic matter. Concerning low concentration, dissolved organic matter made the major contribution to the photoreduction to the extent that the contribution of other active species could be neglected.

Liu et al. (2020) developed an approach through coating $ZnIn_2S$ on the membrane surface (polyvinylidene fluoride) to elevate photocatalytic activity and reduce the membrane fouling concurrently. To fabricate a dynamic photocatalytic membrane, membrane separation and photocatalytic technology were coupled. Due to the large specific surface area and porous structure of $ZnIn_2S_4$ and the creation of the photocatalytic layer, the dynamic photocatalytic membrane showed notable accomplishment in the removal of fluvastatin (97.19%) and antifouling properties in comparison with the initial membrane (5.69%).

Wang et al. (2020) investigated the role of 28 oxidated aromatic compounds (OACs) in natural water on the photo-generation of $^1O_2$. They found that the types of functional groups of OACs can be influential in the $^1O_2$ production, and OACs containing -$OCH_3$ group and benzoquinone are the best choices. Eventually, the effect of 2, 6-dimethoxy-1, 4-benzoquinone upgrade on the photodegradation of ATV was mediated by $^1O_2$ production.

Zero-valent copper ($Cu^0$) nanoparticles synthesized using ultrasound were used in a hybrid procedure for the degradation of lovastatin (Dinesh et al., 2020). The experimental conditions included pH = 2 to 12, catalyst doses of 0.001 ~ 0.075 g/L, as well as different concentrations of $H_2O_2$. The results showed that adding the catalyst to the lovastatin solution increases the removal efficiency of the drug from 4.08 to 54.86 due to radical production and an increase in the reaction rate. Further, the addition of $H_2O_2$ also increased degradation efficiency, and finally, 93.2% of the drug removal efficiency was carried out under optimal conditions with a pH of 4.

Electrooxidation (known as electrochemical or anodic oxidation) is considered the other technique of AOPs, which have grown in popularity due to the removal of difficult degraded chemicals. Two electrodes, including anode and cathode with a power source connected, play a vital role in the destruction of contaminants during the electrooxidation process. So that, either anodic reaction degrades adsorbed pollutants on the surface of anode (direct oxidation process) or formed strong oxidants interact with pollutants in the presence of an electrolyte (indirect oxidation process) (Babu et al., 2009). Accordingly, Babu et al. (2009) utilized electrochemical degradation of dexamethasone (and gentamicin) from an industrial pharmaceutical plant effluent. The treatment process was performed in a continuous flow reactor, as well as the electrolyte contained NaCl. It was found that as high as 85.56% of chemical oxygen demand (COD) removal could be achieved under the optimum operating conditions (applied current density of 4 A/$dm^2$, the flow rate of 10 L/h, and 3 g/L of NaCl).

Seeking a cost-effective alternative for conventional treatments which couldn't efficiently degrade simvastatin and its derivatives. Mussa et al. (2016) adopted the electrochemical oxidation treatment using graphite-poly vinyl chloride (PVC) electrode as the anode for both synthetic and real wastewater.

In the case of a synthetic water sample, initial concentration of simvastatin (30 and 50 mg/L), electrolyte (NaCl) concentration (0, 2, and 4 g/L), and applied voltage (6 and 10 V) were chosen so that their influence on the efficiency of the process could be evaluated. Based on the results, 4 g/L of NaCl and applied voltage of about 10 V could end in the complete removal of simvastatin after 40 min of electrolysis time. In addition, it was suggested the lower the initial simvastatin concentration, the higher the removal efficiency of simvastatin. Furthermore, since the electrolyte plays a vital role in the electrochemical oxidation process, a noticeable difference could be seen in the results of experiments conducted with or without NaCl. In the case of a raw sewage sample, about 68% removal of simvastatin could be achieved, which is much less than that obtained in the synthetic samples during 40 min of the reaction. This observation may root in the competition between simvastatin and organic matter compounds existing in the wastewater for degrading through the electrochemical oxidation treatment.

Arsand et al. (2013) investigated the effects of electrocoagulation in the removal of dexamethasone from hospital effluent and aqueous solution. They found that with increasing electrolyte concentration and electrocoagulation current, the degradation efficiency of dexamethasone increased. Under optimal conditions, 38% of the drug was removed, the same results for the aqueous solution and hospital wastewater. In addition, colloids were removed and the organic load of the hospital wastewater was reduced by electrocoagulation.

