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Review

Low-Carbon Technologies to Remove Organic Micropollutants from Wastewater: A Focus on Pharmaceuticals

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Abstract: Pharmaceutical residues are of environmental concern since they are found in several environmental compartments, including surface, ground and waste waters. However, the effect of pharmaceuticals on ecosystems is still under investigation. To date, the removal of these micropollutants by conventional treatment plants is generally ineffective, in addition to producing a considerable carbon footprint. In this sense, to achieve the current zero-pollution ambition, a reduction in the negative impacts of chemical substances such as pharmaceuticals on the environment must be aligned with initiatives such as the European Ecological Compact, Environment Action Programme, and Circular Economy Action Plan, among others. This review provides insight into the key drivers for changing approaches, technologies, and governance of water in Europe (Germany, Switzerland, and the UK), including improving wastewater treatment in sewage treatment plants for the removal of pharmaceuticals and their carbon footprint. In addition, an overview of emerging low-carbon technologies (e.g., constructed wetlands, anaerobic membrane bioreactors, and enzymes) for the removal of pharmaceuticals in sewage treatment works is provided. In general, the removal efficiency of pharmaceuticals could be achieved up to ca. 100% in wastewater, with the exception of highly recalcitrant pharmaceuticals such as carbamazepine (removal <60%). These technologies have the potential to help reduce the carbon footprint of wastewater treatment, which can therefore contribute to the achievement of the Europe Union's objective of being carbon neutral by 2050.

Keywords: carbon neutral; carbamazepine; diclofenac; emerging green treatment technologies; ibuprofen; sulfamethoxazole; wastewater

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1. Introduction

Micropollutants are organic and mineral contaminants, including industrial chemicals, pharmaceuticals, pesticides, and personal hygiene products, that enter the water cycle (ground and surface waters) from human activities. They are found in trace concentrations and do not completely break down, accumulating and posing a risk to the aquatic environment and water resources [1,2]. Micropollutants such as pharmaceuticals and personal-hygiene products have been detected in different matrices (e.g., wastewater, natural water, groundwater) [3–5]; in spite of this, a large number of them are often not yet included in regulations [6]. Moreover, prioritized micropollutants in different countries (e.g., the UK and USA) could be varied according to the individual studies [7]. Apart from instrumentation constraints, the diverse sources of these micropollutants to the environment can lead to large uncertainties in the identification/quantification of them. The procedures for micropollutant analyses are generally expensive, and most of the studies focus on the quantification of pre-selected targeted analytes rather than the identification of all the compounds present in the natural matrices [4].

Evidence that traces of pharmaceuticals in the environment, in particular in water and soil, could have an adverse impact on wildlife such as fish, birds, and insects and knock-on effects on wider ecosystems, including antimicrobial resistance, has been widely reported [8–11]. Pharmaceutical residues have been found across Europe's soils, sediments, surface waters and wastewaters and have even reached the drinking water, although not in quantities that cause immediate concern [12]. A wealth of ongoing research focuses on the development of suitable wastewater treatment to reduce the discharge of pharmaceuticals into the environment [13–15]. Typically, upstream (prior to release) and downstream (post-release) strategies may be adopted for pollution control, with the first being preferred and more effective. However, in the case of pharmaceuticals, although some improvements may be made upstream (e.g., manufacturing, distribution, prescription, consumption or management), and albeit education and awareness campaigns are very important [16], restrictions cannot be applied using a similar approach to that for other micropollutants, since pharmaceuticals are essential to satisfy the population's healthcare needs.

In addition, the zero-pollution ambition for a toxic-free environment, as expressed in the European Green Deal [17], aims to protect both public health and ecosystems through avoiding the negative effects of chemical substances, including certain pharmaceutical residues in air, soil and water. The recently adopted Farm to Fork Strategy [18] includes the target to reduce overall EU sales of antimicrobials for farmed animals and in aquaculture by 50% by 2030, thus reducing this source of environmental contamination. Other initiatives, including the 8th Environment Action Programme [19], the Circular Economy Action Plan [20], the Chemicals Strategy for Sustainability [21] and the Biodiversity Strategy [22], set a framework for generating an overall shift to a production and consumption of resources, materials and chemicals, which is safe and sustainable by design and creates the lowest possible impact on the environment, including considering pollutants of emerging concern. Work is ongoing on a variety of interlinked topics, which includes the improvement of wastewater treatment at sewage treatment works (STW). In March 2019, the European Commission adopted the European Union Strategic Approach to Pharmaceuticals in the Environment (PiE), which focuses on actions to address the environmental implications of all phases of the lifecycle of (both human and veterinary) pharmaceuticals, from design and production through use to disposal [23].

The EU water law is under evaluation, and the 2019 evaluation of the Urban Wastewater Treatment Directive (UWWTD) highlights that it has delivered a reduction in loads and thereby contributed to the improvement of water quality as compared to 1990 [24]. However, it has also addressed the presence of contaminants of emerging concern (e.g., microplastics and pharmaceuticals) as well as the energy use during wastewater treatment (0.8% of all energy consumed in the EU) and associated sludge management [25,26]. A revised and modernised UWWTD should be a key legal instrument to properly address the European ambitions and the UN Sustainable Development Goals (SDG) for the coming decades [27].

The Water Framework Directive (WFD)—Directive 2000/60/EC—launched a strategy to define high-risk substances to be prioritized, with 33 priority substances and their corresponding environmental quality standards being ratified by Directive 2008/105/EC. This directive also set up the establishment of a watch list of 10 substances, in the first instance, to be monitored across the EU to gather support information for future prioritization exercises, and to be dynamic and updated every two years to respond to new information on the potential risks. Then, Directive 2013/39/EU established that the non-steroid anti-inflammatory diclofenac, the synthetic hormone 17-alpha-ethinylestradiol (EE2), and the natural estrogen 17-beta-estradiol (E2) should be included in the first watch list. Accordingly, Decision 2015/495/EU set the definite first watch list, which, besides the referred substances, also contained three macrolide antibiotics, namely azithromycin, clarithromycin, erythromycin, and another natural estrogen, viz. estrone (E1). Decision 2018/840/EU indicated that sufficient high-quality monitoring data were only available on diclofenac, which was removed from the list; the rest of the pharmaceuticals remained on the second watch list, which also added the antibiotics amoxicillin and ciprofloxacin. Most recently, Decision 2020/1161/EU established that, since four years is the maximum that any substance may be on the watch list, EE2, E2, E1, and macrolide antibiotics should be removed, while amoxicillin and ciprofloxacin should be maintained in the third watch list. This Decision, in agreement with the EU Strategic Approach to PiE and with the European One Health Action Plan against Antimicrobial Resistance (AMR), also set the inclusion of the sulfonamide antibiotic sulfamethoxazole, the diaminopyrimidine antibiotic trimethoprim, the antidepressant venlafaxine together with its metabolite O-desmethylvenlafaxine, and a group of ten azole pharmaceuticals [28].

The Green Deal [17] and the evaluation of the WFD [28] and UWWTD [26] identified the main challenges for the future: climate change (mitigation and adaptation) and energy consumption, zero pollution, circular economy, biodiversity, protection of aquatic ecosystems, protection of water resources, contaminants of emerging concern and other pollutants, and the speed of implementation of EU water directives. For example, a recent review by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) is endorsing concentrations of diclofenac of 0.04 μg/L (40 ng/L) for freshwater and 0.004 μg/L (4 ng/L) for saltwater as the annual average evaluation of quality standards (EQS). These challenges are strong drivers to change approaches, technologies, and governance of water in Europe.

To date, conventional WWTPs are still not able to eliminate many micropollutants found in wastewaters [6], and based on the above information, greener technologies are urgently needed for the effective removal of pharmaceuticals in wastewater treatment plants without having a detrimental impact in the environment. Despite advances in wastewater treatment for pharmaceutical removal through the use of adsorption technologies, advanced oxidation processes (AOPs), and multiple treatment processes [29], we still face limitations in terms of cost and carbon footprint. Based on this, researchers have globally sought efforts to introduce and/or improve natural-based technologies with the potential to be consistent with the demands of a low-carbon future. Some technologies that are receiving particular interest for the removal of a variety of pharmaceuticals are discussed further in this work. They are: (i) constructed wetlands (CWs), which consist of a plant-based technology, offering low maintenance and operation costs, in addition to low energy demand [30–32]; (ii) anaerobic membrane bioreactor (AnMBR), an integrated system of anaerobic bioreactor and ultrafiltration (or microfiltration) considered as a low-energy-footprint technology and capable of efficiently producing biogas, with different recovery paths, and is used for energy neutrality of the system [33,34]; and (iii) enzymes, which are basically alternative biologically made catalysts with high efficiency for the removal of micropollutants and certain pharmaceuticals [35,36].

