From Laboratory Tests to the Ecoremedial System: The Importance of Microorganisms in the Recovery of PPCPs-Disturbed Ecosystems

María Carmen Molina [1], Luis Fernando Bautista [2], Myriam Catalá [1], María Rosa de las Heras [1], Pilar Martínez-Hidalgo [1], Jon San-Sebastián [3] and Natalia González-Benítez [1,*]

[1] Department of Biology, Geology, Physics and Inorganic Chemistry (Area of Biodiversity and Conservation), ESCET, Rey Juan Carlos University, 28933 Madrid, Spain; carmen.molina@urjc.es (M.C.M.); myriam.catala@urjc.es (M.C.); mrdelasherasglez@gmail.com (M.R.d.l.H.); pilar.martinezh@urjc.es (P.M.-H.)

[2] Department of Chemical and Environmental Technology (Group of Chemical and Environmental Engineering), ESCET, Rey Juan Carlos University, 28933 Madrid, Spain; fernando.bautista@urjc.es

[3] Department of Studies and Consulting (Area of Engineering and Building), Tragsatec, 28037 Madrid, Spain; jsss@tragsa.es

* Correspondence: natalia.gonzalez@urjc.es; Tel.: +34-91488-0282

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Abstract: The presence of a wide variety of emerging pollutants in natural water resources is an important global water quality challenge. Pharmaceuticals and personal care products (PPCPs) are known as emerging contaminants, widely used by modern society. This objective ensures availability and sustainable management of water and sanitation for all, according to the 2030 Agenda. Wastewater treatment plants (WWTP) do not always mitigate the presence of these emerging contaminants in effluents discharged into the environment, although the removal efficiency of WWTP varies based on the techniques used. This main subject is framed within a broader environmental paradigm, such as the transition to a circular economy. The research and innovation within the WWTP will play a key role in improving the water resource management and its surrounding industrial and natural ecosystems. Even though bioremediation is a green technology, its integration into the bio-economy strategy, which improves the quality of the environment, is surprisingly rare if we compare to other corrective techniques (physical and chemical). This work carries out a bibliographic review, since the beginning of the 21st century, on the biological remediation of some PPCPs, focusing on organisms (or their by-products) used at the scale of laboratory or scale-up. PPCPs have been selected on the basics of their occurrence in water resources. The data reveal that, despite the advantages that are associated with bioremediation, it is not the first option in the case of the recovery of systems contaminated with PPCPs. The results also show that fungi and bacteria are the most frequently studied microorganisms, with the latter being more easily implanted in complex biotechnological systems (78% of bacterial manuscripts vs. 40% fungi). A total of 52 works has been published while using microalgae and only in 7% of them, these organisms were used on a large scale. Special emphasis is made on the advantages that are provided by biotechnological systems in series, as well as on the need for eco-toxicological control that is associated with any process of recovery of contaminated systems.

Keywords: microorganisms; bioremediation; ecotoxicology; pharmaceuticals and personal care products; waste water treatment; ecoremediation; circular supply chain management

1. Introduction

Ecosystem degradation is mainly due to anthropogenic actions that directly and indirectly affect aquatic and terrestrial ecosystems. Among the different phenomena linked to global change, three stand out due to their ubiquity and high impact: habitat loss [1], global warming [2,3] and environmental pollution [4]. In the latter, the effect of emerging pollutants is overriding. Most of these substances are micro- or nanocontaminants dispersed almost ubiquitously with unknown impacts. While the effects of eutrophication and heavy metal pollution have been relatively well characterized, the outcome of emerging contamination has been barely elucidated, and less known regarding their interaction with abiotic factors as well as responses in non-target organisms [5]. Among the substances of emerging concern, pharmaceutical and personal hygiene products (PPCPs) such as medicines for veterinary and human use, fragrances, personal hygiene products, or food supplements and additives, are occupying the interest of researchers because many of them are being continuously and massively discharged into the environment and possess high biological activity [6]. In fact, more than 3000 active organic components have been approved in Europe just for human medical care [7] and a high consumption of pharmacological substances has been reported in North America, Brazil, Europe, Australia and some areas of Asia [8].

2. Pharmaceuticals and Personal Care Products (PPCPs) in the Ecosystems

PPCPs can enter the surface water via direct discharge by industries, hospitals, households etc. and there is emerging evidence showing that wastewater treatment plants (WWTP) can act as hotspots that release large amounts of PPCPs into the environment, which is of particular concern in the regions or WWTP without adequate monitoring management. The low concentrations at which some these pollutants are found in the WWTP represent a greater risk, since conventional analytical techniques do not often detect them. These compounds have been reported ubiquitously in the aquatic environment including surface water and groundwater and even seawater, as well as agricultural soils and terrestrial ecosystems even in pristine areas such as Antarctica [9,10]. They are adsorbed and immobilized on soil particles or absorbed, metabolized and/or bioaccumulated by microorganisms and plants for animal and/or human consumption [11,12]. In many cases, their toxicity or possible mode of action on non-target organisms is unknown [7,13,14] but many have chemical structures resembling natural signaling compounds and allelochemicals, resulting in gene expression, blockage of membrane receptors or disruption of signal transduction [15].

PPCPs affect a wide variety of living beings, from the simplest prokaryotes to the most complex eukaryotes (Tables 1 and 2). In the case of bacteria, they can promote changes in the structure and function of the ecosystem, including the primary production of biofilms [16–19]. Nutrients and micropollutants exert combined effects on the configuration of α and β diversity of fluvial microbial communities. Surprisingly, PPCPs have a hitherto unrecognized disruptive effect on abundance variations of central species and on module communities, suggesting the key role that micropollutants play in relationships of microbial coexistence in lotic ecosystems [20].

In arid and semi-arid regions, recovered residual water is used to irrigate agricultural crops or gardens. Among the effects generated by these substances in soils is the appearance of bacteria resistant to multiple drugs, which could lead to the failure of antibiotic treatments [21,22]. PPCPs also affect the fungi from the rhizosphere [23]. The knowledge of the toxicological effects of residual pharmaceutical compounds on crops is very limited. Wheat shoot and root elongation decreased and the antioxidant defensive system in roots was damaged after exposing *Triticum aestivum* to paracetamol [24]. Little is known regarding the risks to wildlife species, but ecotoxicological relevant effects on fern spores germination and development, a vascular plant model, has been demonstrated in vitro [15,25–28].

Regarding vertebrates such as birds, fish and small mammals, for example, the inappropriate use of diclofenac and the associated cultural practices related to the disposal of animal carcasses, combined with the high sensitivity of the vultures to diclofenac, were responsible for the decline of the populations of three species of vultures in Asia and northern Africa [29–32]. Human populations are

directly exposed to varying concentrations of PPCPs, such as cosmetics application or through diet and the health risks involved are not completely known [30–36]. Humans exposure, especially children, to some of the PPCPs may cause serious allergies, antibiotic resistance or even toxicity [33]. Using OMICs (genomic, proteomic, transcriptomic) approaches, other authors described the effect of these micropollutants in mice and confirmed injuries in liver and kidney because of induced perturbations of metabolism and dysregulation of signal transduction processes [34]. Their continuous discharge, bioaccumulation and synergistic combination can cause serious adverse effects to the environment and humans [35]. In addition, PPCPS can have combined synergistic effects (Tables 1 and 2). Thus, [36,37] using mixtures of common PPCPs their individual and combined effect on the marine bacterium *Vibrio fischeri* was evaluated All of the compounds that presented narcosis as a toxic mode of action at high doses also showed stimulation at low concentrations, an effect known as hormesis. The maximum stimulation effect of a mixture was greater than the highest stimulation effect of each individually tested compound. In addition, when the exposure time increased, the hormetic effect decreased [37]. These synergistic or antagonistic effects can also be found with other pollutants such as microplastics [38].

PPCPs could be removed by physical adsorption processes (e.g., activated carbon, graphene or carbon nanotubes) and chemical advanced oxidation processes (e.g., ozonation, UV treatment or ionizing irradiation) [39]. However, the mineralization to CO_2 is not always complete moreover, intermediate substances generated in physical-chemical processes may be even more toxic than the preexisting ones [40,41]. Techniques that use living organisms (or their by-products) for the elimination of contaminants (biological remediation) have a number of advantages, such as low cost, mild operational conditions and the transformation of PPCPs to non-toxic substances (or complete mineralization) because, in some cases, different microorganisms can cooperate among them for the complete mineralization of the pollutant [39,42]. Thus, some authors [43–47] suggest expanding research on the use of biodegradationtechniques of PPCPs, due to their benefits to the environment. Therefore, when considering that biological techniques are fast, clean and inexpensive, their study should be prioritized, to be able to corroborate or not their degradation efficiency and apply them promptly. Nonetheless, currently physic-chemical techniques are more common than biological techniques (Figure 1) probably due to their ease of standardization.

Circular supply chain management (CSCM) has been recently described as: the integration of circular thinking into the management of the supply chain and its surrounding industrial and natural ecosystems. It systematically restores technical materials and regenerates biological materials toward a zero-waste vision through system-wide innovation in business models and supply chain functions from product/service design to end-of-life and waste management, involving all stakeholders in a product/service lifecycle including parts/product manufacturers, service providers, consumers, and users [48]. Within this framework, ecoremediation is a tool of undoubted value, which refers to the restoration or prevention of disturbances in ecosystems, maintaining or recovering their original balance state with multi-purpose approaches for removing pollutants by a vast array of biological components [49,50]. The basic characteristics of ecorremedial measures are their high buffer and self-protective capacities and the preservation of natural habitats and biological diversity [51]. Hence, these measures can be considered as ecosystemic services, which include:

- the use of organic compounds and natural substances used as adsorbents (activated carbon, clay, bamboo canes . . .) or biosurfactants [52,53];
- living organisms and their active principles as remedial components or biological remediation [54–57];
- improvements in ecological engineering [58];
- development of ecological numerical models [59];
- environmental and economic assessment [60]; and
- software solutions development for multi-parameter decision making and management tools [49].
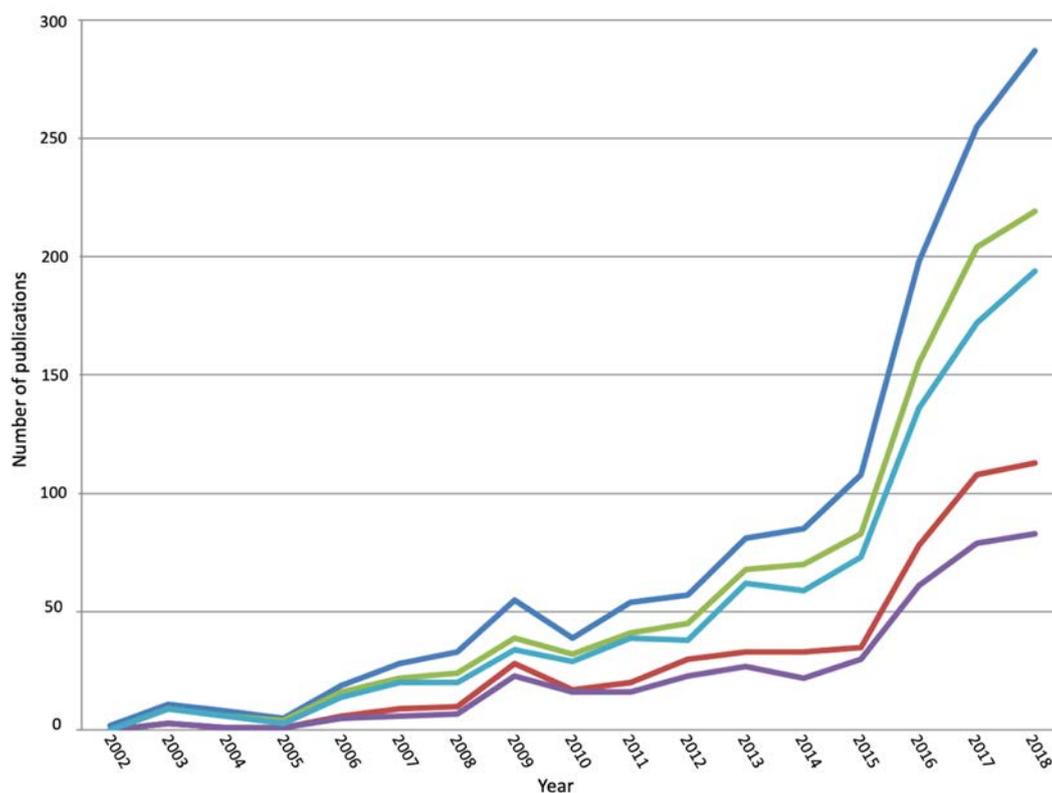
Figure 1. Number of papers published each year on the topic of pharmaceuticals and personal hygiene products (PPCP) and its removal according to Scopus database. Dark blue represents all papers that contain the search term "PPCP", the red line encloses the terms PPCP and the following terms associated with their biological degradation (bacteria, archaea, fungi, microbial consortium, biological or degradation). The green line represents the terms PPCP and other terms associated with physicochemical removal of PPCP, namely: ozonation, Fenton, oxidation, UV, ionizing, irradiation, chemical, activated, carbon, graphene or nanotubes. Purple line counts the articles that reference PPCP and their biological degradation stated before, but excluding all terms related to physicochemical degradation to avoid overlap. Light blue considers the search terms PPCP and the physicochemical degradation terms stated before while excluding any term related to biological degradation of PPCP.

