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Removal of pharmaceutical and personal care products (PPCPs) from wastewater using microalgae: A review

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60 **Abstract**

61 Pharmaceuticals and personal care products (PPCPs) are a group of emerging micro-pollutants
62 causing detrimental effects on living organisms even at low doses. Previous investigations have
63 confirmed the presence of PPCPs in the environment at hazardous levels, mainly due to the
64 inefficiency of conventional wastewater treatment plants (CWWTPs). Their stable structure
65 induces longer persistence in the environment. Microalgae are currently used to bioremediate
66 numerous pollutants of different characteristics and properties released from the domestic,
67 industrial, agricultural, and farm sectors. CO₂ mitigation during culture and the use of biomass as
68 feedstock for biodiesel or biofuel production are, briefly, other benefits of microalgae-mediated
69 treatment over CWWTPs. This review provides a comprehensive summary of recent literature,
70 an overview of approaches and treatment systems, and breakthrough in the field of algal-
71 mediated removal of PPCPs in wastewater treatment processes. The mechanisms involved in
72 phycoremediation, along with their experimental approaches, have been discussed in detail.
73 Factors influencing the removal of PPCPs from aqueous media are comprehensively described
74 and assessed. A comparative study on microalgal strains is analyzed for a more efficient
75 implementation of future processes. The role of microalgae to mitigate the most severe
76 environmental impacts of PPCPs and the generation of antibiotic-resistant bacteria is discussed.
77 Also, a detailed assessment of recent research on potential toxic effects of PPCPs on microalgae
78 was conducted. The current review highlights microalgae as a promising and sustainable
79 approach to efficiently bio-transform or bio-adsorb PPCPs.

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89 *Keywords:* PPCPs; Microalgae; Hybrid system; Wastewater; Ecological risk

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97 **1. Introduction**

98 Over the last few years, numerous studies have reported the presence of new pollutants in
99 different compartments of the environment at trace concentrations ranging from ng/L to µg/L.
100 These pollutants have been termed emerging micro-pollutants (Kummerer, 2009). Emerging
101 micro-pollutants are chemical compounds of no regulatory status. However, in 2000 the
102 European Union (EU) confirmed that 33 priority substances were to be removed from surface
103 water to achieve a satisfactory status of ecology within a period of 20 years. Few common
104 pharmaceutical and personal care products (PPCPs) were added to this list in 2007 (e.g.,
105 diclofenac, ibuprofen, iopamidol, musks, carbamazepine, clofibrac acid, triclosan, and phthalates).
106 While phthalates were declared as carcinogenic, the others were stated as toxic or endocrine
107 disruptors (Ebele et al., 2017). Micro-pollutants comprise natural and anthropogenic substances,
108 including pharmaceuticals, personal care products, pesticides, and industrial chemicals. PPCPs
109 are the largest group of chemical reagents used in varied fields such as livestock, agriculture, and
110 the daily life of human beings. Specifically, pharmaceuticals are used for therapeutic purposes in
111 humans and animals, while personal care products are used in personal hygiene and for
112 beautification. Currently, the growing scientific attention towards PPCPs is due to their (i)
113 ubiquitous presence in every compartment of the environment; (ii) ecological risk (i.e., mainly
114 creating antibiotic resistance in bacteria and endocrine disruptor), and (iii) instrumental analysis,
115 making it possible to detect PPCPs at trace levels. The ubiquitous presence of PPCPs in the
116 environment is due to their excessive use, poor removal in wastewater treatment plants
117 (WWTPs), and their stable structures that maximize their biological activity (Jackson et al.,
118 2007); thus, increasing their resistance to degradation (Daughton and Ternes, 1999). Interestingly,
119 PPCPs have been present in the environment for a long time; however, their concentrations in
120 surface water have recently risen to the level of identification and risk (Jjemba, 2006; Fent et al.,
121 2006). The development of new coupled analytical techniques such as liquid chromatography
122 (LC) and gas chromatography (GC) coupled with mass spectrometry (MS) has made possible the
123 detection of compounds present in extremely low concentration in complex matrixes of aqueous
124 and solid phases (Ternes and Joss, 2006; Diaz-Cruz and Barcelo, 2006), surface water (Drewes
125 et al., 2003), and wastewater (Hernandez et al., 2007). Although PPCPs are continuously
126 introduced into the environment in small amounts, they potentially affect the quality of drinking
127 water, human health, and ecosystems (Sires and Brillas, 2012; Yuan et al., 2009). The potential
128 chronic health effects associated with long exposures of combined low concentrations of each of
129 the many PPCPs and their metabolites and conjugates in drinking water are not well known
130 (Stackelberg et al., 2004; Rivera-Utrilla et al., 2013). Consequently, it is a rising priority of
131 environmental science and engineering sectors to improve, modify, or couple the CWWTPs with
132 advanced techniques to efficiently remove PPCPs (i.e., along with other regulated standard
133 pollutants) from wastewater before they are discharged into nature.
134 Numerous review papers have summarized and discussed the occurrence of PPCPs in different
135 compartments of the environment, such as groundwater (Lapworth et al., 2012) and wastewater
136 (Wang and Wang 2016), as well as the instrumental analysis of PPCPs (Pérez-Lemus et al.,
137 2019), and the treatment methods for their removal (Bolong et al., 2009). Luo et al., (2014)
138 focused on PPCPs removal in conventional and advanced treatment processes, including
139 membrane-based, advanced oxidation, adsorption, and coagulation-flocculation processes.
140 Verlicchi et al., (2012) summarized the comprehensive studies on pharmaceutical removal
141 efficiency by conventional activated sludge in municipal wastewater treatment systems, while