Further, the electrochemical process could be done in conjunction with other AOPs to enhance the performance of the process. In this regard, the combination of electrochemical oxidation by boron-doped diamond with UV irradiation and sonication was studied by Bensalah et al. (2020). Hydroxychloroquine was considered the drug contaminant, and the aim of the study was dedicated to its degradation from aqueous solution. They demonstrated that complete hydroxychloroquine degradation was achieved by electrochemical oxidation with the presence of a boron-doped diamond anode. Meanwhile, applying UV irradiation or sonication led to the improvement of the hydroxychloroquine and process intermediate removal efficiency, and also the kinetics.

It is worth noticing that the electrochemical procedure could result in the ferrate (Fe(VI)) generation as the supercharged iron molecule, which is a potential chemical for water and wastewater treatment. The dual functions of Fe(VI) as an oxidant and a subsequent coagulant/precipitant lead to both oxidative eliminations and removal of phosphate. In this connection, Yang et al. (2012) applied Fe(VI) treatment technology for the removal of androgens, progestogens, and glucocorticoids. Among the different types of drugs, the removal efficiency of dexamethasone was investigated by 13.3% under the Fe(VI) exposure (20.2 ± 3.0 mg/L min) at the best-operating conditions.

The other effective type of AOPs for degrading pharmaceutical compounds is the ozonation process. This process includes both direct ozonation, a reaction between the contaminant and ozone molecule, and indirect ozonation, a hydroxyl radical reaction. In terms of using ozonation for drug removal, Mathon et al. (2021) studied the kinetic rate constants for 47 organic micropollutants (contained dexamethasone) between micropollutants and ozone. They also classified dexamethasone into the low-oxidizable group based on $k_{O_3} = 1.96 \pm 0.6$ L mol$^{-1}$ s$^{-1}$ in batch reactors. Hence, the indirect pathway should be preferred for dexamethasone, which is considered a low-oxidizable micropollutant.

Fenton/Fenton-like processes are classified as one of the most frequently used AOPs. In these processes, $Fe^{2+}$ and hydrogen peroxide ($H_2O_2$), respectively, play the role of the catalyst and the oxidant. The mechanism of Fenton/Fenton-like processes contains the degradation of $H_2O_2$ to supply essential HO•. Accordingly, Midassi et al. (2020) investigated the electro-Fenton oxidation decomposition of the chloroquine. Since the formation of $H_2O_2$ affects the electro-Fenton process significantly, various operating conditions related to $H_2O_2$ formation, including pH, $O_2$ flow rates, and the current density, were evaluated. 60 mA/cm$^2$ of the current density and 80 mL/min of the $O_2$ flow rate at pH = 3 and applying boron-doped diamond anode and carbon felt cathode led to the high $H_2O_2$ production, as well as total chloroquine degradation. Moreover, compared with anodic oxidation using Pt and electro-Fenton-Pt and boron-doped diamond anodes, electro-Fenton-boron-doped diamond oxidation revealed more practical performance. Interestingly, oxamic, 7-chloro-4-quinolinamine, and oxalic acids were detected as the intermediates during the decomposition process.

It should be emphasized that exposure to any light source irradiation, individually, results in chemical decomposition or splitting based on free radical reactions (photolysis). Therefore, the important role of photolytic degradation in the environmental fate of drugs must be regarded as a better understanding of AOPs for pharmaceutical degradation under light irradiation. In this way, the hydroxychloroquine degradation dissolved in ultrapure and three natural waters was investigated by photolysis under simulated solar exposure. During the hydroxychloroquine photodegradation, adding pH (alkaline conditions), humic acids, nitrate, and iron increased the hydroxychloroquine degradation. On the other side, the presence of chloride, bromide, and sulfate diminished the efficiency of the process (Dabić et al., 2019). The aquatic environmental fate of favipiravir and two other anti-influenza drugs was investigated by Azuma and co-workers for the first time. Based on their monitoring of an urban river located in Japan for a nine-month period, it was reported that the amount of favipiravir dramatically decreased under sunlight irradiation through photodegradation processes (Azuma et al., 2017).