An integrative approach of all these measures will render high efficiency removal-systems [61–63]. Regarding PPCPs present in waters and soils ecosystems, biological remediation (or bioremediation) could be an eco-friendly solution, since some organisms can immobilize PPCPs in their biological structures (bioadsorption and bioaccumulation) or even use them as nutrients (carbon, phosphorous, nitrogen source) or electron source. Therefore, bioremediation could be an alternative towards zero-waste vision, with an adequate waste management, main objective for CSCM. Essentially, the biological techniques used to eliminate these contaminants have been defined after the organisms that are directly involved in the process: prokaryotes (bioremediation or bacterial remediation), fungi and yeast (mycoremediation) and plants (phytoremediation). The objective of this mini-review is to screen from basic recovery mediated by microorganisms in pure culture, going by the new biotechnological systems applied to WWTPs, up to the latest advances in in/ex situ construction of ecoremedial systems, emphasizing the importance of microorganisms in each of these processes. The search is framed within the period 2002–2018 and it includes some of the more frequent PPCPs in wastewater: diclofenac (DFC), estradiol (EST) and its derivatives, carbamazepine (CBZ), ibuprofen (IBU), naproxen (NPX), codeine (CDN), sulfamethoxazole (SMX), caffeine (CFN), gemfibrozil (GFZ), triclosan (TCS), nonylphenol (NP), artemisine (ATN) and flumequine (FLU). For the collection of bibliographic data, a systematic review of academic articles related to the descriptors was carried out using SCOPUS electronic databases.

Review, original articles, chapter books and books were included in this study. Special emphasis will be made on the advantages provided by biotechnological systems arranged in series and we will end with the ecotoxicological tests, since often, after the depurative process, the toxicity persists since the intermediate metabolisms remain toxic.

Table 1. Effects of different types of mixture of PPCPs on several species of aquatic organisms.

Phylum	Species	Mixture Type	Endpoint/Biomarker Effect	Reference
Bacteroidetes	*Flavobacterium* sp.	Psychostimulant + Antihistamine + Antibiotic + Antidiabetic, cholesterol reducer	Relative decreases on bacterial community composition	[16]
	Pseudomonas sp.	Psychostimulant + Antihistamine + Antibiotic + Antidiabetic, cholesterol reducer	Relative increases on bacterial community composition	[16]
Firmicutes	*Paracoccus yeei*	Analgesic and antipyretic drug + Nonsteroidal anti-inflammatory drug	Susceptibility	[13]
	Staphylococcus aureus	Analgesic and antipyretic drug + Nonsteroidal anti-inflammatory drug	Susceptibility	[13]
Proteobacteria	*Enterobacter aerogenes*	Analgesic and antipyretic drug + Nonsteroidal anti-inflammatory drug	Resistance	[13]
	Enterobacter cloacae	Analgesic and antipyretic drug + Nonsteroidal anti-inflammatory drug	Resistance	[13]
	Escherichia coli	Hair dyes	Cytotoxicity and mutagenic effect	[64]
	Vibrio fischeri	Antibiotics + Disinfectant + H2 blocker + Lipid regulators + Nonsteroidal anti-inflammatory drug + Preservatives	Narcosis	[37]
Rotifera	*Plationus patulus*	Antidepressant + Psychostimulant + Disinfectants + Nonsteroidal anti-inflammatory drugs	Egg reduction and detachment	[65]
Phanerogams Magnoliophyte	*Lemna minor*	Antibiotics	Growth reduction	[66]
Chlorophyta	*Chlamydomonas microsphaera*	Antidepressant + Disinfectants	Inhibitory effect on algal growth	[67]
	Chlorella pyrenoidosa	Antidepressant + Disinfectants	Inhibitory effect on algal growth	[67]
	Chlorella ellipsoidea	Antidepressant + Disinfectants	Inhibitory effect on algal growth	[67]
	Dunaliella salina	Antidepressant + Disinfectants	Inhibitory effect on algal growth	[67]

Table 1. *Cont.*

Phylum	Species	Mixture Type	Endpoint/Biomarker Effect	Reference
Chlorophyta	*Dunaliella parva*	Antidepressant + Disinfectants	Inhibitory effect on algal growth	[67]
	Pseudokirchneriella subcapitata	Lipid regulators + Nonsteroidal anti-inflammatory drugs	Increased the level of lipid peroxidation, glutathione transferase and metallothioneins. DNA damage. Destabilization of the lysosomal membrane	[68]
	Scendesmus obliquus	Antidepressant + Disinfectants	Inhibitory effect on algal growth	[67]
	Scendesmus quadricauda	Antidepressant + Disinfectants	Inhibitory effect on algal growth	[67]
	Scenedesmus vacuolatus	Antibiotics	Growth redution	[66]
	Tetraselmis suecica	Antibiotics	Inhibited growth. Decrease in esterase activity and alteration of chlorophyll a, cellular content and autofluorescence	[69]
Mollusca	*Elliptio complanata*	Analgesic + Antibiotics + Antidepressant + Anticonvulsants + Lipid regulators + Nonsteroidal anti-inflammatory drugs	Adverse effects on the immune system	[70]
	Dreissena polymorpha	Lipid regulators + Nonsteroidal anti-inflammatory drugs	High levels of lipid peroxidation	[68]
	Lampsilis siliquoidea	Antibiotics + Hormones + Lipid regulators	Reduction in filter-feeding	[71]
	Unio tumidus	Hormones + Disinfectants + Nonsteroidal anti-inflammatory drugs	Elevated levels of lactate/pyruvate ratio, lipofuscin, DNA fragmentation and caspase-3 activity	[72]
Arthropoda	*Chironomus riparius*	Hormones	Deformities in the mouth, decreased fertility	[73–75]
	Daphnia magna	Antidepressant + Hormones	Population growth rate	[76]
		Antibiotics	Viability reduction	[66]
	Antocha	Antidepressants	Metamorphosis occurred earlier and more frequently	[77]
	Corydalus	Antidepressants	Metamorphosis occurred earlier and more frequently	[77]
	Ectopria	Antidepressants	Metamorphosis occurred earlier and more frequently	[77]
	Psephenus	Antidepressants	Metamorphosis occurred earlier and more frequently	[77]
	Gammarus fossarum	Antibiotics	Increase in body mass	[78]
	Gammarus pulex	Beta blockers + Disinfectants + Nonsteroidal anti-inflammatory drugs	Alterations in metabolite concentrations	[79]
	Palaemonetes pugio	Antibiotics + Psychostimulant	Negative effects on offspring survival and development	[80]

Table 1. *Cont.*

Phylum	Species	Mixture Type	Endpoint/Biomarker Effect	Reference
Chordata	*Danio rerio*	Antidepressant + Anticonvulsant + Antihistamine + Nonsteroidal anti-inflammatory drug	Perturbations in both the metabolome and transcriptome	[81]
		Antidepressant + Anticonvulsant + Lipid regulators + Nonsteroidal anti-inflammatory drugs	Decreased embryo production	[82]
	Oncorhynchus mykiss	Hormones	Inhibitor of estrogenicity	[83]
		Sunscreen agents	Increased activity of certain P450 cytochromes	[84]
		Antidepressant + Anticonvulsants + Beta blockers + Psychostimulant + Hormones + Nonsteroidal anti-inflammatory drugs + Thiazide diuretic + Fragrances	ROS production and the ß-gal inhibition *(RTG-2 cell line)*	[85]
	Oryzias latipes	Nonsteroidal anti-inflammatory drugs	Antiovulatory activity	[86]
		Anticonvulsant + Disinfectant + Nonsteroidal anti-inflammatory drug	Effects on feeding behavior and swimming speed	[87]
	Pimephales promelas	Antihistamine + Beta blocker + Psychostimulant + Disinfectants + Hormone + Lipid regulators + Nonsteroidal anti-inflammatory drugs	Molecular estrogenic effects	[88]
	Pseudorasbora parva	Antidepressant + Disinfectants	AChE and EROD activities inhibitionLipid peroxidation	[89]
	Trematomus bernachii	Hormones + Component in plastic and epoxy resins + Disinfectants + Precursors to the non-ionic surfactants + Preservatives	Preferential accumulation in fish correlating negatively with fillet size	[90]

Table 2. Effects of different types of mixture of PPCPs on several species of terrestrial organisms.

Phylum	Species	Mixture Type	Endpoint/Biomarker Effect	Reference
Nematoda	Soil nematode community	Hormones	Number of nematodes was decreased and change the sex ratio in a free-living nematode community	[91]
	Soil nematode community	Antibiotics + Anticonvulsants + Antipsychotic, antiemetic + Beta blockers + Psychostimulant + Component in plastic and epoxy resins + Diuretic + Fragrances + Hormones + Lipid regulators + Nonsteroidal anti-inflammatory drugs + Preservatives	The diversity and structure of the soil nematode community vastly altered	[92]
Annelida	*Eisenia andrei*	Disinfectants	Affect the growth and reproductive performance	[93]
Arthropoda	*Culex quinquefasciatus*	Antibiotics + Psychostimulant + Hormones + Nonsteroidal anti-inflammatory drugs	Increase developmental time of larvae. Altered the mosquito bacterial microbiome	[94]
Magnoliophyte	*Allium cepa*	Hair dyes	Cytotoxic and mutagenic	[64]
	Triticum aestivum L.	Analgesic and antipyretic drug	Wheat shoot and root elongation decreased. The antioxidative defensive system in roots was damaged	[24]

2.1. Microbial Remediation in Culture

Although microorganisms can be an important ecosystem resource and offer eco-friendly solutions against PPCPs contamination, few researches have been done regarding the degradation of PPCPs in water and soil by microorganisms. Overall, the research works are focused on the description of the levels of these emerging contaminants in water and more sparingly, in which soil or plant matrices they are easily absorbed or adsorbed (Figure 1). When it comes to eliminating these contaminants, the most commonly used solution is the use of physicochemical techniques (Figure 1). However, bioremediation has the hallmark of effective and inexpensive means for the removal of PPCPs, provided that a well-directed and systematic approach is found to study and implement these complex mechanisms in existing or new WWTPs and in situ aquatic and terrestrial systems. The convenience of using combined physic-chemical and biological techniques should be evaluated [95].