142 Liu et al., (2009) covered biological, chemical, and physical methods of removal of endocrine-
143 disrupting compounds. Leng et al. (2020) broadly discussed the mechanisms of antibiotics
144 removal using microalgae and the combination of other technologies with microalgae.
145 Nevertheless, the contribution of microalgae in PPCPs removal and its comparison with
146 conventional wastewater treatment have not been comprehensively reviewed. Consequently, the
147 recent applications of microalgae in the removal of PPCPs, and the ecological risk of PPCPs on
148 microalgae are summarized and discussed in this current review.
149

150 **2. Mechanisms involved in the removal of PPCPs by microalgae**

151 The mechanisms involved in the removal of PPCPs by microorganisms (bacteria, fungi, or
152 microalgae) are similar and include biosorption, bioaccumulation, biodegradation, photo-
153 degradation, and volatilization (Fig. 1.). The detailed mechanisms of PPCPs removal by
154 microalgae are discussed in this section. The differences in the physicochemical properties of
155 PPCPs (Table 1) are the main cause for microalgae to select a particular or preferably combined
156 mechanism (Table 2) to remove these pollutants from the water as their response for survival.
157 For instance, galaxolide and 4-octylphenol (OP) exclusively showed volatilization due to high
158 Henry law constant values in a High Rate Algal Pond (HRAP) system (Matamoros et al., 2016),
159 while *Chlorella vulgaris* remediates levofloxacin by bioaccumulation as well as biodegradation
160 (Xiong et al., 2017a). Recently, Hena et al. (2020) confirmed that metronidazole was removed by
161 adsorption onto exo-polymeric substances of *Chlorella vulgaris*. Yu et al. (2017) demonstrated
162 that the removal of micropollutants by microalgae could be divided into three steps: 1) rapid
163 adsorption due to physicochemical interactions between the cell wall and the pollutants, followed
164 by a 2) comparatively slow transference of molecules via cell wall, and finally 3) either ending
165 up as bioaccumulation, biodegradation, or both.