To elucidate the pros and cons of advanced oxidation processes in the elimination of fluvastatin, Liu et al. (2019) provided a detailed comparison between its degradation by photolysis and $ZnIn_2S_4$ photocatalysis in synthetic samples under UV-Vis radiation based on reactive oxygen species, degradation pathways, and toxicity evaluation. In accordance with the results of the photolytic process, 71.01% degradation of the target pollutant was achieved while no reactive oxygen species were found. Furthermore, limited photon energy not only ended in preferential cleavage of lower energy bonds (i.e., the C–C, C–N, and C=C bonds) compared with higher energy ones (i.e., the rings), but also broke up fluvastatin to a series of stable products whose

inherent complexity inhibited their further mineralization to $CO_2$ and $H_2O$. The latter observation caused only 15.62% COD removal. Moreover, such stable products, including cyclization and carbonyl functional ones were exhibited higher toxicity in comparison with fluvastatin itself. In the case of $ZnIn_2S_4$ photocatalysis, the synergetic effect of reactive oxygen species ($\bullet O^{2-}$ and •OH) brought about the enhancement of fluvastatin removal up to 99.79%. In addition, direct cleavage of the chemical bonds and the hydroxylation reaction was regarded as the main reaction pathways. Concerning COD, contrary to photolysis, the presence of photocatalyst in photocatalytic reaction and its sequential activation facilitated the decomposition of fluvastatin which in turn resulted in increasing the COD removal up to 43.05%. The ability of photocatalytic reaction in the degradation of a wide variety of compounds gives rise to creating less toxic products, which is of great importance in regards to environmental issues.

Wang et al. (2018) conducted research on the potential of photolysis of atorvastatin in synthetic water solutions and its degradation process by solar irradiation. It was found that singlet oxygen ($^1O_2$) had a dominant effect in the photolysis of the atorvastatin, with a 67.14% contribution to the photolysis of the drug under optimal conditions. In comparison, it accounted for 0.66% for $^1OH$.

Guo et al. (2017) developed gamma irradiation to generate •OH and •H, which directly interacts with organic compounds, and was used to remove dexamethasone with distinct concentrations in aqueous solutions. According to their study, the performance of the method was more remarkable for a low concentration of dexamethasone in the solution. They also investigated the effect of additive presence such as $H_2O_2$ in the solution on the target pollutant degradation using gamma irradiation.

Drug deconstructing and removal sometimes require the synergic cooperation of AOPs, where combined methods of AOP are needed. Under this combination, one of the obvious advantages would be the prevailing destructive influences of individual methods. In the number of different types of AOPs, the combination of sonolysis with other techniques could be a practical choice in drug degradation efficiency. In this case, radical reactions, which were promoted by sonication, result in the pharmaceutical decomposition to other products. In an investigated study by Dinesh and Chakma (2019), lovastatin degradation was evaluated under different combinations of AOPs initiated by a metal-free g-$C_3N_4$ catalyst. The degradation efficiency was achieved 59% by sonolysis in the presence of a g-$C_3N_4$ catalyst. Since more combinations of AOPs can help improve the degradation efficiency, a maximum decomposition of ~93% was obtained in the presence of a g-$C_3N_4$ catalyst and $H_2O_2$ enhancer under the UV-C radiation during the sonolysis. Additionally, the fitted results demonstrated pseudo-first-order reaction kinetics for lovastatin degradation.

Patibandla et al. (2018) devoted their survey to studying the toxicity of simvastatin before and after the treatment with ferrate (VI). The influence of parameters including the concentration of the contaminant (10 and 100 µg/L), the dosage of ferrate (VI) (1 ~ 5 mg/L), and pH of the solution (4 ~ 11) were assessed. The results implied that over 70% removal could be achieved in a solution containing 100 µg/L simvastatin and 3 mg/L of ferrate (VI) at pH = 6. Estimating the toxicity was performed through investigating the changes in the expression of specific genes (i.e., CAT, TNF-α, IL-1β, and Bcl-2) in the Zebrafish as a model organism by conducting the Vibrio fischeri luminescent test. It was concluded that changes in the expression of the all-aforementioned gene were detected, which revealed a high degree of toxicity of simvastatin. However, the ferrate (VI) treatment could effectively decrease its toxicity while no additional harmful products were generated.