2.1.1. Bioremediation or Bacterial Remediation

A total of 271 papers were found in this section. In 78% of them, the prokaryotes were used in advanced remediation systems, such as active sludge, bioreactors or constructed wetlands. Most pharmaceuticals are toxic to bacterial strains (especially antibiotics), but some naturally occurring bacteria have the ability to biodegrade these contaminants. Thereby, bacteria isolates from water, soil and sediment (usually contaminated) have been used to remove the frequently detected PPCPs [39]. They are able to remove the pollutants by aerobic and anaerobic oxidative degradation, intra and extracellular degradation, and biosorption (absorption and adsorption) (Figure 2).
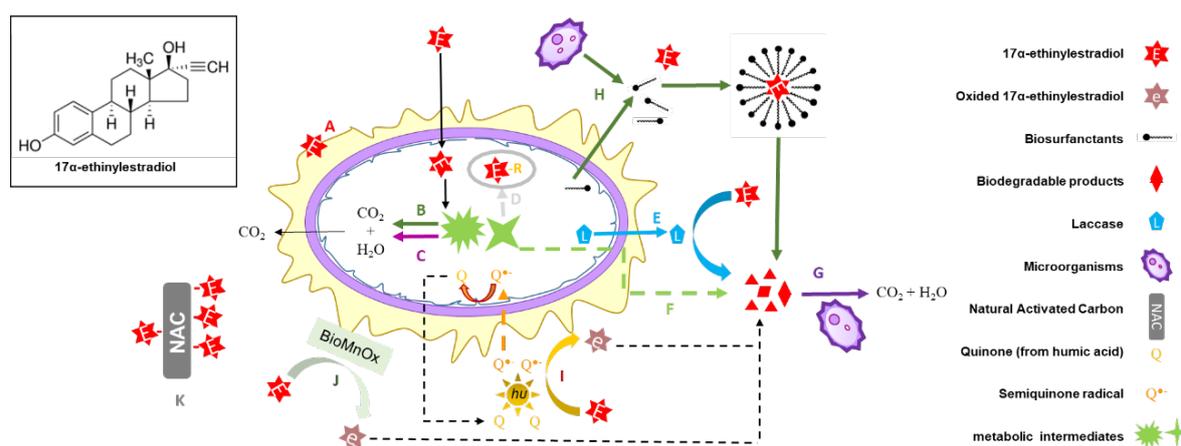
Figure 2. Different mechanisms to PPCPs bioremoval, case of 17α-ethinylestradiol from wastewater. **A**, hydrophobic bioadsorption [96]; **B**, Absorption and bacterial intracellular degradation [97,98]; **C**, Absorption and microalgae intracellular degradation [99]; **D**, bioaccumulation [100]; **E**, extracellular degradation by laccase, other lignolytic enzymes do not seem to be involved [101–103]; **F**, intermediate metabolites secretion; **G**, synergistic degradation mediated by other microorganisms [39,42,104]; **H**, Desorption and mobilization by biosurfactants [105]; **I**, photodegradation coupled to biodegradation [106–108]; **J**, Degradative way by biogenic manganese oxides [109,110]; and, **K**, adsorption to natural activated carbon [111]. Discontinuous lines probable degradative pathways, but not proven.

The acclimatization of prokaryotes is an essential factor to improve the effectiveness of the process. Many of the enzymes involved in the PPCPs removal are inducible so that a previous contact of the microorganisms with the PPCPs is important. For example, the presence of TCS induces the production of ammonia monooxygenase, which can degrade this compound [112]. However, constitutive systems such as oxidation through cytochrome P_{450} via [113,114] or bacterial aerobic lignocellulolytic enzymes [115,116], are also involved in bacterial degradative processes. Other mechanisms for the removal of PPCPs have been described (Figure 2), for example, desorption and mobilization by biosurfactants [105]; photodegradation coupled to biodegradation [106,108,117] and a degradative pathway by biogenic manganese oxides [109,110].

Most of the PPCPs-degrader bacteria belong to the Proteobacteria or Actinobacteria group, although *Planococcus* (little used) and *Bacillus* genera (Figure 3A), both Firmicutes, are used less frequently. All in all, whenever the degradation capacity of a microorganism is detected in the laboratory, it is evaluated as beging potentially useful in biotechnology. Thus, bacterial taxa have been first studied in the laboratory and subsequently applied in situ, except for Actinobacteria that, frequently, have been directly identified in active sludge or bioreactors (Figure 3A). Among the most used, *Pseudomonas* spp. can be highlighted since they are able to degrade, among other compounds, CBZ, TCS, cephalexin, CFN, SMX and diagnostic contrast media [118–123]. A 47% degradation of CBZ in 20 days was reported by *Pseudomonas* species [124]. *P. putida* activates the successful degradation of 17α-ethinylestradiol (E2α) through redox reactions mediated biogenic manganese oxide [109,110] (Figure 2). The synergistic action of these processes with engineered *Escherichia coli* cells transformed with an anchoring motif from *P. syringae*, allows for the complete mineralization of bisphenol A and NP [125]. Recently, 17β-hydroxysteroid dehydrogenase and its regulators were characterized [126]. *Bacillus thuringiensis* is capable of degrading NPX, IBU, sulfonamides, trimethoprim, NP, TCS and GFZ, among others [45,108,127–131]. Recently, a new pathway for NPX utilization by *B. thuringiensis* has been described [132]. Several *Sphingomonas* are linked with successful PPCPs biodegradation [133–137]. They have been used as bioinocula in recovery processes with successful results [135,138]. The use of nanoparticles in *Sphingomonas* spp. could be a potential strategy for improving degradation [139]. Recently, it has been immobilized on polydopamine-coated Fe_3O_4 iron nanoparticles, showing high

efficacy in the elimination of NP polyethoxylates and during a greater number of cycles. Furthermore, separation and recycling were more readily achieved for immobilized cells as compared to free cells [137].
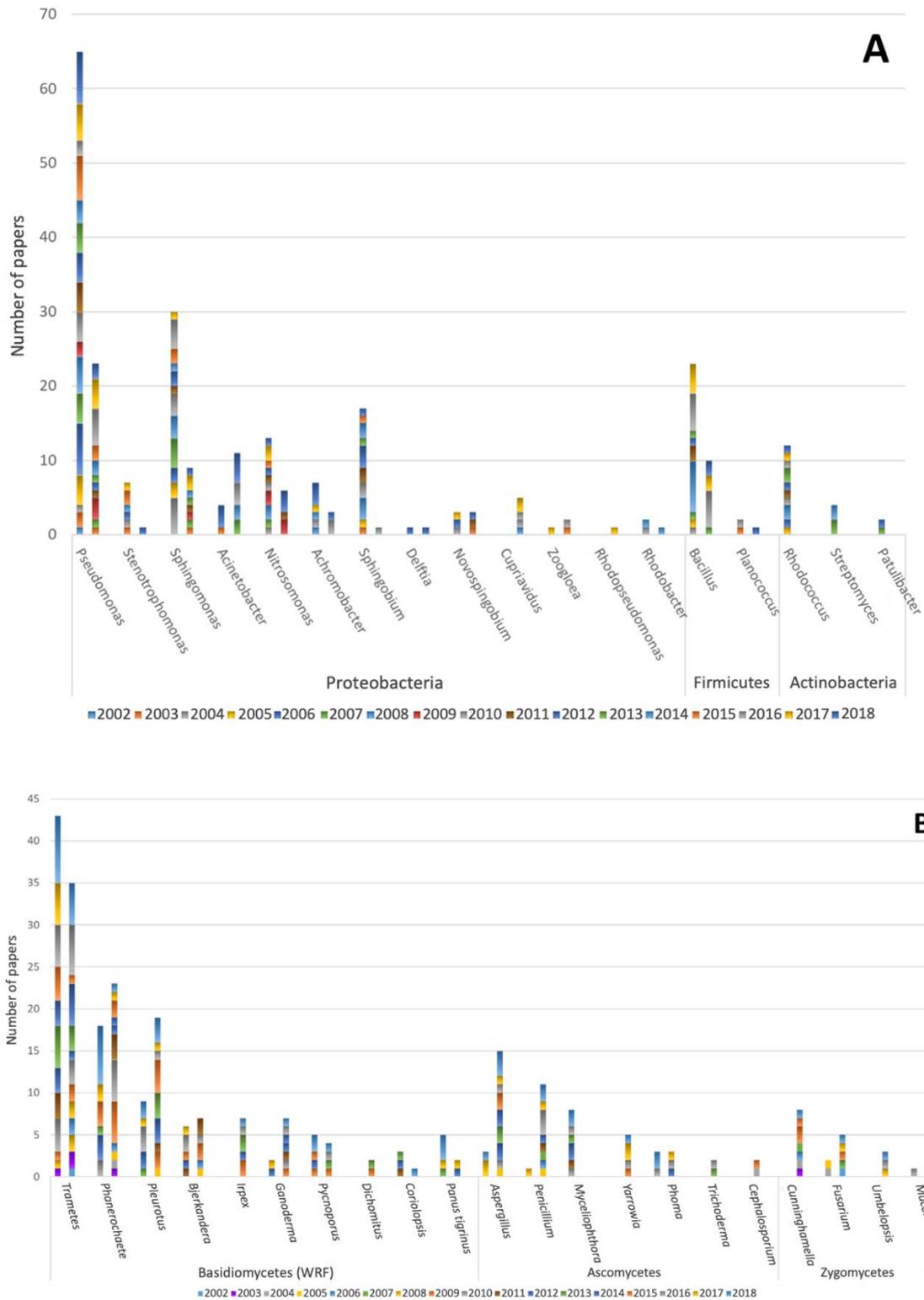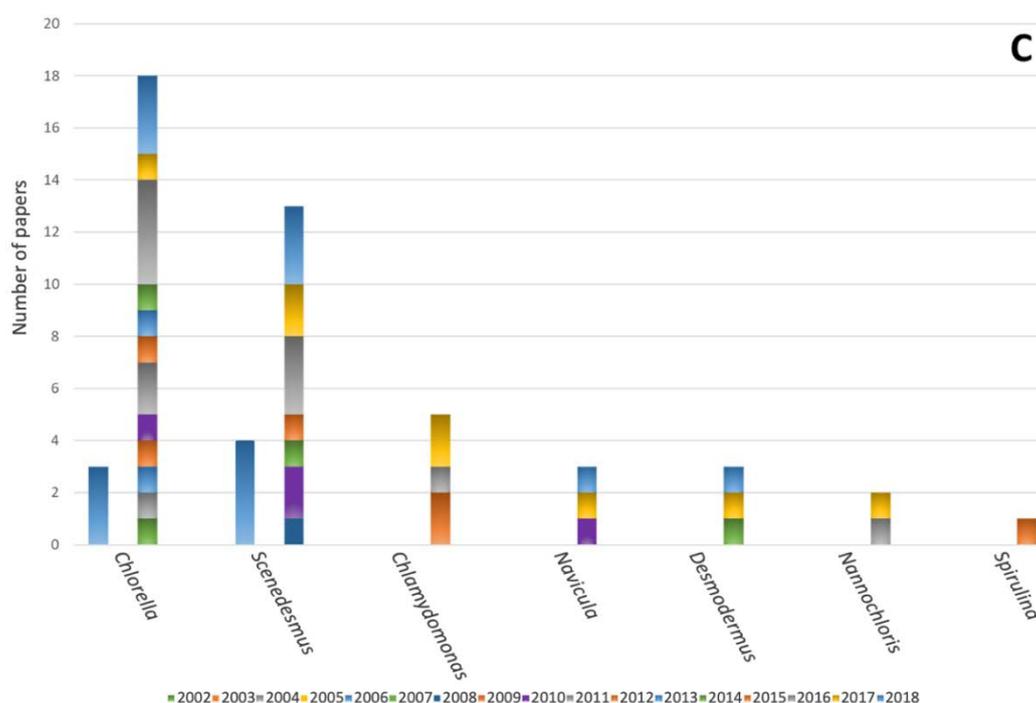

Figure 3. *Cont.*

Figure 3. Scientific production on bacteria (**A**), fungi (**B**) and algae (**C**) associated with the elimination of PPCPs from contaminated systems. Left column. Laboratory-scale publications related to identification of useful strains, determination of degradative and/or accumulative capacity, metabolic pathways, toxicology and OMIC (proteomic, genomic, transcriptomic) approach. Right column. Cellular or enzymatic immobilization, activated sludge with or without bioaugmentation, membrane bioreactors, photobioreactors, commercial products, nanoparticles).