166 *2.1. Bioadsorption*

167 Bioadsorption is a passive process in which the soluble molecules or ions of PPCPs are
168 distributed between the liquid phase and the cell wall or the extracellular polymeric substances
169 (EPS) of microalgae. This distribution of PPCPs mainly occurs due to the hydrophobic or ionic
170 interaction between the pollutants and the solid surface of microalgae. The cell wall of the
171 microalgae consists of cellulose, hemicelluloses, alginate, chitin, glycan, lignin, and pectin,
172 which are encapsulated by EPS. EPS are mainly a combination of polysaccharides, lipids,
173 proteins, and nucleic acids, generally protecting the cell from harsh environments. There are two
174 types of EPS: bonded EPS are attached to microalgal cells, while free EPS are excreted by
175 microalgae in suspension, both providing available sites for pollutants to adsorb (Fomina and
176 Gadd 2014). The bioadsorption of PPCPs depends upon its structure, hydrophobicity, the
177 presence of a functional group, and microalgal species as well. The cell wall and the EPS of
178 microalgae mainly carry negative charges due to the presence of carboxyl, hydroxyl, and
179 phosphoryl functional groups, which favor electrostatic interactions with positively charged
180 PPCPs molecules. The ionization or dissociation of PPCPs in water mostly depends upon the pH
181 of the aqueous media. De Godos et al. (2012) observed that 50-71% tetracycline could be
182 removed by *Chlorella vulgaris* in HRAP through an adsorption mechanism within 43 hours
183 under different biomass of inoculation ranging from 44 to 355 mg TSS L⁻¹. The removal of
184 tetracycline increased with increasing inoculum size. According to De Godos et al. (2012), the
185 pH of the culture varied from 7.5 to 8, allowing tetracycline to exist as zwitterions which favored

186 strong adsorption onto the surface of microalgae in HRAP. Carrasquillo et al. (2008) and
187 Vasudevan et al. (2009) stated the same mechanism for the removal of tetracyclines and
188 fluoroquinolones via soil surface. Also, the adsorption of pollutants onto the cell wall and EPS is
189 a rapid process, as proven by many studies. Adsorption phenomena generally take place
190 immediately and passively onto the cell wall of both viable and dead cells and on EPS and cell
191 debris. Wang et al. (2013) reported that *Chlorella pyrenoidosa* was capable of removing 50% of
192 triclosan from aqueous media present in the range of 100 to 800 µg/L within 1 hour of contact.
193 Guo et al. (2016) evaluated the feasibility of three freshwater green microalgae (*Chlorella* sp.,
194 *Chlamydomonas* sp., and *Mychonastes* sp.) to remove 7-amino-cephalosporanic acid (7-ACA)
195 from wastewater within 10 minutes. Among all three microalgae, *Mychonastes* sp. exhibited the
196 lowest adsorption capability (2.95 mg/g) of antibiotic 7-ACA followed by *Chlamydomonas* sp.
197 (3.09 mg/g) and *Chlorella* sp. (4.74 mg/g).

198 In general, the literature has shown that PPCPs are removed by combined mechanisms, where
199 bioadsorption is one of the most common. However, the contribution of bioadsorption depends
200 upon the microalgae and the micropollutant. *Chlorella sorokiniana* can remove 62% of mixed
201 pharmaceuticals (estrone (E1), β-estradiol (E2), ethynylestradiol (EE2), carbamazepine,
202 ibuprofen, diclofenac, metoprolol, paracetamol, and trimethoprim) by combined mechanisms,
203 while 34% were removed by adsorption (De Wilt et al., 2016). Amongst all the pharmaceuticals
204 above mentioned, carbamazepine was adsorbed the most onto microalgal biomass and accounted
205 for the highest percentage (16.7%), followed by diclofenac (9.1%) and trimethoprim (7.6%),
206 whereas the rest showed minimal contribution. Several results indicate that the adsorption of
207 micropollutants is species-specific. Briefly, *Selenastrum capricornutum* showed 46% and 40%
208 adsorption of the maximum removal of E2 and EE2, respectively, while *Chlamydomonas*
209 *reinhardtii* removed 86% and 71% of E2 and EE2, respectively, by adsorption from anaerobic
210 sludge in 7 days (Hom-Diaz et al., 2015). *Scenedesmus dimorphus* adsorbed <10% of the
211 maximum removal (85%) of E2 and EE2 in 8 days (Zhang et al., 2014).