### 5.3. Biological Processes

The technology of biological treatment is commonly used to remove emerging contaminants and pharmaceutical compounds. Currently, different prescription drugs during the Covid-19 pandemic can become one of the main sources of water pollution. Therefore, monitoring of relevant medical effectors in wastewater appears to be necessary prophylaxis for future environmental water management. Among the wastewater treatment systems, biological systems have received specific attention due to their ability to withstand severe conditions in fluctuations of pollutant loads as well as energy-saving efficiency and low cost (Tormo-Budowski et al., 2021). There are several biological processes for removing pharmaceuticals, such as the activated sludge process, membrane bioreactor, biological activated carbon, constructed wetlands, trickling filters, microalgae, and fungi bioreactors (Nagda et al., 2021).

In the Covid-19 pandemic, many patients are treated with various medications such as statins, dexamethasone, etc. High levels of these drugs are excreted and enter WWTPs in biologically active forms. The activated sludge process is a biological wastewater treatment in which bacteria and microorganisms remove biodegradable organic compounds in the presence of dissolved oxygen with returned sludge. Therefore, the basic elements of this process include an aeration tank for mixing continuously activated sludge and oxygen for growing degrading microorganisms (Sipma et al., 2010). The stability studies of statins reported that the atorvastatin, simvastatin, and rosuvastatin were unstable in both water and sludge. To be more precise, the degradation rate in sludge was higher than in water due to the existence of different bacterial species having a variety of enzymes, which can catalyze the processes of degradation (Sulaiman et al., 2015).

The occurrence of atorvastatin and simvastatin as cholesterol-lowering statin drugs was detected in WWTP of the Southeastern USA. Ottmar et al. (2012) measured the presence of both statins in the influent of the WWTP and evaluated biodegradation parameters during activated sludge treatment. It was found that the removal efficiency of the targeted compounds during conventional treatment was in the range of 85 to 90% of each drug. The results showed toxicity effects of these statins are not currently a significant environmental problem. In another study, the removal of 42 pharmaceutical compounds has been investigated in the WWTP influent and effluent. The removal efficiency of pharmaceuticals was verified in the range of 30 to