Less frequently used (Figure 3A), but with a higher potential, we find other bacteria such as *Stenotrophomonas maltophila*, which can degrade CBZ, triclocarban, TCS [119] and NP [140]. *S. maltophilia* can degrade NPX by co-metabolism and enzymatic induction [141]. *Acinetobacter* sp. can degrade sulfadiazine, sulfamethazine (SMT) and SMX but with different mineralization efficiency [131] and degrade E2α in cometabolization with other hormones [142]. The biotransformation of sulfonamides by *Arthrobacter denitrificans* gave high degradation values [143,144]. The draft genome from two sulfadiazine *Arthrobacter* bacteria has been compared with other bacteria genomes in a metagenomic approach that might help to identify the functional genes that are involved in degradation of these PPCPs [145]. *Achromobacter denitrificans* bioaugmented into laboratory-scale membrane bioreactors increases the SMX degradation rates [146]. *Nitrosomonas europaea* is an ammonia-oxidizing bacterium that is frequently associated with the degradation of hormones (e.g., [42]). Studies on the evolution of microbial populations in the presence of 17β-estradiol established a relationship between the presence of some bacteria (*Nitrosomonas*, *Bacillus*, *Pseudomonas*, *Sphingomonas*, *Novosphingobium*, *Alcaligenes*, *Rhodanobacter* and *Mycobacterium*) and the biomineralization of the contaminant [147,148]. The complete sequencing of different species of *Sphingobium* are being carried out to characterize and compare the expression activities of NP-degrader genes [149]. Recently, the *Cupriavidus* sp. complete genome has been sequenced, a caffeine-utilizing bacterium [150] and other PPCPs such as CBZ [123]. *Cupriavidus* sp. with other bacteria such as *Sphingomonas* sp., *Delftia* sp., *Acinetobacter* sp. And *Methylobacterium* sp. obtained by a wood-rotting microbial consortium (BOS08) have shown an optimized CBZ biodegradation of 40 % in 8 days [123]. All these bacteria including *Planococcus*, *Zoogloea*, and *Patulibacter* can potentially be PPCPs degraders but they have been poorly studied (Figure 3A). *Rhodococcus rhodochrous* promote degradation of a variety of drugs such as CBZ [151], TCS [152] and

endocrine disruptors [153] among others. *Streptomyces* sp. has been linked to the degradation of some medications such as CBZ [115].

Purple phototrophic bacteria are anoxygenic commonly found in rivers, lake sediments, and wastewater treatment systems. They are metabolically the most versatile among all prokaryotes; anaerobically photoautotrophic and photoheterotrophic in the light, or microaerobic light, condition. They are distinguished by their ability to perform photosynthesis under anaerobic conditions and without producing oxygen [154]. Some of them have been described as emergency pollutants degraders (Figure 2) and have a high value added because they produce, from pollutants, substances of commercial interest [155,156]. *Rhodobacter spheroides* has proven to be effective in ameliorating hazardous pollutants found in pharmaceutical wastewater [157]. *Rhodopseudomonas palustris* and *Rhodobacter capsulatus* are also capable of metabolizing emerging organic compounds present in domestic wastewater, establishing synergy or competition relationships depending on the oxidized organics [154,158]. Recently, a study showed that *Rhodopseudomonas* contained genes associated with xenobiotic degrading pathways [119].

2.1.2. Mycoremediation

272 papers have been published while using fungi, or their components, as a tool for bioremediation and, in 40% of them, they have been used in complex systems. White rot fungi (WRF), are the most frequently used (Figure 3B). They belong to Basidiomycota and are recognized for their tolerance to high concentrations of pollutants [47] and for their ability to metabolize and degrade a wide variety of persistent organic compounds. This remarkable capacity has been attributed to extracellular enzymes (ligninolytic enzymes) with low substrate specificity [47], and they can be amplified an 80% using redox mediators [159,160] Three enzymes make up fungal extracellular matrix: laccase, manganese peroxidase and lignin peroxidase, whose relative importance in the degradation processes is species-specific [161,162]. Bioabsorption and intracellular degradation, as well as bioadsorption have also been described [163–165] (Figure 2). Some of them have been successfully used in the PPCPs degradation [166], given the constitutive nature of their enzymatic battery, they do not require acclimatization processes [167], although inducible laccase from fungi have been also described [168]. Other key that are reactions involved in these WRF pharmaceutical transformations are formylation, hydroxylation, dehalogenation, deamination, conjugation and polymerization [164,169]. The degradative capacity has been traditionally tested in laboratory and subsequently incorporated into WWTPs through cellular or enzymatic products immobilized in bioreactors, although in some cases such as *Irpex* and *Dichomitus*, only the laboratory scale has been approached (Figure 3B). Many applications regarding WRF have been reported in the literature [47].

Trametes versicolor is the most widely studied basidiomycete, showing a high oxidative capability to completely degrade PPCPs [162] (Figure 3B). More than 20 PPCPs susceptible to degradation by *Trametes versicolor* have been described [121,128,129]. Because *Trametes* laccases are more active than those of other fungi and bacteria (e.g., [170]), they have been used in numerous biotechnological applications and commercial products (e.g., [46]). *Phanerochaete chrysosporium* can also degrade several PPCPs under different aeration conditions. Isolated laccases from *Trametes versicolor* and *Phanerochaete chrysosporium* have been used in the formation of hybrid-nanoparticles that are capable of eliminating both inorganic and drug compounds from contaminated water [171,172]. Other widely reported WRF are *Phanerochaete sordina*, *Pleurotus ostreatus* and *Bjerkandra* species (for more details see [162,163], Figure 3B). In recent years, WRF such as *Panus tigrinus* and *Dichomitus squales* are being evaluated as potentially degrading fungi (Figure 3B). *Ganoderma lucidum* has been tested as a degrader of different drugs, with good results for diclofenac and ifosfamide [173]. Manganese peroxidase aggregates from this fungus transform NP and TCS [174,175]. *Irpex lactatus* is another suitable WRF in the biotransformation of PPCPs such as FLU [176], hormones [177,178] NP, TCS [179,180], CBZ and diclofenac [173]. Immobilized laccases from *Pycnoporus sanguineus* have been used successfully in the biotransformation of different antibiotics [181], hormones [182,183], TCS and NP [184] and from *Coriolopsis gallica* to remove TCS, diclofenac and hormones, NP [185–187]. Recently, other WRFs such

as *Stropharia rugosoannulata*, *Gymnopilus luteofolius*, *Agrocybe erebia* [173] and *Moniliophra roreri* [188] have been tested for their potential as PPCPs-degraders (Figure 3B).

Much less explored is the degradative capacity of other non-lignolitic fungi groups such as Ascomycota and Mucoromycota (Figure 3B). Cultures of *Rhodococcus rhodochrous* and *Aspergillus niger* have reported the removal of CBZ up to 10% [189]. *Aspergillus* species biotransform diclofenac, TCS, estradiol, CFN, NP [159,163,190–194]. Genetically modified *Aspergillus* increases laccase production, which can be used for biotechnological purposes [163,195,196]. The other study shows the optimization and scale-up of the degradation process regulated by *Penicillium oxalicum* in a batch reactor and compared the degradation between free and immobilized biomass [197]. Some species of *Penicillium* can be used effectively in TCS, NP and hormones degradation [198–202]. The yeast *Yarrowia lipolytica* has been studied for the expression of cytochrome P450 and it seems capable of degrading diclofenac and NPX [191,203]. *Trichoderma harzianum* is able to degrade 17 β-estradiol [204] and CBZ with a performance similar to that of *Pleurotus ostreatus* [205]. Free laccase from *Myceliophthora thermophile* and *Lentinula edodes* can be used to remove estrogens (e.g., [101,206]), diclofenac, NPX [207] and antibiotics [208]. A recent study has underlined the potential of ascomycetes in purification mycotreatments both for their degradative capacity and for their possibilities in bioadsorption [209].

Regarding Mucoromycota, *Cunninghamella elegans* can transform ATN [210], GFZ [211], NPX [212] and FLU, in two compounds with less antimicrobial activity [213]. Native lipases from *Mucor javanicus* were tested for the degradation of IBU [214] without very good results. *Mucor hiematis* associated with commercial fungi can establish synergistic relationships for water purification [215]. *Fusarium* species degrade estrogens and NP [216,217]. *Umbellopsis isabellina* is able to degrade and reduce the toxicity of hormones and NP [218,219].

Some Ascomycota and Mucoromycota could be better PPCPs degraders than basidiomycetes, not only for their high tolerance to extreme conditions, but also by the high presence of cytochrome P450 family (CYP) epoxidases and transferases involved in the metabolism of xenobiotics in both groups [164]. However, the improvement of these filamentous fungi through the development of commercial products, biotechnological advances or applications on an industrial scale are in their infancy (Figure 3B).

2.1.3. Phycoremediation

Traditionally, microalgae cultures have not been used for the elimination of PPCPs since these compounds are often toxic to photosynthetic organisms (e.g., [220–222]). In fact, some of them are used as ecotoxicity testing organisms due to their sensitiveness to pollutants (Table 1). This is probably the reason why, so far this century, only 52 manuscripts have been published using these microorganisms as PPCPs-removers and only 7% of them propose an important role in advanced biorecovery systems for microalgae (Figure 3C). *Scenedesmus obliquus* and *Chlamydomonas mexicana* have some capacity to eliminate CBZ at low concentrations, but higher concentrations inhibited algal growth [223]. IBU stimulated the algal growth of *Navicula* sp. at lower concentrations, but growth decreased substantially at high concentrations (Figure 4). In addition, the inoculation of *Navicula* sp. to water systems, can inhibit the degradation of IBU, implying that it could prolong the stress time by this anti-inflammatory drug [224]. However, using wastewater as a source of nitrogen and phosphorus for mass production of rich added-value microalgae with the simultaneous contaminant removal represents an extraordinarily attractive option. Overall, the energy (biogas and biodiesel), pharmaceutical, food and feed industries are an attractive market of microalgae applications (Figure 4, [225–228]). In fact, estimations for demand in microalgae products project an increase up to US$ 44.6 billion by 2023 [227,229]. Recently, a geographic information system model was built to identify the areas in Mexico with high potential for microalgae production [227].
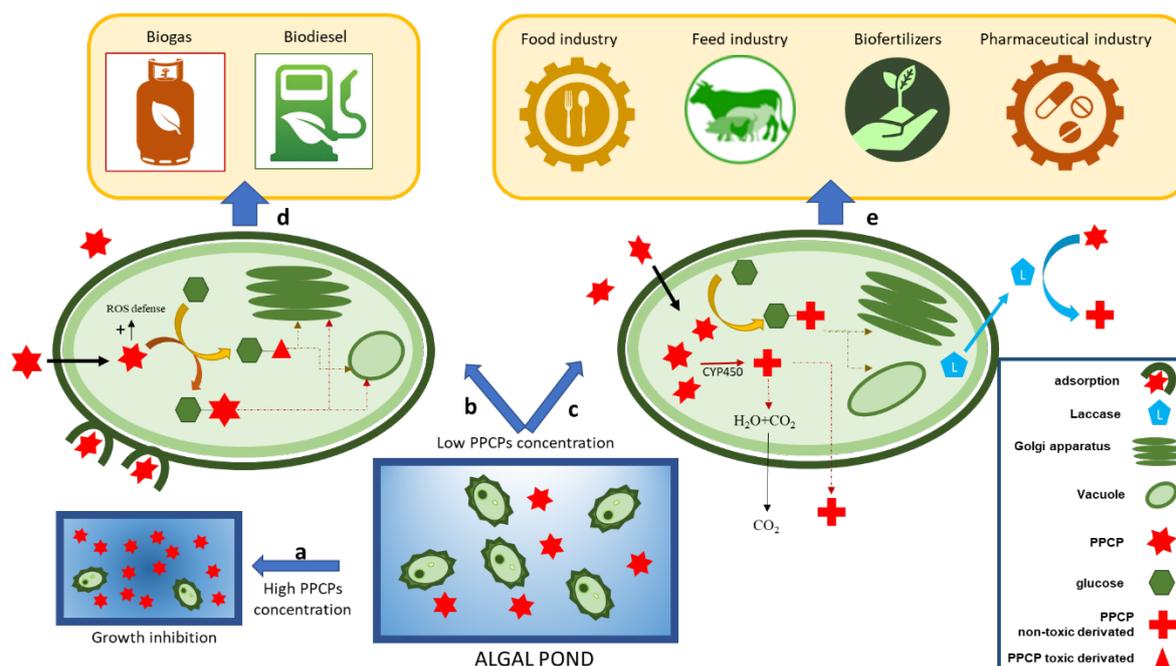
Figure 4. Towards the circular supply chain management (CSCM) reactivation. **a**. High PPCPs concentration inhibit algae growth [196,197] but low concentrations can allow bioaccumulation (**b**) or metabolism (**c**) and therefore, the increase in biomass [180]. **b**. PPCP bioadsorption and bioabsorpiton associated to glucosil-conjugation bioaccumulation of PPCP or PPCP toxic derivatives [230]. Increase of ROS defense reactions [231]. **d**. Increase in the production of algal biomass useful by acclimatization in the production of biodiesel and biogas [182]. **c**. Bioabsorption and intracellular degradation by cytochrome P450 and associated enzymes [223] and extracellular degradation mediated by laccases [102,103]. **e**. Biomass usable in food and feed industry [227], biofertilizants [232], and pharmaceutical industry [233].