212 The adsorption of micropollutants onto the surface of microorganisms/solid phase mainly
213 depends upon the hydrophobicity of the compounds. Rogers (1996) discussed the lipophilicity or
214 hydrophobicity of a substance in terms of log K_{ow} (i.e., the octanol and water partition coefficient
215 of the compounds). It has been estimated that the higher the log K_{ow} value, the higher the
216 adsorption of compounds onto the solid phase or the surface of microorganisms. Avdeef (1996)
217 reported that ionized species are more water-soluble and, thus, less available to solid-phase than
218 its neutral form. Trimethoprim produces cationic species in aqueous media. However, its
219 adsorption on different microalgae, i.e., *Chlorella sorokiniana* and *Nannochloris* sp., has been
220 reported as either considerably low (De Wilt et al., 2016) or zero (Bai and Acharya., 2016),
221 respectively, due to its low log K_{ow} of 1.4 and ionized species. The solid-water distribution
222 coefficients (K_d) of compounds also play a role in the sorption mechanism along with
223 hydrophobicity. For instance, the moderate octane-water partition coefficient of ibuprofen (3.5-
224 4.5) does not allow it to adsorb on solid surfaces due to its low K_d value (>0.3). Also, Tadkaew
225 et al. (2011) reported that compounds of log K_d > 3.2 could be easily removed from water. Ding
226 et al. (2017) reported adsorption as high as 26% of the initial concentration of ibuprofen onto the
227 surface of a freshwater diatom *Navicula* sp. over four days of inoculum. Kang et al. (2018)
228 measured the adsorption capacity of ibuprofen onto periphyton (mixed microalgae and bacterial
229 consortium) as less than 20% of the initial concentration, while the pH of the periphyton culture
230 was 8. This pH condition was high enough to deprotonate ibuprofen and induces hindrance in the

231 adsorption of negatively charged microalgae. Some lipid-containing microalgae could effectively
232 remove antibiotics by adsorption. The biomass of lipid-containing *Scenedesmus quadricauda*
233 has shown considerably high adsorption capacity (295 mg/g) to remove tetracycline (Daneshvar
234 et al., 2018). Likewise, the biomass of *Chlorella* sp. could remove 82.7% of cefalexin from
235 wastewater before lipid extraction, while 71.2% removal was observed after lipid extraction
236 (Angulo et al., 2018). Hom-Diaz et al. (2017a) demonstrated that the dark and light cycle also
237 regulates the mechanisms. During the dark phase, adsorption was the only phenomenon, while
238 during light conditions, both photodegradation and adsorption played a role. However, as
239 biomass increased, the adsorption was observed as the dominant mechanism due to the shading
240 effect of biomass in which microalgal biomass prevented light from penetrating deeper within
241 the bioreactor. It is clear from the above discussions that solely one factor does not dictate the
242 adsorption mechanism of micropollutants onto microalgae.

243 2.2. Bioaccumulation

244 Unlike bioadsorption, bioaccumulation is an active process that consumes energy and is
245 relatively slower than the adsorption process. Along with nutrients, microalgae can uptake and
246 accumulate pollutants within the cell for growth processes. EPS and the cell wall act as front line
247 barriers. Numerous microalgae can accumulate pollutants against the concentration gradient
248 difference between the cytoplasm and external environment, e.g., *Spirogyra* can accumulate 850
249 times more radio-phosphorus than that of water (Sen *et al.*, 2013). Although the mechanisms of
250 bioadsorption and bioaccumulation of pollutants are completely different, the quantification of
251 bioaccumulation and bioadsorption of pollutants is a difficult task since both processes are
252 continuous. To decrease this uncertainty, many researchers have used general terms such as
253 biosorption and uptake of pollutants, which includes both bioadsorption and bioaccumulation.
254 Several strategies have been analyzed in section 3 to differentiate the contribution of pollutants
255 removal via bioadsorption and bioaccumulation inside the cells of microalgae. Adams and
256 Rowland (2003) described bioaccumulation as the accumulation of pollutants inside the
257 cytoplasm of the cell from an external environment. Bio-concentration has been explained as the
258 accumulation of pollutants into and onto the organism. However, in this review, the term
259 bioaccumulation specifically refers to pollutants exclusively accumulated into the cell, while the
260 terms uptake or biosorption refers to pollutants quantified into the cell and onto the surface of
261 microalgae. Bioadsorption is the first step of bioaccumulation. Hence, to bio-accumulate inside
262 the cell, the molecules must first fulfill the necessary key criteria for bioadsorption. However,
263 not all pollutants adsorbed onto the surface of microalgae can enter into the cell to bio-
264 accumulate (Wu et al., 2012). Polysaccharides are the most common compounds stored inside
265 the microalgal cell during photosynthesis. Once the concentration of these stored compounds
266 decreases to a certain level, the adsorbed compounds onto the cell or bonded EPS enter into the
267 cytoplasm or intracellular fractions through ion channels, carriers present in cell membranes, or
268 simply via cell membrane diffusion (Yu et al., 2017). Bai and Acharya (2017) demonstrated
269 green microalgae *Nannochloris* sp. low uptake of trimethoprim (11%), sulfamethoxazole (11%),
270 and carbamazepine (13%) under dark conditions over 14 days, while 27% of triclosan was
271 uptaken in 7 days. The above results were considerably close to those shown for these
272 compounds following bioadsorption mechanism; thus, reflecting the dependence of biosorption
273 or uptake on bioadsorption. In general, all microalgae store their food as lipid inside the cell,
274 which facilitates the bioaccumulation of lipophilic compounds and assists in the trophic transfer.
275 A freshwater green microalga *Cladophora* sp. could accumulate triclosan (TCS), triclocarban,
276 and methyl-triclosan as high as 50–400 ng/g fresh biomass of microalgae, while the