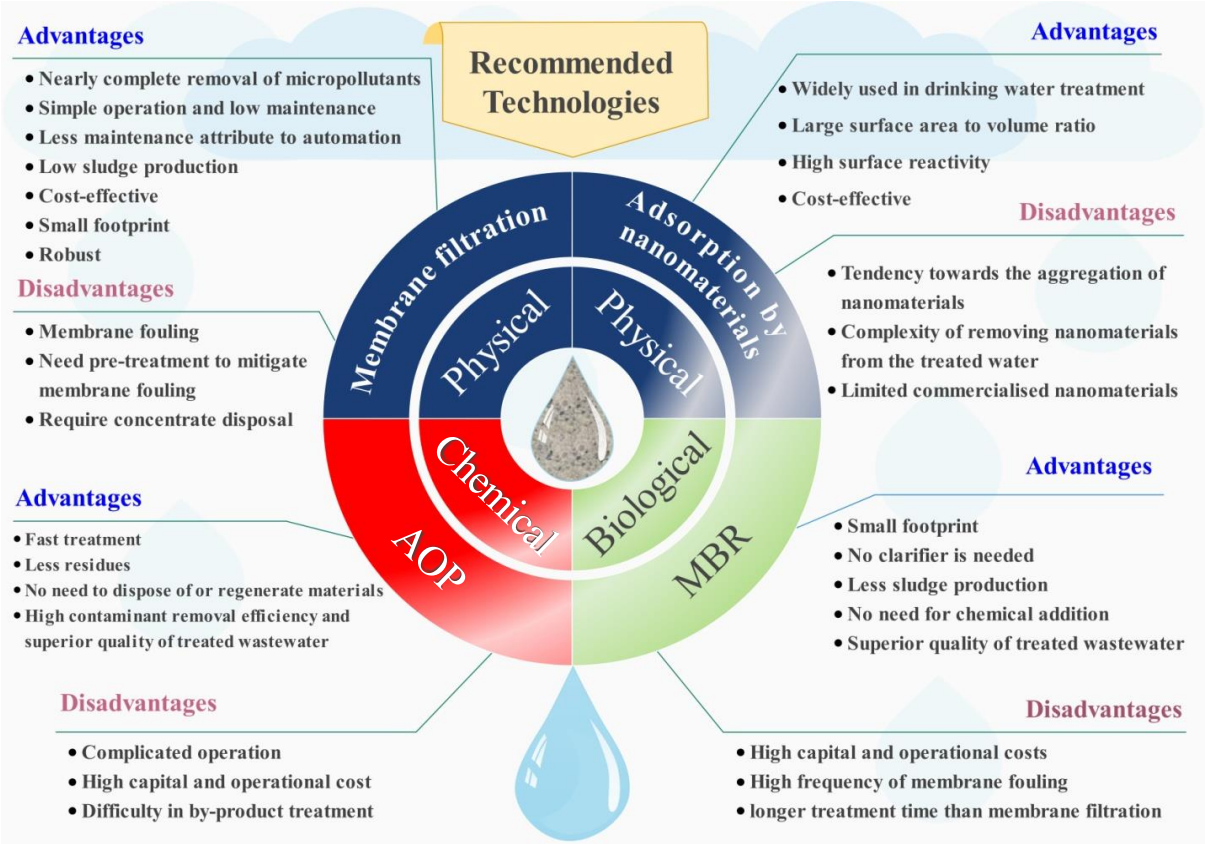


**Figure 2.** The summary of advantages and disadvantages of recommended technologies by this study for PhACs removal in water/wastewater treatment.

60% during anaerobic co-digestion (AcoD) of sewage sludge, which removal of atorvastatin was around 60% in AcoD (Jelic et al., 2012). In a single biological reactor combining anaerobic and aerobic processes for removing simvastatin from domestic sewage, da Silva et al. (2020) showed that the rate of simvastatin degradation was 62%, and COD removals were estimated at 80% in domestic sewage treatment.

In terms of the membrane bioreactor (MBR), the membrane, such as MF or UF, is employed as a clarifier instead of settling based on gravity. There are two main MBR configurations according to the membrane position, including side stream or cross-flow MBR and submerged MBR (Nagda et al., 2021). In 2012, the performance of a pilot-scale submerged MBR during one year was examined for the removal of 68 pharmaceutical compounds collected directly from a Swiss hospital wastewater effluent. In this study, over 21 and 78% were reported as the removal efficiencies of azithromycin and ritonavir, respectively. The results show that the MBR was not sufficient in removing more pharmaceutical compounds (Kovalova et al., 2012). Lindroos et al. (2019) recently covered *Escherichia coli* with melanin, a heterogeneous biopolymer with the high adsorbent ability for biding to chemicals like micropollutants, for use in a cross-flow MBR to remove chloroquine. According to their study, the removal efficiency of chloroquine with the initial concentration of 0.1 mM was 98.2% during the initial 20 hours.

Successful pharmaceutical removal with fungi and algae via biosorption and/or bioremediation mechanisms was reported by Silva et al. (2019). Hospital wastewater treatment using white-rot fungi such as *Trametes versicolor* has been under research for their capability to degrade a wide range of pharmaceutical pollutants through the production of extracellular enzymes and non-specific intracellular (Tormo-Budowski et al., 2021). In the case of fungal treatment, three models of reactors can be classified with regard to the form of reactant contact: flow reactors, batch reactors, and semi-batch reactors. Different studies of fungal treatment have used different reactor configurations such as batch and continuous stirred reactors, fluidized bed, packed bed, and perfusion basket reactors in the removal of pharmaceutical compounds from wastewater. In a fluidized bed reactor, the most common method for fluidizing fungal biomass is the generation of air or oxygen using an electrovalve. Aeration regime is essential in the performance of fungal reactors (Jahandideh et al., 2018). A fungal fluidized bed bioreactor treating real hospital wastewater in Spain was operated for 56 days. In this study, two bioreactors were considered in parallel treatment processes: the bioreactor inoculated with *Trametes versicolor* and uninoculated control bioreactor without the fungus. After comparing the results of two bioreactors, removing anti-inflammatory drugs such as dexamethasone in non-sterile hospital wastewater was successful by fungal operation (Mir-

Tutusaus et al., 2017).

Similarly, fungal treatment was compared with conventional activated sludge for the removal of 81 pharmaceuticals, including statins and dexamethasone, in various types of wastewaters (urban, hospital, veterinary hospital wastewaters, and reverse osmosis concentrate). The results show that conventional activated sludge was superior in removing more pharmaceutical compounds (except psychiatric and antibiotics drugs) than the fungal treatment in terms of environmental risk reduction (85 and 76% of reduction, respectively) (Lucas et al., 2016).