Some studies have shown that algal treatments of wastewater considerably reduce a high number of PPCPs (Figure 3C), but the toxicity of the water persists, due to the presence of ammonium, a metabolism toxic derivative, [99,234,235]. Although in some analyzes, on a laboratory scale, this toxic compound has been eliminated [103], the number of laboratory tests should be increased in order to confirm these results. Most of the focuses mainly on studies in continuous open ponds (e.g., [236,237]). As far as we know, the PPCPs algae-removal mechanisms are like those described for bacteria and fungi: intracellular and extracellular biodegradation, bioadsorption or/and bioaccumulation, (Figure 2, [238]). Extracellular processes appear to be mediated by laccases, like fungi and bacteria. Thus, *Tetracystis* laccase converts bisphenol A, 17α-ethinylestradiol, NP and TCS in the presence of a redox mediator [102]. The intracellular degradative metabolic pathway would be mediated by cytochrome P450 and conjugation with the implication of several other enzymes [223], Figure 2). External digestion could be carried out by laccases and other extracelluar enzymes [102,103]. Metabolic pathways for phycodegradation of SMT and SMX have been proposed elsewhere [239]. The degradation of these antibiotics was higher at higher concentrations, indicating that biodegradation might be an efficient mechanism of microalgae acclimatization to antibiotics [240]. *Desmodesmus subspicatus* uptake and biotransform E2α but yields a very toxic brominated product [241]. Green algae *Desmodesmus* sp. and *Scenedesmus obliquus* were used to carry out hydrolysis and reductive dechlorination of TCS, suggesting the possibility of mineralization by these algae [38]. Similarly, [242] not only report the bioremediation of DFC using *Chlorella sorokiniana*, *Chlorella vulgaris* and *Scenedesmus obliquus*, but also show an important reduction in the toxicity of the effluents, especially with *S. obliquus*. Even non-living *S. obliquus* can be an effective option in the elimination of DFC and other PPCPs by bioadsorption [243,244] since pollutants with cationic groups are actively attracted to the cell wall through electrostatic interactions [238].

Microalgae such as *Desmodesmus subspicatus*, *Chlamydomonas mexicana* and *Scenedesmus obliquus* can bioaccumulate emerging contaminants along with growth nutrients [223]. The accumulation of PPCPs in microalgae cells can induce the generation of reactive oxygen species (ROS) that are related to defense and adaptation mechanisms [231]. Moreover, Nordic microalgae isolated from nature can remove lipophilic active pharmaceutical ingredients, equally or more efficiently than the investigated culture collection strains. While *Coelastrella* sp. and *Coelastrum astroideum* were most efficient in accumulating certain compounds in their biomass, two algae species, *Chlorella vulgaris* and *Chlorella saccharophila*, were not only highly efficient in removing all 19 pharmaceuticals but also only small amounts of these compounds accumulated in their biomass allowing for its further use [222]. *Nannochloris* sp. mediated photo- and bio-degradation were the primary pathways for the removal of 17α-, 17β-estradiol and salicylic acid but the incomplete removal of all steroidal hormones demonstrates that there is still an endocrine disrupting potential in the ecosystem [108]. Recently, the use of an unidentified microalgae consortium, isolated from ponds enriched with emerging contaminants, has improved the results of phycoremediation [236].

2.1.4. Mixed Culture

The complete mineralization of emerging contaminants is achieved while using mixed cultures because the synergistic enzymatic activities of the members of a consortium are often more effective than the individual action of each (Figure 2). However, the response of mixed cultures depend on multiple factors, so if synergistic interactions are not generated, or even if competitive interactions occurred, the results may not be better [151].

Controlled co-cultures have expanded our knowledge. Thus, *Trametes versicolor* and *Ganoderma lucidum* were used to remove 13 different pharmaceuticals and generate biodiesel from the generated sludge. Combining both strains increase the removal efficiency as a result of the interactions developed between them [161]. The antibacterial activity of antibiotics could be eliminated after treatments with pure and co-culture of *P. chrysosporium* and *Pycnoporus sanguineus* [245]. Co-culture of *Alcaligenes faecalis* and *P. sanguineus* degrade well SMX [246]. *Cunninghamella* sp. could be involved in the degradation of endocrine disrupting chemicals by a mixed culture with WRF [247]. The complete mineralization of E2α by metabolization was achieved by ammonia oxidizing bacteria, together with heterotrophic bacteria [42]. Microbial interactions between *Arthrobacter* sp. and *Pimelobacter* sp. also allow for the complete mineralization of sulfadiazine. Synergistic effects were observed in mixed cultures of bacteria and fungi that could effectively and completely remove some PPCPs, while neither fungi nor bacteria alone could remove the compound, suggesting that bacteria and fungi can adopt different but complementary metabolic pathways to remove organic compounds [104,248].

The consortia of cyanobacteria/microalgae and bacteria can be efficient in the detoxification of organic pollutants from wastewaters, as compared to the individual microorganisms. These associations have been frequently used in photoreactors (see Section 2.3.1). *Chlorella-Aspergillus* pellets were investigated for the degradation of seven pharmacological compounds. In this lab-test, only one of them was degraded and the presence of algae did not suppose a benefit in the final degradation [249]. One of the troubles associated with the use of microalgae in WWTP is the subsequent collection of them (clarification). Co-pelletization using *T. versicolor* provided a solution to problems that are associated with current energy-intensive and costly algae harvesting processes [250]. Microalga-duckweed association can completely eliminate estrogens from wastewater mediating processes of sorption and biodegradation [99].

Figure 2 shows the documented biodegradation of E2α where different types of microorganisms and natural processes can intervene. Hydrophobic bioabsorption [107] and bioaccumulation can derive in PPCPs stabilization within the biomass, white bioabsorption, and biodegradation up to mineralization (CO_2 + H_2O) can remove completely pollutants from the ecosystem. Fundamentally bacteria [97,98] and also microalgae [99] usually perform intracellular degradation, whereas fungi metabolize this compound by extracellular degradation that is mediated by laccase. So far, the

intervention of other lignolithic enzymes has not been described [101]. Intermediate metabolites could be secreted into the medium and biodegraded through a chain of synergistic reactions that are mediated by other microorganisms [39,42] or bioaccumulated by conjugation and/or accumulation in cellular organelles. Natural adsorbents, such as active carbon, favor the elimination of this hormone [111] and the biosurfactants help with its mobilization and subsequent elimination [105]. Recently, it has been described how photooxidic humic acids (mainly semiquinone radical) not only favor the oxidation of E2α but can also be used as the last acceptors of electrons in respiration, activating the development of bio-degraders [106,107]. A degradative pathway by biogenic manganese oxides has been described [109,110].

2.2. Phytoremediation

Plants can retain PPCPs in their roots by adsorption or translocate soluble pollutants in the water by hydrophilicity-regulated transport via xylems [251]. The uptake of more than 100 PPCPs by plants has been studied both in soil and water systems [33]. Vegetables are known to successfully remove gaseous pollutants, such as benzene [252] although systems must be improved [253]. Several plants can uptake, stabilize and accumulate (Figure 5A), metabolize, mineralize, volatilize, secrete or detoxify contaminants (Figure 5B) through in situ treatments (e.g., [254]). Because of these processes, some plants can use these pollutants as nutrients (source of carbon, nitrogen and phosphorus) generating an increase in their biomass and canceling the toxic effect that they have on other organisms of the ecosystem (Figure 5B), while other plants accumulate them in their vegetable structures (Figure 5A). In both cases, biomass can be harvested and then, the by-products can have a second life or added value (Figure 5A,B).
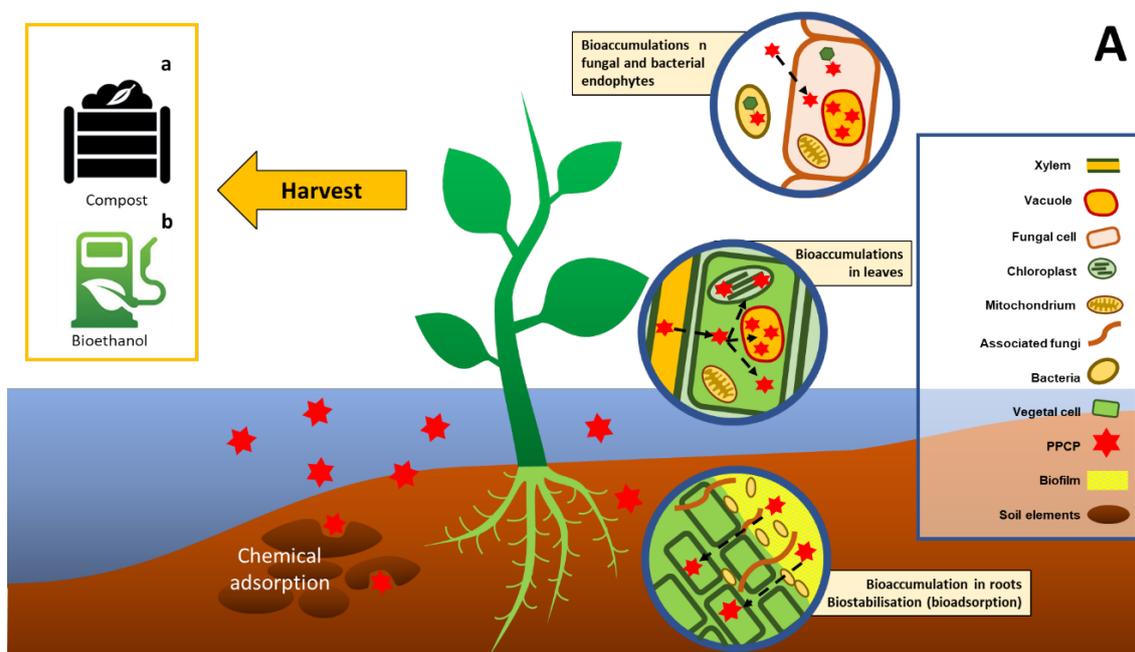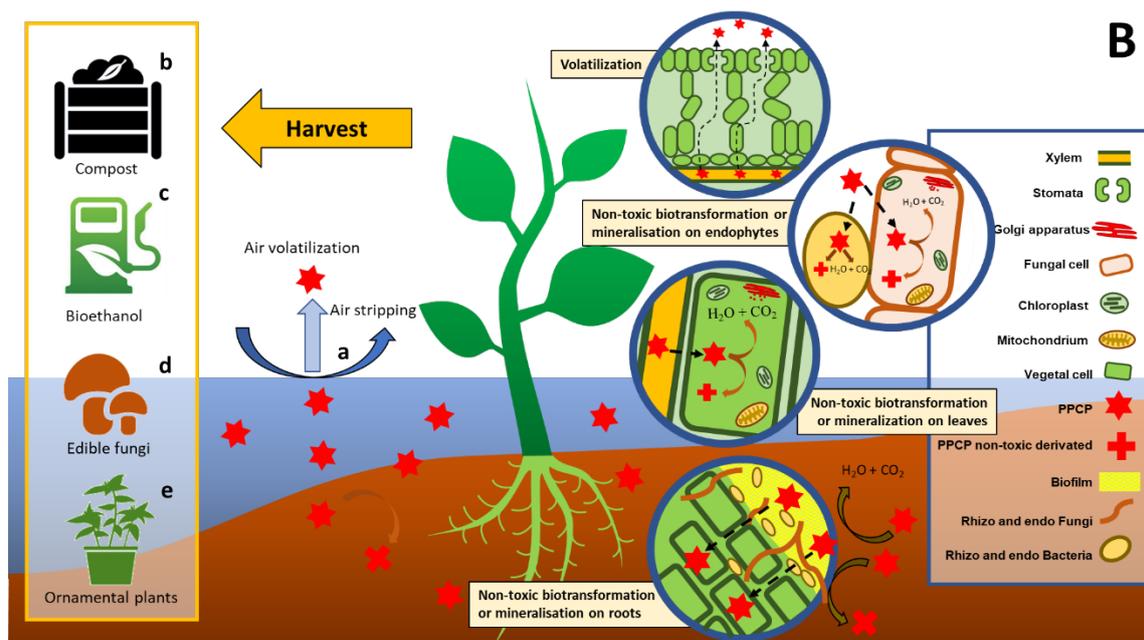