277 environmental concentration was in a range of 50-200ng/L (Coogan et al., 2007). In microalgae,
278 some bio-accumulated pharmaceuticals at a low concentration assist in the production of reactive
279 oxygen species inside the cell, which essentially control the cellular metabolism (Xiong et al.,
280 2018a).

281 2.3. Biodegradation

282 Biodegradation is a metabolic degradation or breakdown of compounds catalyzed by enzymes.
283 Generally, microalgae turn complex parent compounds into simpler compounds. This process
284 might involve several enzymatic reactions (e.g., hydrogenation, dehydrogenation, hydroxylation,
285 dehydroxylation, carboxylation, decarboxylation, oxidation, reduction, hydrolysis, ring cleavage,
286 demethylation, and glycosylation). Microalgae biodegrade xenobiotic compounds via series of
287 enzymes through three phases (Peng et al., 2014; Maes et al., 2014; Xiong et al., 2016;
288 Matamoros et al., 2016; Ding et al., 2017; Xiong et al., 2017a). In the first phase, the
289 detoxification of xenobiotic compounds by the enzyme Cytochrome P450 involves oxidation,
290 reduction, or hydrolysis processes. During this phase, the lipophilic compounds are turned into
291 hydrophilic compounds via the incorporation of hydroxyl groups. In the second phase, the
292 compounds with electrophilic groups (CONH₂, epoxide ring, COOH) form a conjugate bond
293 with glutathione in the presence of enzyme glutathione-S-transferases or glucosyltransferases
294 (Nakajima et al., 2007) to protect the cell from oxidative damage. The third phase involves
295 several enzymes (e.g., carboxylase, glutamyl-tRNA reductase, dehydrogenase, transferase,
296 laccases, hydrolases, pyro-phosphatase, decarboxylase, mono(di)oxygenase, and dehydratase) to
297 bio-transform the xenobiotic compounds into simpler and detoxified forms (Petroustos et al.,
298 2008; Otto and Schlosser, 2014). Ding et al. (2017) confirmed the glycosylation reaction with
299 ibuprofen along with eight bio-transformed products in freshwater diatom *Navicula* sp. Green
300 microalgae *S. obliquus* and *C. pyrenoidosa*, showing 95% biodegradation or biotransformation of
301 progesterone and norgestrel present in an aqueous medium via hydroxylation, reduction, and
302 oxidation pathways (Peng et al., 2014). Biodegradation is one of the most effective mechanisms
303 by which microalgae remove micropollutants from aqueous phase as well from biomass
304 (intracellular or intercellular). Compounds biodegrading at an intracellular or intercellular phase
305 bioaccumulate and adsorb onto the biomass, respectively. Naghdi et al., 2018 observed that some
306 toxic antibiotics are broken down into less or non-toxic intermediates by extracellular enzymes
307 produced by microalgae, which are further bioaccumulated and biodegraded by intracellular
308 enzymes. The complexity of the structures also regulates the biodegradability of compounds. A
309 compound with linear, unsaturated, and electron-donating groups was found to biodegrade more
310 readily than compounds possessing cyclic structure, saturated long linear carbon chain, and
311 electron-withdrawing groups in their structure. However, some pharmaceutical compounds do
312 not follow these trends. Two structurally similar non-steroidal anti-inflammatory drugs
313 (NSAIDs), i.e., ketoprofen and ibuprofen, performed differently during removal from wastewater.
314 Ibuprofen was removed more efficiently than ketoprofen by CWWTPs as well as microalgae-
315 mediated treatment (Hom-Diaz et al., 2017b). Other structurally similar NSAIDs, i.e.,
316 paracetamol and ibuprofen, showed similar removals (100%) while treated with *Chlorella*
317 *sorokiniana* (De Wilt et al., 2016). EPS are hygroscopic in nature and form a matrix around the
318 cell that assists compounds to adsorb and accumulate and eventually biodegrade due to the
319 presence of extracellular enzymes.