The framework of this work aims at providing information on the approaches being currently used for the removal of micropollutants in general and, in particular, pharmaceuticals, suggesting new approaches that could be used, either alternatively or to complement existing ones, and taking into consideration the potential reduction in carbon emissions in our race to zero carbon. Therefore, this paper provides an overview on the main drivers to change approaches, technologies, and governance of water in Europe. It presents current technologies being used for the removal of micropollutants in STW in selected countries in Europe (i.e., Germany, Switzerland, and the United Kingdom), with a particular focus on the removal of pharmaceuticals and associated carbon footprint of the approaches being used. A global overview of emerging low-carbon approaches and technologies to remove micropollutants in STW, with a focus in constructed wetlands, anaerobic membrane bioreactors, and enzymatic technologies, that may help meet the EU aim to be climate neutral by 2050 is also presented.

2. Materials and Methods

The review was carried out by collecting documents from multiple databases (Scopus, Google Scholar) and grey literature as well as interviews with key stakeholders in the water sector. Using keywords such as “micropollutants” and “advanced wastewater treatment”, documents were retrieved and selected based on relevance to the subject and analysed.

Citation tracing was also employed to include important documents that did not feature in the databases. This was especially important to include grey literature. From that, papers and reports exploring concepts such as pharmaceuticals, water framework directive, environmental risk assessment, and removal were included in the review sample. From the review sample, a total of 87 references were submitted to a qualitative analysis. These documents were selected because they could be examined in terms of drivers for the removal of micropollutants with a focus in pharmaceuticals and other microcontaminants of current concern in STW in Europe. In addition, documents with a focus on current technologies being used for the removal of micropollutants in selected countries in Europe with a focus on their efficiency and carbon footprint as well as global emerging low-carbon technologies that can remove micropollutants and meet net zero carbon were selected.

3. Removal of Micropollutants: A Focus on Pharmaceuticals

The review on current technologies used for the removal of micropollutants (e.g., pharmaceuticals) from wastewater focused on the experience from Germany, Switzerland, and the United Kingdom. This is because utilities in these countries are leading the way in the adoption of established and emerging technologies to remove micropollutants from municipal wastewaters, taking into consideration the carbon footprint and cost to achieve their targets [37]. It is anticipated that their experiences can prove invaluable to other key stakeholders, including utilities, policymakers, industry, consumers, technology developers, and researchers around the globe.

3.1. Critical Review of the Swiss Approach

Switzerland (8.6 m inhabitants) has a relatively fragmented wastewater infrastructure that is owned and operated by municipal utilities. The journey towards micropollutant removal from municipal wastewaters started with extensive sampling campaigns, which revealed a need for action to protect small rivers with a high percentage of discharged wastewater in particular. Between 2009 and 2014, a cost–benefit survey and analysis were carried out, subsidised trials of advanced wastewater treatment technologies were conducted, and the effect of potential measures to reduce micropollutant concentrations in wastewater and surface waters was examined using a computer-based mass-flow model [1,2,16]. On this basis, in 2014, the parliament decided on a mandatory upgrade of around 100 Swiss STWs [17].

The requirement to install an advanced treatment step for micropollutant removal is linked to specific criteria, including a treatment plant's size, location and the ecological sensitivity and cumulative wastewater percentage of the up-taking water course. Both piloting trials and the full-scale implementation of an advanced treatment stage are subsidised by a federal fund, which in turn is financed by a nationwide increase in sewage fees. The selected STWs must reach an average removal of $\geq$80% for specific indicator substances, calculated from the plant inlet and outlet concentrations. A list of 12 indicator substances (among which 10 are pharmaceuticals) was defined based on their chemical properties, occurrence, detectability, and removal behaviour, in order to pragmatically represent the occurrence and removal behaviour of a broad range of relevant micropollutants.

Today, 14 Swiss STWs are already operating an advanced treatment stage for micropollutant removal, and 46 other plants are currently in the planning or construction phase [18]. The majority of these STWs has chosen activated carbon adsorption technologies, either in the form of granular or powdered activated carbon (Figure 1). It is expected that by 2030, 50% of the municipal wastewater in Switzerland will be treated by advanced technologies to remove micropollutants, and that this will lead to an increase of 10–30% of the treatment plants' energy consumption [1,19]. This reflects a 0.1% increase in the countrywide electricity consumption.

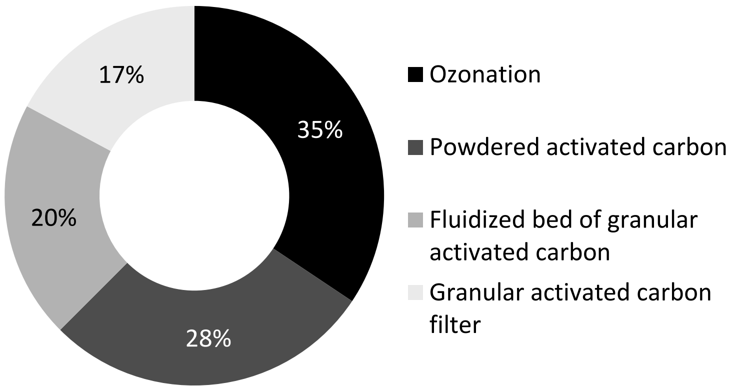

Figure 1. Percentage of technologies chosen for the upgrade of Swiss STWs, including plants in operation, in the planning and in the construction phase [18].

3.2. Critical Review of UK Situation

The UK has a population of 67 m, with municipal wastewater treatment undertaken by one of the twelve water and sewerage companies. The treatment plants have been improved and upgraded since the transposition of the UWWTD. Any requirements for the removal of micropollutants came from the now repealed Dangerous Substances Directive, with several treatment plants having numeric permits for metals such as copper, zinc, and nickel. Much of the more recent investment has focused on nutrient removal, as a result of the WFD. With Brexit, it is expected that the majority of current requirements as they stand in UK law will remain, although future updates to EU Directives may not be incorporated in the UK.

There has been a series of investigations into the presence of micropollutants through the Chemical Investigations Programme (CIP), established in response to emerging legislation on surface water quality [38,39]. The programme is run through UK Water Industry Research Ltd. (UKWIR) and has been ongoing since 2010. It has included monitoring of influent and effluent, and of removal rates through conventional and innovative wastewater treatment. Work has also been undertaken to understand the presence of micropollutants upstream and downstream of wastewater treatment works, and within sewer catchments to identify the major sources.

Estimations of the total cost of installing advanced treatment for micropollutants removal have been made under the CIP, totalling tens of billion in net present value terms [40]. Even with this level of investment, it is expected that many receiving waters will still not meet quality standards as set out in the WFD and its daughter directives. This is due in part to a lack of suitable technologies that can address the range of micropollutants that are found in domestic sewage, including both organic pollutants and metals.

Discussions between the economic regulators, the environmental regulators and the water companies are still ongoing regarding the permitting of micropollutants at STWs.

3.3. Critical Review of the German Situation

In Germany (83.2 m inhabitants), municipal treatment plants were upgraded with micropollutant removal stages already from the 1970s on, in order to protect the environment mainly from local industrial pollution. Since then, a total of 18 plants has been upgraded, and 15 more are currently in the planning and construction phase [18]. These measures were all taken on a case-by-case basis, partially voluntary and partially promoted by federal state programs. A regional clustering can be seen in the German south-west, with a clear majority (54%) of STWs traditionally applying powdered activated carbon processes (Figure 2).

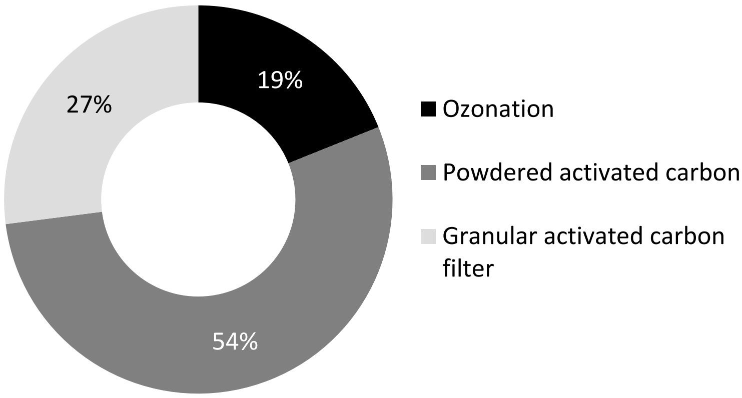

Figure 2. Percentage of technologies chosen for the upgrade of German STWs, including plants in operation, in the planning and in the construction phase [18].