Figure 5. *Cont.*

Figure 5. Towards the CSCM reactivation. (**A**). Pathway of PPCPs uptake and bioaccumulation in plants (roots, leaves and endophytes) and chemical adsorption on substrate. Harvest of macrophytes biomass, use in secondary applications. **a**. [255]; **b**. [256]. (**B**). Pathway of PPCPs uptake and complete mineralization (metabolic interactions between plants and associated microorganisms), air and plant-mediated volatilization in constructed wetlands. Harvest of macrophytes biomass, use in secondary applications. **a**. [103]; **b**. [255]; **c**. [256]; **d**. [257,258]; **e**. [259,260].

Although phytoremediation is an excellent biotechnology strategy in soil and water systems, it does not recover 100% of the contaminated area and requires that prior to planting, complementary methods should be used to reduce the amount of pollutants in the area. Additionally, when selecting a plant for phytoremediation, it is necessary to consider its physiological requirements for growth, its condition as a native or introduced plant [261], as well as its effectiveness against a specific pollutant, as well as the secondary added value of the plants (Figure 5), for example, ornamental uses or primary biomass to produce bioethanol [255,258,262]. Hitherto, studies have focused on the effectiveness of recovery processes, the detection of ultra-trace substances along with the identification of metabolites that are produced in the plant upon treatment with active pharmaceutical ingredients [263,264] and in the understanding of metabolic pathways associated with their degradation [265]. However, it would be important to have a more integrated vision proposing a new paradigm.

A plant is a complex multi-genomic organism that is formed by the plant itself and its microbiome [266]. Microbiome (endosphere, rizhosphere and phylosphere) is mostly composed of prokaryotes and fungi. They produce plant growth beneficial effects by the production of nutrients, phytohormones, siderophores and enzymes. They also control plant pathogens and favor acclimation to stress situations. In addition, endophytes play an essential role in detoxification processes. Most of the studies have focused on organic pollutants, heavy metals and metalloids [267–273]. In relation to organic compounds, *Burkholderia kururiensis* and *Agrobacterium rhizogenes* are phenolic tolerant and degrading bacteria. When they are inoculated into root hairs of plant systems, the plant-degradative capacity of some of these pollutants significantly increases [274]. A shallow aquifer planted with *Juncus acutus* was able to remediate bisphenol-A and another organic compounds from contaminated groundwater, observing that several endophytic strains were tolerant and able to use them [275,276]. However, specific research of rizhophytic and endophytic microorganisms associated with PPCP detoxification is scarce. Some of them claim that associated rhizosphere bacteria are involved in accelerating the degradation of some PPCPs [277,278]. Another study described an efficient biotransformation of anti-inflammatory drugs by endophytic and epiphytic fungi isolated by *Plantago lanceolate* [279].

An interesting work [280] proposed that enantiomeric-ibuprofen phytodegradation by endophytic bacteria can be involved in its metabolism by lettuce. *Rhizobium radiobacter* and *Chriseobacterium nitroreducens*, endophytes in horseradish, improve CBZ removal plant. Of the four metabolic pathways described to degrade CBZ in plants [265], at least one (acridine pathway) is activated by the presence of endophytes [281,282]. It is necessary to highlight the need for further advanced studies on the synergistic effect between plants and PPCPs-degrader endophytic bacteria [265]; however, as far as we know, only the data referred to in this review are available.

2.3. Combined Chemical Engineering-Biological Methods

2.3.1. Bioreactors

Conventional municipal WWTPs, in general, have a very low efficiency for the elimination of PPCPs from polluted waters, as mentioned above These WWTPs could be improved with physical-chemical and biological process. Among the biological processes capable of transforming the original organic compounds into other simpler and less toxic molecules, ideally carbon dioxide, those using controlled bioreactors can be performed at large scale with high PPCPs removal efficiency (Figure 3A–C).

- Conventional activated sludge

Although the secondary biological treatment in WWTPs is not specifically designed to remove organic compounds at very low concentrations or trace levels, conventional activated sludge (CAS) processes can be optimized to improve the PPCPs removal efficiency. CAS effectiveness depends on the synergistic effect of the consortium, or microorganism mixture, to remove the PPCPs [283], which is constituted by complex communities that are formed by fungi, bacteria and algae [284]. However, both to lab and full-scale, little evidence of this type of synergistic relationship has been described so far and what is the ecology that steers the degradation processes is [187,285].

Conventional municipal WWTPs achieved removal efficiencies of >80% for fragrances, such as galaxolide and tonalide, after the secondary stage, while the uptakes for IBU, NPX, 17 β-estradiol and SMX were within the range 50–65% and the X-ray contrast iopromide was not significantly degraded [286]. However, other studies reached 93% depletion of IBU and 71% of SMX in different sewage treatment plants in Italy, showing important seasonal variations in the removal efficiency of 19 different PPCPs [287]. These variations comprised two main types of factors that, in turn, variate along the year: on one hand, the physical factors that are associated to the environmental conditions and, on the other, the chemical composition of the wastewater influents. Among the physical factors, temperature has the largest impact on the microbial activity, increasing degrading efficiency as temperature increased from winter to summer. With respect to the chemical composition of wastewaters, the load of some PPCPs, especially antibiotics, was lower in summer than in winter because these pharmaceuticals are less used in summer [287]. The removal efficiency of beta-blockers in CAS systems is usually low, ranging from 10% to 81% [287,288] for different waters, seasons and geographical locations, although it has been hypothesized that the removal rate of these drugs also depend on the solid retention time (SRT) of the activated sludge process too [289]. IBU and NPX are compounds showing the desired behavior in CAS treatments since they usually reach very high removal rates (typically 90–99%). On the other hand, CBZ usually shows poor removal values (<25%) in most CAS systems developed [289]. Bioaugmentation might be one strategy for improving the effectiveness of active sludge. For example, adding *Spingomonas* sp. or *Nitrosomonas europea* to activate sludge increases the degradation of TCS [112,135]. In relation to the elimination of PPCPs, the composition of the bacterial community (i.e., the identity of the taxa) could be more relevant than the bacterial diversity (i.e., number of different taxa) [290]. The increase in hydraulic retention time and the use of CAS augmented with acclimatized sludge substantially improves the elimination of CBZ and DCF, among others [291].

- Membrane bioreactors

Membrane bioreactors (MBR) combine the conventional activated sludge technology with the use of a filtration (micro- or ultra-) membrane system. The activated sludge is suspended inside the membrane and drives the biodegradation of organic matter. Meanwhile, membrane retains microorganisms and particles and allows for the permeation of the treated water, avoiding the need to use a settler [292]. MBR have been increasingly adopted by industrial and municipal wastewater treatment plants because of their high efficiency to remove emerging organic pollutants, yielding a high quality water effluent, which is especially suitable for reclamation and reuse [293]. MBR systems have demonstrated good performance for the elimination of some emerging organic pollutants that were not effectively removed by activated sludge treatments. The cause could be the concentration of the biological sludge on the membrane surface thus facilitating the degradation of persistent organic compounds and the retention of larger molecules than the corresponding molecular weight cut-off of the membrane [294,295].

Although MBR processes have been applied for the removal of a wide range of compounds, the effectiveness of elimination can vary greatly from one case to another depending on the nature of the microbial population, the chemical properties of the pollutant and the operation conditions of the process, as in CAS processes. In a pilot scale MBR system, which was equipped with a flat submerged membrane, 23 diverse emerging organic pollutants were evaluated [296]. Five steroid hormones (hydrocortisone, estriol, testosterone, estrone and progesterone) showed high removal degrees (>90%). Similar values were reached by other pharmaceutical products including diuretics, beta-blockers, antibiotics, analgesics and anti-inflammatory drugs such as atenolol, bisoprolol, enalapril, tetracycline, ciprofloxacin, trimethoprim, ketoprofen and NPX, with almost complete removal (>99%) of furosemide, paracetamol (acetaminophen), IBU and the stimulant caffeine. However, the removal of other compounds ranged from relatively high (propanolol 84.2%) to very low (DFC 38.8%, hydroxychlorothiazide 10.2%), or even negligible values (CBZ ~0%).

The solid retention time (SRT) is the most important operating parameter affecting the removal efficiency of PPCPs in MBR systems. In the case of labile and easily degradable compounds, such as IBU, high removal efficiencies were achieved when SRT was above a critical value of 10 d. For recalcitrant pharmaceutical compounds, for example, CBZ, the removal was low whatever the SRT value [293]. However, for PPCPs with intermediate stability, the removal efficiency can be significantly affected by SRT values. For example, when SRT increase from 8 d to 80 d the removal of ketoprofen and clofibric acid in an MBR increased from ~55% to ~91% and from ~4% to ~35%, respectively [297]. The higher degree of PPCPs removal is associated, not only to a higher microbial activity for larger SRT values, but also for the higher microbial diversity reached as SRT increases [293]. Membrane fouling and clogging are two major operational drawbacks with high economic impact on MBR systems [33]. Both aerobic and anaerobic granular sludge have been used to inoculate membrane bioreactors to overcome these limitations. These granular sludge membrane bioreactors (GMBR) allowed for a high biomass loading while nitrogen and organic compounds were effectively removed from wastewaters. The removal of five PPCPs (sulphamethoxazole, norfloxacin, prednisolone, NPX and IBU) from a synthetic wastewater loaded with 50 µg/L of each drug in a GMBR has been studied under aerobic conditions [39]. The continuous bioreactor was formed by a polyvinylidene hollow fiber membrane module (0.22 µm pore size) working under a hydraulic retention time (HRT) of 4 h. Prednisolone concentration decreased >98%, while norfloxacin, NPX and sulphamethoxazole reached 87.8, 84 and 79.8%, respectively. In fact, a dynamics in the microbial populations has been observed in aerobic granular sludge membrane bioreactor, where an increase in the presence of bacteria capable of degrading PPCPs is observed throughout the exposure time [39]. These studies show results that exemplify the complex relationships that are established in communities for the complete removal of emerging pollutants.