320 2.4. Photo-biodegradation

321 Many PPCPs have been observed to degrade under sunlight irradiation, which refers to as photo-
322 degradation or photolysis (Matamoros et al., 2008; Hanamoto et al., 2014). This process is
323 effective, environmentally friendly, economical, and easy to optimize. There are two types of
324 photolysis involved in the degradation of PPCPs in wastewater: direct and indirect photolysis.
325 During direct photolysis, the targeted pollutant molecules with conjugated π bond, aromatic rings,
326 and other functional groups can directly absorb UV-range sunlight irradiation and eventually
327 break down without any involvement of microalgae (Challis et al., 2014).

328 During indirect photolysis, the free radicals singlet oxygen (1O_2), peroxy radical ($ROO\bullet$), and
329 hydroxyl radical ($\bullet OH$) generated during sunlight exposure take part in the photolysis. The
330 compounds taking part in the generation of free radicals in the presence of UV are known as
331 photosensitizers. Rontani et al. (1997) reported the same mechanism of indirect photolysis or
332 photo-biodegradation for sterols removal by *Skeletonema costatum*. Zepp et al. (1987) and Liu et
333 al. (2004) demonstrated the rate of decomposition of organic pollutants and photo-production of
334 singlet oxygen (1O_2) and $\bullet OH$ by microalgae. In microalgae cells, a small portion of singlet
335 chlorophyll (1Chl) undergoes intersystem crossing to form triplet chlorophyll (3Chl), which
336 forms reactive oxygen species (1O_2 , $O_2^{\bullet -}$, $\bullet OH$, $\bullet OOH$) by reaction with ground-state oxygen (3O_2)
337 as depicted in Fig. 2. During irradiation, algal cells gradually get destroyed and released
338 carboxylic acid, which is associated with the cell wall and membranes of microalgae. The
339 released carboxylic acid forms another reactive oxygen species: peroxy radical ($ROO\bullet$). In
340 microalgae culture, these reactive oxygen species take part in the photolysis of recalcitrant
341 compounds in the culture medium. Singlet oxygen is detected by furfuryl alcohol produced in the
342 algal suspension. Furfuryl alcohol traps singlet oxygen in water (Haag et al., 1984). The
343 photolysis of PPCPs is an essential mechanism due to the ubiquitous presence of sunlight and
344 microorganisms. Bai and Acharya (2017) reported a 100% removal of ciprofloxacin and
345 triclosan in *Nannochloris* sp. mediated culture over 7 days of incubation under 24 h of irradiation
346 via photolysis mechanism. The higher the concentration of microalgae, the higher the generation
347 of free radicals; thus, enhances photolysis degradation (Liu et al., 2004). Zhang et al. (2012)
348 found that the photo biodegradation of norfloxacin increased with the concentration of
349 microalgae. The seepage of chlorophyll from dead cells of microalgae acted as a photosensitizer
350 and enhanced the photodegradation of benzo[a]pyrene (Luo et al., 2015). Huang et al. (2016)
351 observed a better photodegradation of triclosan in the presence of EPS from *Microcystis*
352 *aeruginosa*.

353 2.5. Volatilization

354 There are minor differences between volatilization and stripping. Stripping is the removal of
355 gaseous compounds from (WWTPs), while volatilization is the removal of volatile compounds.
356 Stripping or volatilization is more prominent in the aerobic chamber or the bioreactor tank and
357 depends upon the airflow in contact, the vapor pressure of the liquid, Henry coefficient (H), and
358 hydrophobicity (K_{ow}). Based on Henry's law, compounds having an H value below 0.005
359 showed negligible stripping. Suarez et al. (2010) reported that the stripping of PPCPs is
360 negligible in WWTPs except for celestolide, which showed up to 16% removal. Volatilization is
361 a compound-specific mechanism; however, it is more prominent in open pond systems than
362 closed photobioreactors.