Around 2010, the considerations around micropollutant emissions finally reached a national level, and the scope has shifted from industrial contaminants towards a broader range of chemicals, including pharmaceuticals. An organized dialogue process was launched in 2016 to systematically approach a national micropollutant strategy by involving all kinds of stakeholders, e.g., industrial companies, research institutions and legal authorities [20]. The results of the dialogue process included recommended measures to reduce the emission of micropollutants into the environment. Rather than focusing on end-of-pipe activities, these recommendations explicitly comprised the entire lifecycle of chemicals, e.g., the optimization at the development and production level or public information and education campaigns. Expert panels were convened to systematically evaluate the relevance of specific substances using defined criteria, e.g., their occurrence, environmental behaviour, and toxicity. An orientation framework for the extension of STWs was published, giving guidance on the identification of STWs to be upgraded and technologies to be selected. It was suggested to consider not only technology costs and efficiencies but also their resource consumption and broader environmental impact [21]. A potential amendment of the German Wastewater Levy Act to reduce the emission of micropollutants into water bodies is currently under discussion [22].

4. Current Technologies: Efficiency and Carbon Footprint

Pharmaceuticals (and many micropollutants of emerging concern) are only partially removed from wastewater during biological treatment [41]. Therefore, usually an oxidant and/or adsorbent process is required, activated carbon and ozonation being the most common processes used by the water industry, as described in Section 3. Their efficiency in the removal of target micropollutants and carbon footprint require particular attention prior to the wider adoption by the global water industry.

There are several review documents on the use of ozonation and activated carbon, including specifics on operational parameters, capacity of plants, and removal efficiencies. The purpose of this section is not to repeat what has already been published in the literature but to provide enough information to the reader to understand why there is a need to search for alternative and less energy-consuming processes to remove micropollutants from wastewater.

4.1. Ozonation

One frequently applied process option to remove micropollutants from wastewater is oxidation, typically using ozone (O_3). In the existing large-scale plants, O_3 is generated from synthetic air on site and then dispersed into oxidation reactors at wastewater concentrations of 4–15 mg/L. Micropollutants are rapidly degraded by O_3 molecules or hydroxyl radicals formed by ozone. While the chemical reaction is generally non-selective, electron-rich compounds have been found to be reduced to a higher degree [23,24]. Pharmaceuticals that are particularly well degradable by ozone are, e.g., diclofenac, sotalol, sulfamethoxazole, and gemfibrozil [24]. The major drawback of ozonation is the formation of mostly unknown and potentially toxic oxidation by-products, e.g., bromate in bromide-rich wastewaters. To overcome this issue, ozonation is typically combined with a post-treatment for by-product removal, either by adsorption, e.g., GAC, or biological degradation, e.g., sand (bio-) filtration [18].

The carbon footprint of ozonation processes mainly originates from the on-site electricity use to generate O_3 from synthetic air. The typical energy consumption for ozone generation is estimated around 0.06 kWh/m^3 wastewater but will highly depend on the required O_3 dose (Table 1). In the ozone generating unit, 90% of this energy is converted into heat, which could potentially be recovered for heating purposes on site [25]. Apart from that, a considerable amount of energy is used for the production of synthetic air and for the operation of a post-treatment stage. The production of construction materials and activities to build the necessary infrastructure (e.g., reactors, piping) account for ca. 20% of the total carbon footprint of an ozonation stage [26]. The more sustainable the generation of electricity is, the higher the fraction of infrastructure carbon footprint becomes. In total, the carbon footprint of an ozonation stage is estimated to be in the range 5–60 g CO_2-equiv./m^3 of treated wastewater, depending on the operating conditions and energy sources.

Table 1. Estimated on-site and primary energy consumption of advanced treatment technologies, assuming average Swiss (182 g CO_2-eq per kWh) and EU (450 g CO_2-eq per kWh) energy sources and the following operating conditions: O_3 dose of 5 mg/L, PAC dose of 12 mg/L and GAC lifetime of 30,000 bed volumes [20,25].

Parameters	Unit	Ozonation	PAC	GAC
On-site electricity consumers		Ozone generation, heating and aeration, pumping, post-treatment	Stirring and pumping, post-filtration	Pumping
On-site electricity consumption	kWh/m^3	0.06	0.02	0.01–0.05
	kWh/p.e. and p.a.	8–27	2.5–9	1–5
On-site carbon footprint	g CO_2-eq per m^3	10.9–27	3.6–9	1.8–22.5
Primary energy consumption	kWh/m^3	0.28	0.37	0.15
	kWh/p.e. and p.a.	34	46	19
Primary carbon footprint	g CO_2-eq per m^3	51–126	67.3–166.5	27.3–67.5

4.2. Activated Carbon

The most frequently used adsorbent to remove micropollutants from wastewater is activated carbon, which is produced from carbonaceous raw materials, e.g., coal or coconut husks. After chemical and/or thermal activation, activated carbon is an excellent adsorption material with a large inner surface of 800–1800 m^2/g and hydrophobic surface properties [42]. Activated carbon has been found to preferably remove non-polar compounds that are positively charged or neutral at wastewater pH. Pharmaceuticals that are particularly efficiently removed by activated carbon processes are, e.g., ibuprofen, ketoprofen, atrazine, and metoprolol [24]. In advanced municipal STWs, activated carbon is applied either in the form of powdered activated carbon (PAC) with particle sizes of 50–100 µm, or as granular activated carbon (GAC) with particle size of 0.5–4 mm. PAC is dosed into wastewater at concentrations of 10–20 mg/L and, after adsorption has taken place, separated from the water stream and typically incinerated together with the sewage sludge. GAC, in contrast, is continuously applied in a fluidized or fixed bed reactor and, once its adsorption capacity is exhausted, can be thermally regenerated and partially reused [27].

The on-site energy consumption for PAC and GAC processes is comparably low, as they only require pumping and/or stirring. The highest carbon emissions are attributed, by far, to the production of activated carbon materials, particularly to the raw material extraction, combustion, and activation [26]. Depending on the raw material used, the carbon footprint of these processes varies between 5 g CO_2-eq per kg PAC in the case of coconut husk as a raw material and 18 g CO_2-eq per kg PAC if lignite or coal is used [25,26]. In GAC processes, used adsorbent can be regenerated and reused up to 90%, which significantly reduces the total carbon footprint of GAC compared to PAC processes. Generally, the major influencing factor for the advanced treatment's carbon intensity is the required PAC doses and the GAC bed lifetime, respectively. Approximately 19–27% of the overall carbon footprint is related to the production of construction materials and to construction activities for the process infrastructure (e.g., concrete basins, piping), depending on the specific plant design [26].

A recent study has used a life-cycle assessment framework to assess net environmental efficiencies for ozone systems and granular activated carbon on the removal of micropollutants with proven removal efficiency values and toxicity and/or ecotoxicity potentials. The results showed that the direct water quality benefits obtained from advanced water treatment were outweighed by greater increases in indirect impacts from energy and resource demands [43].

5. Can the Water Sector Remove Micropollutants and Deliver Net Zero Carbon?

In November 2020, water companies in the UK unveiled a ground-breaking plan to deliver a net-zero water supply for customers by 2030 in the 'Net Zero 2030 Routemap: Unlocking a net zero carbon future' [44]. This was the world's first sector-wide commitment of its kind. Water companies are not like other businesses; they provide a vital public service linked to major infrastructure. In the UK, it is estimated that 2.4 m tonnes of CO_2 are emitted annually by the water sector [45]. One of the biggest challenges to meet this target would be tackling the emissions associated with processing wastewater. Yet, in July 2021, the European Commission, producing 8% of global emissions, set out in detail how the bloc's 27 countries can meet their collective goal to reduce net greenhouse gas emissions by 55% from 1990 levels by 2030—a step towards "net zero" emissions by 2050.