- Photobioreactors

Photosynthetic microorganisms, such as microalgae and cyanobacteria, can, simultaneously, remove nutrients and produce biomass from atmospheric CO_2 and solar radiation (photoautotrophic growth). However, some of these microorganisms are able to grow under mixotrophic condition by using organic compounds as a partial carbon source [298]. Therefore, microalgae photobioreactors have been described as an efficient tool for PPCPs and other emerging pollutants in wastewaters [299]. For large scale applications, continuous raceways (Figure 6) are the most viable types of photobioreactors for microalgae-based micropollutant removal due to their low cost and simple operation and maintenance [300,301]. Raceways consist in shallow channels (approximately 0.30 m), equipped with paddle wheels to keep water flowing and avoid settling. Because of it their open design, the microbial community is usually a dynamic consortium, changing its microbial population along time. [302] measured the removal of 52 different pharmaceuticals by a mixed microalgae culture grown in a pond, initially inoculated with *Tetradesmus dimorphus*. Their results showed a large variability in removal efficiency, ranging from >90% for nine compounds to <10% for 18 compounds. Aeration time improves microalgae activity [303].

A raceway system where microalgae and bacterial species are grown symbiotically is usually referred to as high rate algal pond (HRAP). In these systems, the photosynthesis process developed by microalgae supply the oxygen that is required by aerobic bacteria that, in turn, can degrade the organic pollutants. Therefore, the costly aeration that is necessary to support aerobic growth can be avoided. The metabolites from bacterial degradation of the contaminants and growth promoters synthesized by bacteria, such as vitamin B_{12} and indoleacetic acid, can act as promoters for the growth of algae. Algal exudates are the main carbon sources (carbohydrate, protein, and lipid) for bacteria. In addition, the cell surfaces of microalgae can provide a stable habitat for the bacteria [238]. Thereby, cyanobacterial/algal photosynthesis provides oxygen, a key electron acceptor to the pollutant-degrading heterotrophic bacteria. In turn, bacteria support photoautotrophic growth of the partners by providing carbon dioxide and other stimulatory means [304]. The synergistic relationship in *Chlorella*-bacterial microcosms, substantially improves the removal of aromatic pollutants [305]. Competitive interaction between algae and bacteria also exists, so it is substantial to increase the number of consortium studies, in order to select the most effective systems. An HRAP containing *Stigeoclonium* sp., *Chlorella* sp., *Monoraphidium* sp. and diatoms as predominant species, showed a very high removal efficiency (>95%) for CFN, acetaminophen, IBU, methyl dihydrojasmonate, hydrocinnamic acid and oxybenzone for a HRT of four days. When HRT increased to eight days, other pollutants, such as ketoprofen, 5-methyl benzotriazole, galaxolide and TCS were removed to an extent higher than 95% [103]. In the above study, other important pharmaceuticals reached lower degree of degradation: DFC (92%), NPX (89%) and CBZ (62%). Other results also showed that HRAP are efficient alternatives for the treatment of wastewaters containing emerging and PPCPs micropollutants. For example, high removal (98%) of anti-inflammatory drugs (IBU, paracetamol, salicylic acid, and CDN) and diuretics, such as hydrochlorothiazide (84%) and furosemide (100%). However, the removal degree for several antibiotics (azithromycin, ciprofloxacin, ofloxacin and erythromycin) and anxiolytics (lorazepam) were <48% and <57%, respectively [250]. Tetracycline can also be removed (>99%) from real wastewaters by HRAP operating at seven days of HRT under summer conditions [106].
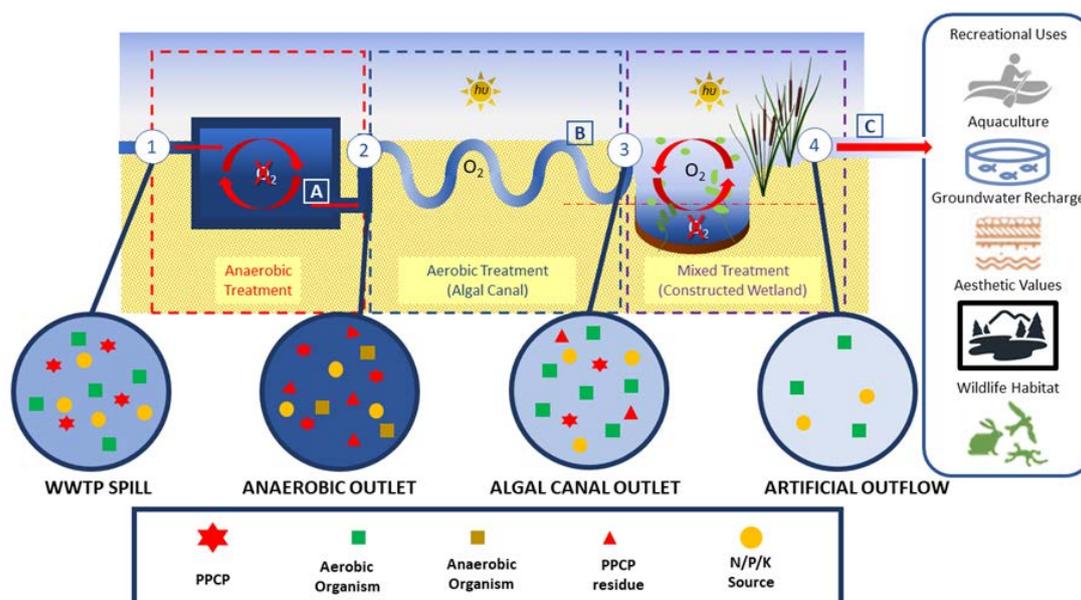
Figure 6. Towards the CSCM reactivation, serial system. **A**. Anaerobic bioreactor-pond. Removal of Aerobic microorganisms and PPCPs [229,236]. **B**. Algal canal-contracted wetland. Removal of anaerobic bacteria, PPCPS and PPCPs residue removal [223]. **C**. Mixed treatment (constructed wetland). Remove of nutrients and contaminants. Reuse of zero waste [306].

Wastewater treatment processes to eliminate micropollutants have been developed in closed bioreactors in order to avoid microbial contamination and population changes that occurs in open systems and to develop axenic cultures, with better control of operating conditions. Although these systems have not been developed on an industrial scale, pilot and laboratory studies proved good performance in the removal of not readily biodegradable pharmaceuticals in conventional raceways or in HRAP, such as salicylic acid, which was removed (>93%) in a bubbling tubular photobioreactor containing a culture of *Tetradesmus obliquus* supplemented with CO_2 [235]. Though more scientific investigations on scale-up studies and technical aspects of microalgae bioremedial system are needed, the future of the PPCPs phycoremediation look promising [106].

2.3.2. Constructed Wetlands

Constructed wetlands (CWs) are ecoremedial engineered systems that are designed to utilize the natural functions of wetland vegetation, sediments, and their associated microbial assemblages for wastewater, greywater or storm water treatment within a more controlled environment [58]. The use of CWs arises from the desire to mimic the ability of natural wetlands to survive and re-establish the functional relationships after out/in disturbances. Nevertheless, on the scale of the impact on planet Earth, anthropic perturbations are the most important detrimental elements [307], so that successful design, the integration of components and the improvement in efficiency are fundamental.

These systems have revealed as excellent solutions for the elimination of emerging contaminants and antibiotic resistance genes [308]. Overall, the effectiveness of these full-scale systems is equal to and even higher than the conventional wastewater treatment plant (WWTP) but at low cost [309,310]. Some of the removal processes that take place in these systems are: phytoremediation, sediment sorption (adsorption, absorption), microbial degradation (anoxic, anaerobic, and aerobic) located on sediment or associated to plants [311,312], and photodegradation [299]. The integration of microalgae-based biotechnologies (such as open algal ponds) and constructed wetlands could increase the efficiency of PPCPs removal systems (Figure 6), since microalgae can accumulate and degrade pollutants, produce oxygen through photosynthesis (a limiting factor in the degradation processes of CW), and the algal debris can be used as the organic substrate for microorganisms ([238], Figure 6). In algal ponds,

photodegradation processes are dominant and removal by biosorption is usually low, except for very hydrophobic pollutants [106]. The association in series of both systems, together with anaerobic bioreactors, favors the elimination of pathogenic microorganisms [313] in addition to the degradation of PPCPs (Figure 6). Technical details on the types of wetlands developed, as well as the physical-chemical and biological parameters limiting factors, can be consulted in different reviews [58,299,306,314,315].

The CW success on PPCPs removal depends on multiple factors, such as the type of CW (subsurface flow, horizontal or vertical subsurface flow, etc.), the plant model used and its remediation functions (absorption, degradation, mineralization, volatilization, etc.) and radicular penetration [316], the interaction with the microorganisms present in the CW and the biome that is associated with the plant [316], the chemical nature of each compound [310], the background nutrients and bacterial community evolution in the sediments [125], as well as, abiotic factors such as temperatures, pH, season of the year, aeration systems, etc. [316–319]. These factors can be balanced to stabilize the system. For example, cold-resistant bacteria can compensate for the negative effects of low temperatures [320]. Among them, the selection of the plant is a determining factor. The roots provide surface area for attached microorganisms, and root growth maintains the hydraulic properties of the substrate. Vegetal species present in the CW determine the composition of the microbial community on the roots and the rhizosphere [290]. The vegetation cover protects the surface from erosion and shading prevents unwanted algae growth [321]. Plants are the main factor that regulates the amount of nutrients in aquatic systems, buffering saprophytic processes and reducing eutrophication [322]. Vegetables also generate a microhabitat that regulates light and temperature, favors sedimentation and prevention of the medium clogging in vertical flow systems [323]. Useful plants to constructed wetlands are: aquatic species, including free-floating species such as *Nymphaea* sp., *Eichhornia* sp., *Lemna* sp., *Azolla* sp., *Salvinia* sp., *Pistia stratiotes*, *Eichhornia crassipes*, etc., and helophytes as *Sagittaria* sp., *Juncus* sp., *Phargmites* sp., *Thypha* sp., *Scirpus* sp and *Schoenoplectus* sp. [259,324,325]. In many countries, local plant, especially ornamental plants are used, with an aesthetic and commercial added value (Figure 5B). Some examples are: *Cannae lilies*, *Canna indica*, *Heliconias* sp., *Zantedeschia* aethiopica, etc. [259,260,323].

Microorganisms seem to be less inhibited by PPCPs in constructed wetlands, because plants stabilize and activate the microbial communities by supplying nutrients and oxygen and an adequate microhabitat or biofilms [326,327] increasing aerobic degradation and nitrification [323]. Overall, and as it happens in other full scape systems (active sludge, bioreactors, etc.), the presence of a specific organic pollutant activates and favors certain microbial genomic sequences that may be related to the degradation of pollutants [200,327]. Thus, [200] showed that IBU reduces the diversity of the fungal community, especially within unplanted wetlands. The species enhanced in abundance after IBU exposure were *Aspergillus* sp. and *Trichoderma* sp., suggesting a relationship of these species with the degradation of this anti-inflammatory drug. The presence of plants in CW had a remarkable effect on the structure of microbial community, helping buffer against the stress associated with CFN exposure [200]. Other study indicated that the presence of ciprofloxacin had an adverse effect on the bacterial communities in CW, initially reducing their ability to assimilate anthropogenic carbon-based compounds, but the bacterial communities returned to normal functioning after a 25 weeks acclimatization period [328]. Ongoing monitoring and hydrological and vegetation management are essential to maintain site habitat diversity and its functionality due to the natural dynamics of populations that are established over time in all the living components of a CW.

As previously mentioned, the microbiome associated to plants seems to have a fundamental role in their response to stress situations under CW conditions (Figure 6). In fact, [282] suggests the application of the potential endophytes to improve the performance of these systems. Thereby, plant-endophyte synergism in CW enhances the remediation of nutrients [329,330], heavy metal [30,245,331], metalloids [332], textile industrial effluents [333,334] and rural domestic water [318]. Likewise, bioaugmentation with denitrifying strains can activate the non-endophytic microorganisms that are associated with the rhizosphere, favoring the denitrification of nutrients [335] altering the soil microbial community structure by changing the species of nitrogen-related bacteria, and establishing

a new bacterial community balance in situ [300,336,337]. In some studies, it has been proven that the remediation effect of bacteria is more important than that of plants [338]. There are few studies analyzing the degradation of PPCPs in CW emphasizing the plant-microorganism synergy effect. Some antibiotics, such as DFC and SMX, have been partially degraded in CW implying degrader endophytes [339,340]. Inoculation of an estradiol-degrading bacterium in a CW favors the degradation of this hormone and modifies the bacterial community of the biofilm where it is stabilized [341].