363 3. Quantification strategies for mechanisms involved

364 Internal and external factors control the fate of PPCPs in microalgae-mediated wastewater
365 treatment plants. The internal factors include the physicochemical properties of the PPCPs and
366 the microalgae involved, while external factors are temperature, seasonality, hydraulic retention
367 time (HRT), light intensity, and feeding operational mode.

368 Rather than by one solely mechanism, compounds are removed by a combination of mechanisms.
369 These mechanisms are commonly associated with each other. Consequently, drawing a fine line
370 between two mechanisms to differentiate their contributions in the removal of pollutants is a
371 difficult task. Nevertheless, numerous researchers have followed careful strategies to quantify
372 the contribution of different mechanisms. Additionally, different terminologies are frequently
373 used, especially when describing abiotic removal. Specifically, abiotic removal discusses the
374 experimental setup or strategies to confirm the mechanism involved during the removal of
375 pollutants and includes all pathways (i.e., direct photolysis, hydrolysis, and volatilization),
376 except those involved in biological-related processes (Andreozzi et al., 2003). However,
377 different researchers used the term “abiotic” while not considering all possible abiotic
378 mechanisms. Peng et al. (2014) used the term abiotic removal when comparing the adsorption
379 capacity between dead and live cells during the adsorption of progesterone and norgestrel by
380 dead biomass of *C. pyrenoidosa* and *S. obliquus*. Xiong et al. (2016) defined the abiotic removal
381 as hydrolysis and interrupted direct photolysis by exposing a flask to white fluorescent light
382 (light/dark periods of 16 h/8 h) during removal of carbamazepine. Rather than using the term
383 abiotic, Guo et al. (2016) used a more standard approach and referred to hydrolysis and direct
384 photolysis separately. Zhang et al. (2012) stated hydrolysis as a reaction under dark conditions.
385 Du et al. (2015) used self-degradation as terminology for direct photolysis.

386 3.1. Quantification of adsorption mechanism

387 (i) Adsorption mechanism on live cells of microalgae: A fixed volume of microalgal
388 suspension is withdrawn from the microalgae-mediated treatment flask. The cells are then
389 separated from culture media using centrifugation (i.e., harvesting process). The cell pellets are
390 re-suspended in ultrapure water and re-centrifuged to desorb the compounds that have been
391 adsorbed onto the cell wall of microalgae. The supernatant is collected for further adsorbate
392 analysis. The rpm values during the first and second centrifugation steps should not be high
393 enough to desorb the adsorbate from the cell wall and disrupt the cell, respectively. The integrity
394 status of the microalgal cell wall can be determined by treating the cells with 100 μ L of 1 %
395 Evans Blue solution followed by incubation for 10 min at room temperature and washed with
396 deionized water to remove excess stain. The microalgal cells are then inspected under a light
397 microscope, where cells with broken cell walls would appear blue as Evans Blue solution
398 diffuses into the protoplasm region and stains the cells (Hena et al., 2015a). The adsorption
399 reading of adsorbate from stained microalgae cells is discarded since it includes the value of
400 absorption as well. Different systems (i.e., types of adsorbate, adsorbent, and media) require
401 different rpm values to conduct this procedure. For instance, Xiong et al. (2016) used 4500 rpm
402 for 10 min for detecting the adsorbed carbamazepine onto *Chlamydomonas mexicana* and
403 *Scenedesmus obliquus*, while Xiong et al. (2017a) used 15,000 rpm to desorb levofloxacin
404 from *Chlorella vulgaris*. Bai and Acharaya (2016) used as low as 3000 rpm to centrifuged
405 *Nannochloris* sp. During the re-suspension of cell pellets, ultrapure water is not the only option
406 to desorb the adsorbate. Peng et al. (2014) used 10% methanol-water to desorb progesterone and
407 norgestrel. The selection of solvent depends upon the polarity of the adsorbate.