Additionally, in November 2021, at COP26, water industry trade bodies around the world joined forces in a call for investment to tackle wastewater treatment process emissions and committed to establishing a research directory to help accelerate the sector's global efforts to reduce nitrous oxide and methane emissions.

Traditionally, the water sector has responded to dealing with new standards with the introduction of tertiary treatment stage processes, which are quite often energy intensive. These advanced wastewater treatment processes currently take into consideration the removal of target organic micropollutants before discharge into receiving water bodies and to comply with specific quality standards for reuse. The challenge now is to find effective ways to remove organic micropollutants without having an impact on the carbon emissions. This challenge has been made a bit easier with the grid decarbonizing, which means that the carbon footprint of using more energy is not as big as it was before. Having additional tertiary treatment processes that require more energy, e.g., advanced oxidation processes, could potential still be consistent with a low-carbon future, if the water sector can entirely rely in the use of green renewable energy. A lot of water utilities are already generating green renewable energy, e.g., Severn Trent Water (UK) produces around 50% of their own energy needs [1], and also buy grid tariff. The water sector can therefore still use electricity and be consistent with a reduction in carbon footprint over time.

However, the water sector still needs to use alternative technologies that can treat sewage very effectively, can remove emerging organic micropollutants, and are low carbon and low cost. Emerging technologies that are receiving particular interest include constructed wetlands (CWs), anaerobic membrane bioreactors (AnMBRs), and the use of enzymes:

- CWs are nature-based solutions that can remove organic micropollutants (OMPs) through processes such as hydrolysis, volatilization, sorption, biodegradation, and photolysis. Various studies have shown that CWs can eliminate OMPs with efficiencies in the range of 54–98% [46].
- AnMBR integrates anaerobic process and membrane-based separation. An energy-efficient and -positive process producing high effluent quality and renewable energy in the form of methane. Research shows that biofouling in AnMBR systems improved the removal of certain emerging contaminants [47].
- Enzymes are used where extremely specific catalysts are required and to control and speed up reactions. They are stable and easy to produce and optimise. Microbial enzymes can remove toxic chemical compounds of industrial and domestic wastewater either via biodegradation or biotransformation [48].

5.1. Constructed Wetlands (CWs)

Different types of natural wetlands with important global climate functions are well-known, such as the fixation of CO_2 [49,50]. Recently, some countries, such as Canada, Switzerland, and China, have started to use wetland management as a climate strategy objective [50,51]. Additionally, wetlands can act as filters to retain some micropollutants, which have aroused interest for further studies in wastewater. Such wetlands are called constructed wetlands (CWs) [49,52].

Briefly, CWs are systems that replicate the natural occurrence of wetland under controlled conditions [49]. In STWs, CWs are applied as polishing steps for the removal of several persistent organic micropollutants, such as pharmaceuticals [52,53]. In this scenario, the removal of a wide variety of pharmaceuticals from different therapeutic classes (such as analgesics/anti-inflammatory drugs, antibiotics, and psychiatric drugs) has been studied [49]. Processes involved in pharmaceutical removal from CWs are diverse (e.g., adsorption, photodegradation, volatilization, accumulation, and biodegradation from aerobic/anaerobic process) and can be applied simultaneously depending on the CW design [54,55]. Additionally, CWs have been built from small-scale to full-scale with different flow settings (including vertical subsurface flow (VSSF), horizontal sub-surface flow (HSSF), and hybrid CW) [52,56,57]. These treatment systems have been evaluated as a green technology, offering low maintenance and operation costs, in addition to low energy demand [30,52]. The large footprint (space) required by CWs is, however, sometimes seen as a drawback; this is the case, for example, in Germany and Switzerland.

5.1.1. Recent Studies on Pharmaceutical Removal

Plant-based systems have a great potential for pharmaceutical removal [49]. However, the effective removal of some types of such micropollutants (mainly refractory compounds, e.g., carbamazepine, ibuprofen, and diclofenac) has become a challenge depending of the CW system employed [58]. According to Zhang et al., persistent pharmaceuticals, such as carbamazepine, may be adsorbed in CWs. On the other hand, diclofenac, ketoprofen, and triclosan tend to be removed by photolytic degradation, particularly in the surface flow system [55]. Pharmaceutical removal performed by CWs differs in its effectiveness when different types of drugs are analysed. For example, a recent study evaluating the removal efficiency of the most widely studied pharmaceuticals by CWs found removal rates ranging from 21 to 93% [59].

Furthermore, the variation in pharmaceutical removal by CWs is related to the different design and operational factors, including the area, depth, hydraulic retention time (HRT), physicochemical parameters (e.g., dissolved oxygen, temperature), and physicochemical properties of the pharmaceuticals [52,54]. For instance, the role of temperature and the effect of seasonality can influence the treatment efficiency, affecting the oxygen solubility and microbial degradation kinetics [54]. The removal efficiency of pharmaceuticals was observed to be higher during the summer than winter [57,58], especially for the removal of salicylic acid, caffeine, and naproxen [54]. Additionally, better pharmaceutical removal is expected to occur when both oxic and anoxic zones are present with a long HRT (~10 d) [60]. Additionally, plant selection is essential since some wetland plants can absorb different nutrients from wastewater to achieve the function of removing pollutants [58]. In this sense, the most common investigated plant species in CWs are found in natural wetlands worldwide, including *Typha latifolia*, *Phragmites* spp., and *Cyperus* spp. [52,54,58].

To date, most studies are conducted at a pilot-scale/small-scale level and, in general, significant removal of pharmaceuticals from wastewater has been achieved. A recent study evaluated the CW average removal efficiency of the most widely studied pharmaceuticals and personal care products. Their findings were that the pharmaceutical removal could range on average from 20% to 98% in different CW designs [61], with lower removal for carbamazepine due to its recalcitrant characteristics [57,62,63]. Additionally, in order to optimize the removal of pharmaceuticals, other treatment stages can be combined with CW. Li et al. evaluated slow sand filtration on a lab-scale CW combined with a stabilization tank (ST)-GAC sandwich, and the results indicated almost total removal of paracetamol (99.1%), caffeine (98.1%), and triclosan (97.4%) [64]. Additionally, many assessments have been performed on full-scale systems, where some of them are systems in operation [49]. In current STWs (e.g., Spain, Belgium), the CW treatment reached removal rates of pharmaceuticals (such as caffeine, ketoprofen, diclofenac, diazepam, tramadol, ibuprofen, and naproxen) above 90%, with the exception of carbamazepine [60,65]. However, the removal efficiency was different among the pharmaceuticals. In another investigation, it was found that the water residence time influenced the removal efficiency of a CW located in Ukraine [56].

The pharmaceutical removal from wastewater by different CW operational systems is summarized in Table 2. As it can be seen, previous studies indicate that CWs may be considered as an effective system to remove pharmaceuticals from wastewater. However, future studies should focus on a comprehensive assessment of the CW design as well as in-depth studies on the sustainability of the system from these different operational parameters [49].

Table 2. Constructed wetlands for pharmaceutical removal in wastewater from different designs and operational conditions.

Operational Conditions	Plant	Scale/Localization	Pharmaceutical/Initial Concentration	Removal (%)	Main Findings	Ref.
Aeration of 4 h/d per 10 m^3/d; VSSF part followed by a HSSF—a total surface area of 240 m^2 (40 × 6 m); design capacity of 340 inhabitant; HRT = ~10 days.	*Phragmites australis* and *Iris pseudacorus*	Full-scale/Belgium	Atenolol, bisoprolol, carbamazepine, diazepam, gabapentin, metformin, metoprolol, sotalol, telmisartan, tramadol, valsartan Concentration: 40 ± 20 ng/L—50.66 ± 32.74 µg/L	>90%	- The aquatic risk was estimated low. - The HRT increased the removal of carbamazepine and tramadol.	[60]
Four treatment units (two VSSF and two HSSF). Maximal treatment capacity of 100 m^3/d; discharge ~70 m^3/d; HRT = 10–13 d.	*Phragmites australis* and *Typha latifolia* L.	Full-scale/Ukraine	Ibuprofen, naproxen, diclofenac, ketoprofen, paracetamol, carbamazepine, propranolol, caffein, triclosan Concentration: 0.1–1862.0 ng/L	55–98%	- The removal of some pharmaceuticals increased with greater water resident time and the macrophyte cover. - The removal of diclofenac ranged of 40–90% during the different years of treatment.	[56]
Two-stage hybrid constructed wetlands (HSSF-CWs- SPs and HSSF-CWs-VSSF-CWs); HRT = 3 d.	*Thypha latifolia*, *Iris sibirica* and *Zantedeschia aethiopica*.	Pilot-scale/Mexico	Carbamazepine Concentration: 25 µg/L	59.0–62.5%	- Carbamazepine removal was more effective under near-anoxic conditions (<1.5 mg/L of DO)	[62]
HSSFs units with a surface of 2.64 m^2; aerated system with six aeration pipes (air flow rate of 12.1 m^3/h); HRT = 5.5 d.	*Phragmites australis.*	Pilot-scale/Spain	Acetaminophen, diclofenac, ketoprofen, bezafibrate and gemfibrozil Concentration: 0.04–470 ng/L	>83%	- Aeration improved the removal of pharmaceuticals compared to the non-aerated treatment. - Diclofenac was most efficiently removed in CW with continuous aeration (> 90%).	[63]
Different CWs were operated: SF, SSF, HSSF, and VSSF HRT for SF = 2.55 d and SSF = 1.27 d. Six CWs were consisted of containers with dimension of 0.7 m × 0.5 m × 0.4 m (flow rate at 2 L/h).	*Canna indica* L.	Small-scale/China	Ibuprofen, gemfibrozil, naproxen, ketoprofen, and diclofenac. Concentration: 100 µg/L	80–90%	- The removal of pharmaceuticals was higher in summer and autumn than in winter.	[57]