As far as we know, WRF has not been used in PPCPs-degrader constructed wetlands probably because an aquatic system is not the most suitable habitat for the development of these organisms. However, whole-cell has been used successfully in *P. ostreatus* bioreactors, for water treatment, even under bacterial stress [342]. Additionally, *P. ostreatus* harvested biomass from constructed wetlands has been used as a substrate for production of high-quality oyster mushrooms [258]. Thus, commercial *P. ostreatus* strains used, usually in food, have important degradative potential [342]. The incorporation of the WRF in the constructed wetlands could be considered as a second phase of biomass exploitation (Figure 5B), as long as the plants do not retain the contaminants in their structures for which pollutants analysis protocols on an industrial scale have to be generated. Scarce are also the works in which, ascomycetes potentially beneficial for the performance of these mesocosms, are inoculated into the system. In this respect, constructed wetlands bioaugmented with *Trichodema harzianum* have been developed [343]. This helped in the establishment of *Iris versicolor*, but it did not aid on the performance of the treated effluent.

Thirty years of the research into the use of CW as the most common ecoremedial method, for various types of wastewater, has proven that the great number of early worries and negative arguments have been successfully negated [51]. However, despite the advances described in its use, are still developing systems. Abiotic parameters must be better controlled, and engineering improvements must be undertaken, such as effluent and aeration flow systems. In addition, these systems can be a perfect habitat for the development of a wide variety of annoying mosquitoes and potentially transmitters of diseases [344]. Metamorphosis and the appearance of aquatic insects occurred earlier and more frequently when insect larvae (*Diptera*) were exposed to fluoxetine and citalopram [77], and the cumulative emergency of insects increased up to 89% of exposure to amphetamines [17]. The presence of antibiotic resistance genes in the effluent might entail a risk of antibiotic resistance being spread in the external environments to the system [339], although it has been proven that these systems also eliminate resistance genes [308]. Finally, the benefits that can be potentially obtained from the waste coming from the CWs, such as production of bioethanol, compost, ornamentation, etc. (Figure 5B) are so promising, that they deserve to be studied in detail for their large-scale application.

3. Ecotoxicology

Often, studies do not evaluate the ecotoxicity of PPCPs metabolites or conjugate transformation products, which are sometimes suggested to be biologically damaging [345,346] and often the resulting products can be more toxic [347,348]. In addition, the effects of excipients of the drugs and the additives added to different PPCPs have been poorly studied [349]. NPX photo-transformation products have been suggested to be more toxic than the parent compounds for algae, rotifers and microcrustaceans [346]. When the toxicity of the abiotic degradation products of IBU and 4-acetylbenzoic acid using test organism (*Bacillus megaterium*, *Pseudoaltermones atlantica*, and algae of the *Chlorella* genus) was evaluated, the toxicity was reduced in the case of IBU but the same did not occur with 4-acetylbenzoic acid [350]. Therefore, ecotoxicological evaluation should be a prerequisite for risk assessment of intermediate or non-degraded chemicals in the water and soil recovery processes [351]. Thus, ecotoxicological tests using biomarkers have brought to light important changes in the behavior of populations of aquatic invertebrates [352], stress oxidative in Zebra mussels [68], and delay in fish development and in frog's metamorphosis [353]. Table 1 contains a detailed review of the most commonly used biomarkers to determine the ecotoxicity of recovered water. For example, the global order of sensitivity of the species to 26 PPCPs considered in aquatic environments was: *Vibrio fischeri*

(15 min) > > algae> crustaceans > fish > WWTP biomass [36]. Fewer biomarkers have been used in agricultural soils or terrestrial ecosystems, where some nematodes, anelids and only one species of arthropod (Table 2) stand out.

The selection of the appropriate biomarkers to environmental pollution detection is important, both in aquatic and terrestrial environments. This selection will come determined by multiple factors, among others, the PPCPs mixture composition (Tables 1 and 2). In addition, the degree of sensitivity to pharmaceutical products does not depend on the complexity of the organizations [8]. The monogononta rotifers could be one of these organisms. They have high rates of population growth, what allows the study of multigenerational effects in short times. In addition, they are bioindicators sensitive to water changes are susceptible to a wide range of contaminants and reproduce in a parthenogenic way that allows for comparing genetically identical individuals [354]. A chronic exposure to PPCPs of the rotifer *Plationus patulus* decreased egg production and increased egg detachment [65]. Algae are at the base of aquatic food webs and they play important roles in the transfer of energy and nutrients to species at higher trophic levels. The algae have a rapid reproduction rate and high sensitivity to contamination [67]. Microalgae have ecological relevance, they are easily cultivated in the laboratory and are sensitive [355,356]. In many studies developed with microalgae, after the exposure to PPCPS, an inhibition of the growth has been observed [67,69]. *Daphnia magna,* a planktonic crustacean of the order Cladocera and *Dreissena polymorpha,* a mollusc bivalve, are used in ecotoxicological bioassays for their low phenotypic variation and high sensitivity to toxic compounds. In one study signs of oxidative stress with high levels of lipid peroxidation in zebra mussels (*Dreissena polymorpha*) exposed to GFZ and DFC were proven [68]. Ethinylestradiol and fluoxetine generated changes at hormonal levels, decreasing fertility and fecundity and increased mortality, affecting growth rates in *Daphnia magna* [76]. Meanwhile, antibiotic contaminants that were commonly released in fisheries reduced the growth of green algae (*Scenedesmus vacuolatus*) and duckweed (*Lemna minor*), as well as the viability of the crustacean *Daphnia magna* [66]. Cimetidine, a common antihistamine, reduced the biomass of *Gammarus* when exposed to low concentrations [357] and exposure to low concentrations of a mixture of antibiotics resulted in changes in leaf microbial communities, resulting in an increase in body mass of amphipods (Gammarus) [78]. Fishes of the *Cyprinidae* family, such as *Pimephales promelas* and *Danio rerio* are used for their molecular and genetic similarities with other vertebrates as well as their rapid embryogenesis [353,358]. Soil nematodes are useful indicators of soil health, because they are abundant, have high diversity and several trophic groups. They play an important role in soil ecological processes and they are well-adapted to a wide range of environmental conditions [359]. The diversity and structure of the soil nematode community resulted in being vastly altered after exposition to 26 PPCPs. Mammalian steroid hormones caused a decrease in the number of nematodes and a change in the sex ratio [91,92]. Earthworms are in contact with soil pollutants by their feeding and their skin, so that they are very relevant for the assessment of toxicity of organic contaminants and bioavailability [360]. TCS affected the growth and reproductive performance of the earthworm (*Eisenia andrei*) [93]. The inclusion of multi-omic analyses in these studies, provides improved characterization of biological response, thereby enhancing prediction of toxicological outcomes in whole animals in the absence of morphological effects [81].

Determining the ecotoxicity of PPCP metabolites and transformation products is logistically very demanding, because of the number of the substances produced and released to the environment, their metabolites and environmentally generated byproducts. Therefore, stakeholders demand some prioritization criteria for ecotoxicological risk assessment studies. Two general approaches are proposed to identify the most problematic substances. The first one is the identification of the environmental hazard when considering not only lethality as endpoint, but relevant biological parameters related with species fitness to characterize contaminants adverse effects [9,15]. This is a paradigmatical change slowly taking place in the last few years, which is transforming the traditional one substance—one species assessment towards a real multidisciplinary Ecotoxicology centered on complex ecological networks of interactions in the biosphere. The measurement of environmental levels of substances of

concern allows for modeling increasingly sophisticated environmental risk assessment (ERA) methods allowing to prioritize substances [36,361]. Other environmental assessment tools have been proposed in combination with ERA tools, such as Life Cycle Assessment (LCA) and Material Flow Analysis (MFA) [362]. However, this effort might not be enough and limitation in the number of substances should also be considered. In this sense, the European Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [363] regulation transfers the burden of ecotoxicological testing to producers and traders of chemicals (EC 1907/2006). Application of this kind of strategies, will both help reduce the number of new chemicals and give insight into the amount being released into the environment. This knowledge helps performing a chemical—directed environmental monitoring and ecotoxicology testing. In particular REACH identifies and prioritizes three categories of substances of very high concern (SVHC): (i) carcinogens, mutagens and toxic for reproduction substances (CMR), (ii) persistent, bioaccumulative and toxic substances (PBT) and very persistent, very bioaccumulative (vPvB) substances. Finally, the increasing use of green and bioremediation technologies to decontaminate and buffer urban and industrial effluents such as the ones reviewed in this paper will certainly help reduce the number and load of substances, metabolites and byproducts of environmental concern.

4. Conclusions and Future Perspectives

Ecoremediation allows for the recovery of systems that are altered by organic contaminants and specifically PPCPs. Microorganisms (aerobic and anaerobic bacteria, basidiomycete and ascomycete fungi, and some resistant algae) can function as eco-factories, capable of restoring ecosystems through clean, low-cost technologies, thus being an important link in the CSMC. Since the mineralization pathways of PPCPs can be complex, further research is necessary to systematically establish collaborative relationships between microorganisms. These researches, to the meso and macro-scale, could allow for achieving complete metabolization, while avoiding intermediate metabolites which are also often ecotoxic compounds and with multiple target cells [364]. Furthermore, the association of these microorganisms with macroorganisms (plants and fungi) in series systems, complements the degradation processes and amplifies the possibilities of success [365]. The engineering of the systems as well as the optimization of the processes in the field are lines of research that can be improved in the future. Moreover, rhizo- and endophytes in this type of system not only degrade PPCPs directly but also accelerate plant growth by producing growth-promoting enzymes and, hence, the remediation potential of CWs [366], line of research that is in the early stages of discovery. On the other hand, certain microalgae are proposed as good eco-factories, not only for their capacity as degraders of pollutant compounds, but also as a source of bioenergy and natural pigments, especially in situations of saline stress, that is, for the treatment of polluted sea wastewater. The efficiency and profitability of these must be improved [367].

In terms of circular economy, microorganism and macro-organism workers can offer clean raw materials that can be used in the production chain (food and pharmacological supplements), clean energy (bioethanol, biodiesel or biogas), biofertilizers, etc. More targeted research could provide a focused scope that allows for a better link between renewable raw material sources, composite intermediates, and final products [368,369]. Finally, it is urgent to highlight the need for the integration of chemistry and engineering in order to design truly green and sustainable pharmaceutical or chemical processes [370]. This could allow (1) achieving completely metabolized PPCP in target organisms (animals or men) or (2) obtaining PCPPs there are specific to the target cells (without cross reactions) or (3) producing zero ecotoxic PPCPs. In this manner, we will avoid, from its origin, the presence of toxic organic compounds in ecosystems.

WWTPs should be equipped with advanced technology in order to minimize pharmaceutical release [8]. This requires capital investments and environmentally sustainable entrepreneurship, including the environmental costs as part of the investment assumed benefit to medium and long term. Ethical-environmental values must prevail over economic interest in the short term.

Abbreviation

PPCPs	pharmaceuticals and personal care products
SDG	sustainable development goal
WWTP	Wastewater treatment plants
ROS	reactive oxygen species
UV	ultraviolet
CSCM	Circular supply chain management
DFC	diclofenac
EST	estradiol
CBZ	carbamazepine
IBU	ibuprofen
NPX	naproxen
CDN	codeine
SMX	sulfamethoxazole
CFN	caffeine
GFZ	gemfibrozil
TCS	triclosan
NP	nonylphenol
ATN	artemisine
FLU	flumequine
E2α	17α-ethinylestradiol
MBR	membrane bioreactors
HRT	hydraulic retention time
HRAP	high rate algal pond
CWs	constructed wetlands
WRF	White rot fungi
AChE	Acetylcholinesterase
EROD	Ethoxyresorufin-O-deethylase

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