Constructed wetlands are eco-friendly and cost-efficient treatment systems. The main structure of this system is shallow ponds with floating platforms for plants. In this case, the removal mechanisms of contaminants are mainly transformation, plants uptake, adsorption, biodegradation, and volatilization. More recently, the removal efficiencies of ritonavir, pravastatin, and 34 PhACs and PCPs using the constructed wetlands have been analyzed. Although 43.6 and 29.3% have been reported for ritonavir and pravastatin, respectively, the average removal efficiency of all compounds has been measured over 88%. Considering the high hydrophobicity (Log $K_{ow}$ > 3.9) and high molecular weight of ritonavir, adsorption has been considered the main removal mechanism, while low hydrophobicity of pravastatin has led to removal through only plants uptake (Chatzimpaloglou et al., 2021).

Biochar is a solid residue containing carbon obtained by pyrolysis of biomass such as agricultural waste, organic fertilizers, sewage sludge, etc. This material is produced by the thermal decomposition of organic matter in the presence of a small amount of oxygen at a temperature of less than 700 ℃. Biochar has been discussed as an innovative adsorbent for the removal of water pollutants (Oni et al., 2019). Shi et al. (2020) investigated the degradation of atorvastatin by photochemical activities and physicochemical changes in dissolved state biochar. The study shows the most photocatalytic activity of biochars occurs at 300 ℃ of pyrolysis temperature, and dissolved state biochar can efficiently promote the atorvastatin photodegradation.

The biological treatment processes are eco-friendly (Taoufik et al., 2020) and have lower treatment costs (Tormo-Budowski et al., 2021) for pharmaceutical removal in comparison with other reviewed treatment methods. Therefore, it is expected that more research will be conducted for the biological removal of pharmaceuticals used in Covid-19 treatment because it still faces many challenges. The advantages and disadvantages of recommended technologies by this study for PhACs removal in water and wastewater treatment have been summarized in Figure 2, including membrane filtration (Metcalf et al., 2014), adsorption using nanomaterials (Margot et al., 2013; Cruz-Morató et al., 2014), AOP (Margot et al., 2013; Liu et al., 2019), and MBR (El-Sheekh et al., 2021; Mahathi et al., 2021).

## 6. Future Challenges

Various medications for treating Covid-19 disease have raised one of the main concerns in the field of water and wastewater treatment. On the one hand, since many patients diagnosed with this disease do not need to be hospitalized, they can be simply treated at home. Thus, in addition to hospital wastewater, domestic wastewater also contains coronavirus-related drugs. On the other hand, as not all countries have advanced wastewater treatment plants, the presence of these pharmaceutical active compounds in the environment is predictable. With the exception of some drugs, including baricitinib, anakinra, remdesivir, heparin, and tocilizumab, for which no occurrences have been reported; there are studies for the rest of the drugs affirming their existence in the environment with the possible risks to the aquatic ecosystems.

This study found that making a meaningful comparison among distinct treatment processes for a variety of drugs sounds to be complex. What lies at the root of this problem appears to be the different physicochemical properties of pharmaceutical compounds, which might affect the performance of different treatment methods. Also, the presence of other contaminants such as dissolved organic matter and anions in natural water and wastewater streams (feed streams) and the variation of water or wastewater characteristics, such as pH, alkalinity, temperature, etc., would result in different removal efficiencies. Therefore, different treatment technologies should be compared for targeted pollutant removal using synthetic water or wastewater samples with the same characteristics and under fixed operating conditions.

## 7. Conclusions

Increasing consumption of coronavirus drugs has posed potential risks to aquatic ecosystems and human health. Therefore, it is crucial to remove them from water and wastewater. However, most water and wastewater treatment plants cannot completely remove them. Therefore, there is a pressing need to develop technologies for water utilities to increase the removal efficiencies. Currently, advanced oxidation processes have been widely studied for coronavirus PhACs removal. However, this study suggests that the technology development for the coronavirus drug removal from wastewater be focused on combining biological treatment in conjunction with an advanced oxidation process. The goal is to make this environmentally friendly treatment system more cost-effective and have fewer negative environmental impacts.

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