Note: HRT = hydraulic retention time; VSSF = vertical subsurface flow; HSSF = horizontal sub-surface flow; SP = stabilization ponds; SF = surface flow.

5.1.2. Mitigation Potential

Different factors, such as cost–benefit analysis involved in the land acquisition, investment and operation costs, and energy consumption, may be responsible for the sustainability of the CW treatment [30]. The investments in land acquisition for CWs are much lower compared to the conventional treatments [30]. For example, SF wetlands usually require costs in the range of EUR 10–20/m^2 field area [49]. Comparing the operation costs between conventional wastewater treatment and CWs, the difference can be about 60% lower for CW (EUR 29.74/population equivalent/year for conventional treatment vs. EUR 11.9/population equivalent/year for CW) [66]. Another outstanding advantage of CWs relative to other technologies is the lower requirements for skilled labour, usually good public acceptance, and practically no generation of by-products [49].

Additionally, CWs do not require chemicals addition. In general, CWs demand natural materials, e.g., plants and aggregate materials. This plant-based technology demands lower operational and maintenance costs compared to conventional wastewater treatment processes [49,55], because only periodic inspection is required in CWs and the system has an average operational lifetime of 20–30 years [49,67]. However, in terms of lifetime, due to substrate clogging, SSF CWs may have a shorter life span than free water surface (FWS) CWs [30]. Additionally, it is worth mentioning that in most cases, the energy demand for CWs is lower than that from conventional treatments [30]. This is due to the use of natural light in the facility and, in some cases, the need for a few pumps (although the demand for pumps can be avoided if natural gravity flow is applied along the system) [49]. This is a relevant aspect of CW, since they allow less generation of greenhouse gases and provide, associated with the significant removal of pharmaceuticals, a reduction in the carbon footprint of the system.

However, in cases where artificial aeration is applied, the energy input and its impact on the carbon footprint must be carefully verified. Some pilot-scale studies have shown a better efficiency in removing pharmaceuticals when aeration is used in the system [63], whilst other studies have found better results under near-anoxic conditions [62]. A recent study evaluated the effect of aeration on the removal of pharmaceuticals present in municipal wastewater and hospital effluents at a pilot-scale aerated SSF CW [68]. These authors reported that the aeration was necessary to improve removal rates; however, a reduction in aeration time to 50% did not significantly affect the removal efficiency, which indicated a robust performance of the system. In fact, a removal higher than 95% was reported for atenolol when continuous aeration conditions were used, and higher than 85% when partial aeration was used.

Although several advantages have been reported, CWs still have some limitations. To date, the major drawback of this system is the requirement of a large foot-print area for their implementation in a conventional treatment facility, and in some cases, long periods for achieving the treatment quality standards [30,49].

5.2. Anaerobic Membrane Bioreactor (AnMBR)

Recently, there has been an increasing interest in AnMBRs, mainly for municipal wastewater treatment [69]. The AnMBR is an integrated system of anaerobic bioreactor and ultrafiltration (or microfiltration) under low pressure (or microfiltration membrane), separating HRT from the solid retention time [70,71]. This combined treatment can produce a reliable high-quality effluent [72].

Although the efficiency of anaerobic digestion is generally limited at certain temperatures, due to the growth rate of microorganisms, anaerobic treatment with AnMBR can be optimized [69]. Benefits from AnMBR technology include: (i) the conversion of particulate and organically bound nutrients into soluble nitrogen (N) and phosphorous (P), which can be applied as fertilisers to grow vegetables [72]; (ii) AnMBR can produce significantly less biosolids when compared to aerobic treatment systems [72,73]; (iii) AnMBR has been considered as a low-energy footprint technology and its efficiency is related to the amount of biogas produced [71]—in this sense, AnMBR can produce energy in the form of biogas.

Recent studies reported higher methane production when AnMBR is used (1.02 mL-CH4/h) compared to an up-flow anaerobic sludge blanket (UASB) (0.83 mL-CH4/h) for livestock wastewater treatment [74] and methane production ranging from 50 to 80% from AnMBR performance in different municipal wastewater treatments [33]. Another investigation for domestic wastewater treatment indicated that the methane recovery from AnMBR technology could generate around 73% of the power required for energy neutrality of the system (total HRT of 1–20 h) [75]. Additionally, methane production can increase as the retention time in the AnMBR reactor increases [76]. In this sense, biogas production has been reported to increase considerably in HRT of 36 h for pharmaceutical removal, with an average methane content of 78.5% higher than other HRTs (12, 18, 24 and 48 h) [77]. In general, the HRT applied for pharmaceutical removal in the AnMBR reactors ranged from 6 to 36 h [69,77,78].

5.2.1. Recent Studies on Pharmaceutical Removal

One of the main factors that makes AnMBR technology sustainable is its ability to produce methane gas. A previous study on pharmaceutical wastewater treatment using AnMBR reported that the biogas production increased as the hydraulic retention time (HRT) increased (up to a certain value) [77]. Additionally, the theoretical energy potential in domestic wastewater has already been evaluated, indicating that it is proportional to the influent COD (chemical oxygen demand) [79]. Another study from the removal of pharmaceuticals in wastewater showed an average methane production of 60% from AnMBR technology (in pilot-scale), corresponding to 0.30–0.36 L methane per g COD [80].

Furthermore, temperature is a determining factor for the efficiency of the AnMBR treatment. At higher temperatures (e.g., 35 °C), the metabolism of microorganisms increases, favouring the biodegradation steps [71]. Recent studies on AnMBR treatment have evaluated the removal of pharmaceuticals in wastewater within a temperature ranging from 20 to 37 °C and removal of pharmaceuticals and COD in the range of 45–97% [69,78,80,81]. If the treatment is carried out in colder environmental conditions, there is a need for a long HRT of the wastewater in the reactor to achieve biodegradation. Increasing the temperature in the bioreactor can reduce this residence time; however, there will be an increase in energy consumption and treatment costs [71].

Other factors such as pH and membrane characteristics are also considered relevant for better efficiency of AnMBR technology. The design and operation of membranes are related to the filtration capacity of a given wastewater flux [70]. Additionally, the compounds present in wastewater can affect the metabolism of microorganisms in AnMBR reactors. A study carried out on a lab scale indicated that the treatment efficiency of pharmaceutical industry wastewater was affected by its salinity [81]. According to these authors, the high salinity along with the presence of toxic compounds inhibited the presence of microorganisms in the AnMBR reactor; consequently, there was lower efficiency of organic removal and methane production.

Some studies have reported the applications of AnMBR for pharmaceutical wastewaters with satisfactory COD removal. For instance, a recent pilot-scale study using real domestic wastewater reached a COD removal of around 87% with HRT of 19 h [82]. Regarding specifically pharmaceutical removal, a wide range has been reported in recent years [69,77,82,83], as shown in Table 3. This may be a result of the wastewater composition, the different types and concentrations of the pharmaceuticals, and the different operation conditions of the reactors. Additionally, as reported in Section 5.1, carbamazepine was the pharmaceutical with the greatest resistance to biodegradation.

Table 3. Anaerobic membrane bioreactor for pharmaceutical removal from different designs and operational conditions.

Operational Conditions	Scale/Localization	Pharmaceutical/Initial Concentration	Removal (%)	Main Findings	Ref.
AnMBR operated for 120 d; membrane pore size 0.2 µm; flow rate = 5 L/min; effective volume of 3.2 L. HRT = 12 and 6 h. Pharmaceutical wastewater: synthetic sewage feed of 500 mg COD/L	Lab-scale/Singapore	Antibiotic Ciprofloxacin (CIP) Initial CIP concentration: <1.5 mg/L and 4.7 mg/L	50–76% (for low initial CIP concentration) <20% (for high initial CIP concentration)	- Biological degradation was the main mechanism, while adsorption onto the sludge only contributed a small fraction.	[69]
AnMBR reactor equipped with three submerged membrane housings; membrane pore size 0.1 µm; permeate flux = 5.27 L/m^2/h; volume of 4.5 L. T = 17.7 °C; pH = 7–7.6; HRT = 19 h. Domestic wastewater from STW with 431 ± 53.6 mg COD/L.	Lab-scale/USA	Antibiotic resistance genes (ARGs)	Average of 87.4% (0.90log) COD removal of 87.6 ± 2.27%	- Manure addition may result in increased biological activity.	[82]
AnMBR operated for 170 d; membrane pore size 0.03 µm; flux = 3 L/m^2 h; effective volume of 2 L. T = 35 °C; pH = 7; HRT = 1 d. Synthetic municipal wastewater with 800 mg COD/L.	Lab-scale/China	Antibiotic sulfamethoxazole (SMX) SMX concentration: 10–100,000 µg/L	Average of 88–97.1%	- Removal efficiency decreased as the initial concentration of SMX was higher than 10,000 µg/L. - Methane production of - 75–95%	[78]
AnMBR operated for 160 d; filtration area 0.11 m^2; flux = 5 L/m^2 h; effective volume of 3.2 L. T = 35 °C; HRT = 6 h–24 h. Synthetic sewage with~500 mg COD/L.	Lab-scale/Singapore	Trimethoprim (TMP), sulfamethoxazole (SMX), carbamazepine (CBZ), and Diclofenac (DCF) Total concentration: 2 mg/L	TMP: 94.2 ± 5.5%, SMX: 67.8 ± 13.9%, CBZ: 0.3 ± 19.0%, and DCF: 15.0 ± 7.2%	- Powdered - activated carbon added to the AnMBR improved the removal of all pharmaceuticals, with removal > 80%	[83]
AnMBR operated for 80 d; membrane pore size 0.22 µm; flow rate = 244 L/h. T = 35 °C; HRT = 36 h. Synthetic pharmaceutical wastewater with 4250–5129 mg COD/L	Pilot-scale/China	m-cresol (MC) and iso-propyl alcohol (IPA) MC concentration: 370–440 mg/L and IPA concentration of 60–81 mg/L	MC: 95% and IPA: 96%	- With a reduction in HRT, the biological removal efficiency gradually decreased.	[77]

Note: COD = chemical oxygen demand; HRT = hydraulic retention time.

Previous investigation with AnMBR on a lab scale using synthetic sewage (~500 mg COD/L) presented different pharmaceutical removal efficiencies. The submerged AnMBR reactor removed 94% of trimethoprim whilst carbamazepine was not efficiently removed (<1% of removal) [83]. Additionally, previous investigation reported that the removal of the antibiotic ciprofloxacin was directly affected by the initial concentration of the pharmaceutical in the influent (synthetic sewage) during AnMBR treatment [69]. The results indicated 50–76% removal efficiency for initial concentrations <1.5 mg/L and less than 20% removal for higher initial pharmaceutical concentrations. Other studies performed on a lab scale using synthetic and real domestic wastewater showed antibiotics removal in the range of 67–97% [78,82,83].

5.2.2. Mitigation Potential

The effective removal of micropollutants and the potential of energy recovery have stimulated increased research interest in AnMBRs. In general, AnMBRs technology can achieve ~90% COD removal and methane production around 0.25–0.35 m^3 CH_4/kg COD, mainly from HRT of 1 to 25 days [70,80,82]. However, it is worth mentioning that a short HRT means a smaller volume bioreactor and therefore lower capital costs, which is desirable for reducing the overall footprint of the process [71].

Regarding the energy demand, this may vary according to the AnMBR technology settings. For example, external configurations (which use external membranes) tend to have higher energy requirements compared to submerged AnMBR systems, as there is greater pumping demand to provide high flow velocity to clean the membrane surface [72]. A previous study on energy consumption estimate that submerged systems require 0.69–3.41 kWh/m^3, while external systems consumed 3 to 7.3 kWh/m^3 [84].

Apart from that, a relevant advantage of AnMBR technology for pharmaceutical removal is the low or nil concentration of intermediate products formed after treatment, mainly when the initial pharmaceutical concentration in wastewater is low. For higher initial concentrations of pharmaceuticals in wastewater such as the antibiotic ciprofloxacin, quinolones intermediates can be formed and released into the effluent after treatment [69]. The formation of intermediate products and their potential toxicity are related to the different biotransformation pathways that occur during treatment [78].

To date, although several advantages of AnMBR have been reported, there are still some operational and environmental issues, including membrane fouling and dissolved methane recovery [72,85]. It is known that the dissolution of methane in the treated effluent can affect energy recovery, in addition to increasing the emission of greenhouse gases from the effluent [70]. For fouling control, some strategies have been suggested, e.g., membrane module vibrations in AnMBRs [85]. Additionally, the addition of a chemical cleaning step at the end of each operational stage has been applied with the intent to reduce the impact of membrane fouling [82]. However, such strategies require increasing system complexity and/or regular consumables additions. Besides these, another strategies such as backwashing and cycling of membranes may be an alternative [72]. In general, the energy demands for fouling control in the pilot-scale AnMBRs can range from 0.04 to 1.35 kWh/m^3. For example, these values are lower than those of lab-scale AnMBRs [79].

These results, combined with the fact that AnMBRs can recover energy in the form of biogas, support the application of this technology to manage wastewater more sustainably [82]. However, it is expected further investigations at full scale, including ways to evaluate the sustainability of the system such as energy efficiency and better methane recovery.

5.3. *Enzymes*

Enzymes are biologically made catalysts applied for environmental remediation, which shows high reaction kinetic activity under mild conditions (temperature, pH) [86,87]. In recent years, some studies on wastewater treatment with an enzymatic approach have indicated the potential for the oxidation of pharmaceuticals [87].

The use of enzymes in wastewater treatment depends on enzyme types and their sources [35]. In summary, the removal of specific pollutants can occur by precipitation or transformation to other products [88]. Moreover, the use of enzymes can occur in isolation or through a "consortium" of enzymes. However, the application of specific types of enzymes can be more systematic and controlled alternative to the conventional biological treatment processes [89].

5.3.1. Recent Studies on Pharmaceutical Removal

Some factors may affect the efficiency of the enzyme-based treatments. Besides the effect of the wastewater composition, the pH of the reaction medium is one of the operational factors that can significantly affect enzyme performance. Depending on the pH value, both the stability of the target compound and the enzyme activity are modified, which will influence the extent of pharmaceutical removal [87]. A previous study using enzymes for pharmaceutical removal (from municipal wastewater) reported a higher removal efficiency when neutral pH (range 6–7) was applied in the system, with complete removal of estrogens [90]. However, in another study, the complete degradation of pharmaceutical (diclofenac) was found in the pH range of 3–4.5 from lignin peroxidase activity (which degrade some substrates in the presence of hydrogen peroxide—H_2O_2) [91].

An innovative approach is the application of isolated enzymes which has been shown their potential for the degradation of pharmaceuticals [89]. For instance, batch experiments with commercial laccase enzyme (produced by several fungi) applied in municipal wastewater reached total removal of natural estrogens (Estrone, 17b-estradiol, estriol) and synthetic estrogen (17a-ethinyl-estradiol) after 1 h of treatment [90]. Another investigation using isolated laccase enzyme showed removal of 16% of the antibiotic ciprofloxacin [92]. However, the experiments were carried out without real wastewater. When laccase enzyme was applied as a fungi mediator, the removal efficiency increased to 97.7% [92].

Some studies have applied different enzyme mediators with the intent to improve the pharmaceutical removal [92,93]. This process is denominated as enzyme-mediator system and relevant pharmaceutical removal has been reached from different mechanisms (such as electron transfer, ionic mechanisms, and hydrogen atom transfer) [94]. However, the toxicity of these mediators must be carefully evaluated before applying the system at other scales (e.g., pilot scale) [87].

The application of different enzymes in the reaction medium has also shown significant removal of pharmaceuticals. Terners and co-workers achieved complete removal of pharmaceuticals such as SMX, acyclovir, atenolol, and bezafibrate in 72 h of treatment using a temperature of 30 °C [95]. However, the degradation was very limited for carbamazepine, for example, probably due to its recalcitrant characteristic (as discussed in previous sections) and the biocatalyst origin [86]. Different enzymes involved in Terners' study were native, extracted from activated sludge of a municipal STW and applied at pilot-scale, indicating the feasibility of the process. However, this approach may require energy for the aeration of the system and for maintaining the temperature.

Apart from that, a new approach, the so-called enzymatic membrane reactor (EMR), where the enzyme remains in the reactor being fed continuously, has shown some advantages when compared to other processes such as better enzyme dispersion in the reactor and easier replenishment of fresh enzymes. However, further studies are needed, particularly to assess their viability at large scales [86,87].

The pharmaceutical removal rates from wastewater and synthetic solution by different enzyme operational systems are summarized in Table 4.

Table 4. Enzymes applied directly or as mediators for pharmaceutical removal from different operational conditions.

Operational Conditions	Scale/Localization	Pharmaceutical/Initial Concentration	Removal (%)	Main Findings	Ref.
Activity of isolated Laccase enzyme of 20 U/mL; batch reactors with 1 L; T = 25 °C; pH 7; reaction time of 1 h. Municipal wastewater containing 39 mg COD/L	Lab-scale/USA	Steroid hormones: Estrone, 17b-estradiol, estriol, and 17a-ethinyl-estradiol Concentration: 0.4 nM of each estrogen	100% removal	The effect of the pH was significative on laccase-catalysed treatment efficiency.	[90]
Laccase enzyme-mediator systems (LMS). Mediators: syringaldehyde (SA) and acetosyringone (AS). Activity of Laccase enzyme of 100 and 650 U/L; T = 25 °C; reaction time up to 20 h. Synthetic solution.	Lab-scale/Switzerland	Antibiotic sulfamethoxazole (SMX) Concentration: 20–25 mg/L	SMX was transformed to less toxic products.	Product mixtures were less toxic to algae than untreated pollutants.	[93]
Use of white-rot fungus *Trametes versicolor*-mediator systems (LMS). Mediator: Laccase enzyme. Rotation of 150 rpm; T = 30 °C; reaction time of 30 h. Synthetic solution.	Lab-scale/Spain	Antibiotics ciprofloxacin (CIPRO) and norfloxacin (NOR) Concentration: 10 mg/L	CIPRO: 97.7% and NOR: 33.7%	Laccase excreted by the fungus was able to remove 16% of CIPRO (after 20 h) when used as the only process.	[92]
Native enzymes extracted from activated sludge of a municipal WWTP. T = 30 °C, reaction time over 72 h, under aerobic condition. Synthetic solution.	Pilot-scale/Germany	A set of 20 selected pharmaceuticals. 16.7 µg/L per analyte	Acesulfame, acetaminophen, acetyl-SMX, acyclovir, atenolol, bezafibrate, benzophenone-4 were 100% degraded. Carbamazepine and fluconazole were persistent.	Different enzymes were present in the primary degradation reactions.	[95]

5.3.2. Mitigation Potential

Even though enzyme treatment has shown high efficiency for the removal of certain pharmaceuticals, it is important to highlight that batch reactors with free enzymes may not be an economically viable solution for domestic wastewater treatment. The amount of enzymes needed to treat large volumes of wastewater and the need of removing these enzymes after treatment affect the overall economic viability of the process [86]. Additionally, depending on the operating conditions, periodic replacement of enzymes is necessary to maintain the efficiency of pharmaceutical removal, which can increase the operational cost of the process [87].

In this scenario, for a longer catalytic life of the enzymes, its immobilization on solid supports may be an alternative. The advantages of immobilization include the reuse of enzymes, greater stability compared to free enzymes and the possibility of continuous use. However, such strategy must be carried out carefully to prevent a decrease in the enzymatic process performance [35,87,88]. Additionally, the use of plant-based material as an enzyme source represents an alternative to the use of purified enzymes, which can potentially reduce the costs of the process [88]. The selection of these suitable enzymes can be carried out by means of analytical studies and tools [89].

Another significant factor for the sustainability of the process is the evaluation of sub-product formation and its potential toxicity. The enzymatic degradation of pharmaceutical compounds can produce many metabolites and final products, which indicates the need for more studies on the physicochemical properties of these sub-products formed [94].

To date, systematic investigations regarding the control of different enzymes to remove a wide range of pharmaceuticals under environmental conditions are missing [89]. Additionally, there is still a need for further studies on the treatment strategy to have economical and technical competitiveness. For this, more studies at a pilot scale to better understand the best operating conditions and capital/operating costs are needed [87].

5.4. Overal Remarks

Tertiary processes currently being used at municipal wastewater treatment might not be favourable for the simultaneous removal of micropollutants, energy reduction and carbon neutrality that are required by the water industry; this is why alternative tertiary processes that could also be included as add-ons to existing STWs are of interest [96].

The removal of micropollutants and the delivery of lower net carbon might be possible in the mid-term through different technologies investigated. Additionally, it is well-established that conventional STWs can generate 2 to 15 times more greenhouse gas (GHG) emissions than nature-based systems [97,98]. From this perspective, the achievement of nature-based systems and its optimization for wastewater treatment represent an opportunity to reduce carbon emissions from treatment plants.

Nguyen and co-workers compared the environmental impacts of activated sludge and a CW in wastewater treatment [98]. They found that CW produced 5.69 kg $CO_{2\ \mathrm{equiv.}}$ per m^3, which was much lower than activated sludge plant, which emitted 11.42 kg $CO_{2\ \mathrm{equiv.}}$ per m^3. According to Mander and co-workers, hybrid CWs (a combination of CWs, as reported in Section 5.1.1, Table 2) are more advantageous in relation to GHG minimization. Moreover, the CO_2-C emission showed a lower value in FWS than in SF-CWs, with median values of 95.8 to 137 mg m^{-2}/h, respectively [99].

A previous study assessed the environmental impact of CWs from construction to operation of an already designed full-scale facility (located in Greece) [100]. The operation environmental impact was greater than the construction stage due to the transfer of wastewater to different treatment stages such as to anaerobic tank and first-stage CWs to second-stage CWs. These steps consumed energy from pumps due to the local topography. Therefore, for greater applicability of this technology, the optimization of systems is needed such as the CW location and the most efficient use of energy to reduce carbon emissions [97].

The minimization of GHG emissions during wastewater treatment by replacing aerobic processes to anaerobic technology has also shown promising results, indicating a reduction of around 24–44% in emissions compared to an aerobic system [33,97]. Furthermore, anaerobic treatments produce less biosolids to be handled compared to aerobic systems, which reduces the operating costs and carbon footprint [33]. The operating costs of CWs are in general much lower than those of other technologies, considering that CWs do not need additional chemicals. Besides that, CWs demand lower operational and maintenance costs compared to conventional wastewater treatments [66] (see Section 5.1.2). In general, the energy costs could be close to zero for gravity-driven CWs and low for all types of CWs [101].

Anaerobic treatment by AnMBR technology may be more consistent with carbon footprint reduction if grid energy consumption is replaced by energy recovered from methane gas formed during the treatment [33]. In this way, concomitant to the greater biogas production, and the recovery of biogas for energy use, AnMBRs could be considered more energetically positive. A recent study reported direct GHG emissions from the AnMBR/Biochar process of 138 g CO_2-equiv./m^3 of wastewater treated, while the indirect CO_2 emission was higher, with GHG emissions of 495 g CO_2-equiv./m^3 of wastewater treated [96]. This indirect CO_2 emission was associated with the energy consumption in the process, indicating that the control of indirect carbon emissions is the key to the carbon-neutrality. According to these authors, this value was only about 57.5% of that emitted from the current conventional activated sludge (CAS)-microfiltration.

Additionally, although some AnMBR studies (lab-scale and pilot-scale) indicate significant efficiency of pharmaceutical removal using temperatures of 30–35 °C (removal > 90%) [77,78,83] (see Table 3), from the sustainability point of view, there will be energy demand and more costs in these systems [102]. On the other hand, the operation of AnMBRs using lower reactor temperatures in warmer climate regions is a promising technology to reduce the environmental impacts of WWT systems [33,76]. Indeed, the results of an AnMBR operated at ambient temperature conditions indicated net energy benefits in all the scenarios evaluated [33,76], and some pharmaceuticals have been satisfactorily removed (>80%) under temperatures around 20 °C [82]. Additionally, to further reduce the carbon footprint of the AnMBR treatment and its operational costs, better mitigation of membrane fouling is expected from technological advances, mainly using technologies that do not require energy or the addition of chemicals. For instance, technologies such as membrane vibration (magnetically induced vibration) have medium costs, while technologies such as dynamic membranes (self-forming biological filtering layer) have low operating costs/energy demand [33]. The use of enzymes for pharmaceutical removal in wastewater treatment indicates high efficiency (>90%) [35,92,95]. The energy and chemical demand for this process can be considered low compared to conventional wastewater treatment, indicating better sustainability for the removal of resistant compounds [35,94]. However, the main economic aspect of the enzymatic treatment of pollutants is the cost of the enzyme [103]. A recent study evaluated the costs of applying enzymes for hydrolyses of a municipal solid waste-derived pulp and described enzyme costs in the range of GBP 1–4/Kg [104]. Another study evaluated the techno-economic analysis of the production of enzymes such as Laccase from pumpkin peels as a substrate [105]. They found that the price of this enzyme was USD 0.107/cm^3 compared to USD 1/cm^3 of the current commercial enzyme, indicating potential ways to reduce enzyme costs. Additionally, enzyme immobilization is a relevant aspect, since they are reused for many cycles (e.g., 4–12 cycles), which greatly curtail the treatment cost [35,87,106]. However, the enzyme activity during those cycles needs to be measured, since the industry replaces the immobilized enzyme when the activity is between 50 and 100% of the initial activity [107].

It is still difficult to point out the average costs of enzymatic treatment since several parameters differ from each other in a single process [103]. Nonetheless, it can be considered that the operational cost of enzyme technology can be higher when enzymes are not previously immobilized or produced from alternative/low-cost substrates.

From this scenario, despite the promising features of enzyme-based pharmaceutical degradation, a more practical approach for remediation of pharmaceutical compounds to ensure environmental sustainability is required [94]. For this, the gap between laboratory- and pilot-scale research needs to be overcome [89]. Moreover, additional studies are needed to monitor the toxicity levels of the resulting degraded metabolites from enzyme treatment before implementing for large-scale applications [94].

In summary, alternative technologies for removing pharmaceuticals from sewage presented in this section have shown promising results, including the possibility of reducing costs and carbon emissions. However, there is room for improvement of their design and operation, moving closer to a more sustainable and circular system [33]. In general, some studies are required to better evaluate and define the general costs of the life cycle of these processes and which practices can enhance the reduction in their carbon footprint.

The main sustainability parameters between CWs, AnMBR, and enzyme technologies are summarized in Table 5.

Table 5. Characteristics and comparison of CWs, AnMBR, and enzymes (based on [33,35,49,55,87,89,96,99,108].

Parameters	CWs	AnMBR	Enzymes
Investment	Moderate	Moderate	Moderate
Operational costs	Low	Low to moderate (fouling leads to operation costs)	Moderate to high (e.g., high when enzyme exchange/recovery is required)
Pharmaceutical removal efficiency [a]	Moderate to high (50–98% average)	Moderate to high (50–98% average)	Moderate to high (40–100% average)
Energy input	Low (if there are not pumps for aeration)	Low to moderate (if temperature maintenance and the use of pumps are required)	Low to moderate (if aeration and temperature maintenance are required)
Use of chemicals	Not required	Low (in some cases, for removal of membrane fouling)	Low
Monitoring	Low to moderate	Moderate	Moderate
By-products	No sludge by-product	Low or nil by-products formation	Low to moderate (more studies are needed)
Carbon footprint	1.297–5.8 g CO_2 m^2/d	138–850 g CO_2 equiv./m^3	

Note: [a] Average removal values based on the results reported in this review.

6. Conclusions

Micropollutants, including pharmaceutical residues, have been of growing concern as they are found in both surface and groundwater across Europe which is used for irrigation and drinking water production. Pharmaceuticals are, however, essential to satisfy the population's healthcare needs and in the treatment of many human and animal diseases. When ingested, ca. 30–90% of the active ingredient are washed off in their original form, which can reach the environment mainly through: (i) discharge of effluent from STWs, as their performance for removing pharmaceuticals vary on a substance basis, (ii) the spreading of animal manure, and (iii) aquaculture.

There is documented evidence of the effects of pharmaceuticals to and via the environment. Firstly, it is known that pharmaceuticals are designed to act at low concentrations. Pharmaceuticals that persist in the environment and spread through water and soil or accumulate in plants and wildlife may therefore pose a risk due to their toxicity. Secondly, whilst it is unlikely that pharmaceuticals in drinking water may pose a threat to human health at the low concentrations found, the risk cannot be ignored. In addition, with ageing populations, climate change, and water scarcity, the impacts of pharmaceuticals may only increase in the future if no action is undertaken. In the EU, the WFD, which is the main directive committing EU states to achieving good water quality, does not currently include pharmaceuticals on the priority list of pollutants. However, they have been added to the watch list, meaning they are being investigated to determine the risks they pose and whether environmental quality standards should be set for them at the EU level.

Pharmaceuticals (and many micropollutants of emerging concern) are only partially removed from wastewater during biological treatment. Therefore, an oxidant and/or adsorbent process is usually required, activated carbon and ozonation being the most common processes used by the water industry. Some water utilities in Europe have introduced advanced treatment technologies based on these processes to remove micropollutants. Such is the case of Switzerland—it is expected that by 2030, 50% of the municipal wastewater in Switzerland will be treated by advanced technologies to remove micropollutants. An immediate consequence would be an increase of 10–30% in the treatment plants' energy consumption, which would reflect a 0.1% increase in the countrywide electricity consumption. In the UK, recent estimations of the total cost of installing advanced treatment for micropollutant removal have been made under the CIP, totalling tens of billions in net present value terms. Even with this level of investment it is expected that many receiving waters will still not meet quality standards as set out in the WFD and its daughter directives due in part to a lack of suitable technologies which can address the range of micropollutants that are found in domestic sewage. In Germany, the amendment of the German Wastewater Levy Act to reduce the emission of micropollutants into water bodies is currently under discussion. Currently, an orientation framework is used as a guidance on the identification of STWs to be upgraded and technologies to be selected, considering technology costs and efficiencies, their resource consumption, and broader environmental impact.

While wastewater is one of the main pathways by which pharmaceuticals can reach the environment, not all water utilities are able to completely remove the residues from water and wastewater. The delivery of lower net carbon whilst treating wastewater for the removal of target micropollutants can be considered through the adoption of green emerging technologies including CWs, AnMBR, and enzyme-based processes. These are promising technologies for wastewater treatment, and this research provides evidence of studies that suggest that the removal of pharmaceuticals up to 100% in wastewater might be achieved. In addition to their suitability to reduce the carbon footprint of wastewater treatment, they might have the potential for energy recovery (such as biogas by AnMBR), and in general require fewer chemicals as compared to those needed by conventional (and some advanced) wastewater treatments designed for the removal of micropollutants.

Whilst these green emerging technologies have been well studied at a laboratory scale, there is a need for further research at a pilot scale prior to their adoption at full scale, mainly for the treatment of wastewater using AnMBR or enzymes. In this sense, more studies are expected using real wastewater matrices, with different pharmaceutical compounds at relevant concentrations. Additionally, to reduce the impact of wastewater treatment on the carbon emissions, there are other aspects that need to be considered, such as land acquisition, operational costs, and energy consumption. For this, the reactor design, hydraulic retention time, compounds present in the wastewater, and location/topography of the treatment facilities are relevant. Moving forward, it would be valuable to investigate how efficient green emerging technologies are at full scale towards a carbon-neutral water sector. In addition, due to a lack of data availability in the literature, it is recommended to make a comparative evaluation of ozone and activated carbon technologies in terms of footprints, efficiency, and energy requirements with low-carbon technologies such as AnMBR, enzyme, and CWs.

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