408

409 (ii) Adsorption mechanism on dead biomass of microalgae: The untreated biomass of
410 microalgae is harvested by centrifugation and washed with ultrapure water to remove salts in
411 excess, followed by freeze-drying, and finally ground to obtain a uniform particle size to be used
412 as an adsorbent for PPCPs from aqueous media. Then, the adsorption capability q_e (mg/g) of
413 particular microalgae towards certain PPCPs is calculated as Equation 1; where C_i and C_f are the
414 initial and equilibrium concentrations (mg/L) of solute present in solution, respectively, m is the
415 dry weight (g) of algal biomass (adsorbent), and V is the working volume of the solution (L)

$$q_e = V(C_i - C_f)/m \quad \text{Eq. 1}$$

416
417
418
419 Guo et al. (2016) used this protocol to analyze the adsorption removal of antibiotic 7-amino
420 cephalosporanic acid onto *Chlorella* sp., *Chlamydomonas* sp., and *Mychonastes* sp. The
421 comparison of these two approaches (i.e., adsorption of PCPPs on live/dead cells) has been
422 previously discussed by Yu et al. (2017). The membranes of live cells control the permeability of
423 external compounds, which is lost due to damage in the structures of cell membranes when cells
424 are dead (Tsezos and Bell, 1989). Consequently, the accessibility of external compounds to extra
425 membrane-bound organelles and intracellular compounds increases in dead cells; hence,
426 increasing the adsorption. However, if biodegradation is the dominant pathway of removal, then
427 the total removal of pollutants would be higher in live cells than dead cells.

428 3.2. Quantification of absorption or bio-accumulation mechanism

429 (i) In the thawing process, the cell pellet after second centrifugation (section 3.1 (i)) is used
430 for absorption or bioaccumulation analysis. It is necessary to break the cell walls of microalgae
431 to release the accumulated or absorbed micropollutants. Correa-Reyes et al. (2007) proposed to
432 freeze the algal cell pellet at -20°C , causing the cell wall to break due to the expansion of the
433 aqueous portion of the cytoplasm into ice. Peng et al. (2014) used this method to successfully
434 disrupt the cell of *C. pyrenoidosa* and *S. obliquus* and release bio-accumulated progesterone and
435 norgestrel.

436
437 (ii) Sonication is a mechanical method widely used to disrupt the microalgal cell. The
438 sonicator generates intense sonic pressure waves, which create microbubbles in the liquid that
439 amalgamates and vibrates. The conversion of mechanical energy (i.e., due to the oscillation of
440 the probe) to heat energy causes implosion, resulting in high-speed bursts of liquid that collide to
441 the surface of the cell wall and generate high energy shock waves that are sufficient to disrupt
442 the cell (Middelberg 1995). For sonication, the cell pellet is immersed into a mixture of
443 dichloromethane:methanol (1:2, v/v) and sonicated for 1 h. The supernatant is used to determine
444 the concentration of the compound inside the microalgae. Ding et al. (2017) preferred the
445 sonication method to released bio-accumulated non-steroidal anti-inflammatory drug naproxen
446 from microalgae *Cymbella* sp. and *Scenedesmus quadricauda*.

447
448 (iii) High-pressure homogenization (HPH) is a promising technique to disrupt microalgal cells
449 effectively in an aqueous environment. In HPH, the cells are forced to pass through a narrow
450 orifice, which causes disruption in the cell wall of the microalgae due to the turbulence,
451 cavitation, and shear stress. High pressure is the main parameter of HPH, which can be
452 optimized as a function of the structure or the toughness of the cell wall of microalgae, e.g.,
453 *Nannochloropsis* sp. requires higher pressure (28k-30kpsi) than *Chlorella* sp. (15k-17kpsi).

454 Multiple circulations or passes of the cells through orifice increases the degree of cell disruption.
455 Bernaerts et al., (2019) observed that higher pressure (e.g. 36kpsi) reduced the number of passes
456 required to obtain the same level of cell disruption compared to lower pressure (e.g. 14.5kpsi) for
457 *Nannochloropsis* sp. suspension.

458
459 (iv) Enzymatic hydrolyzation is a biochemical process to disrupt the microalgal cell wall,
460 which requires much less energy compared to other mechanical techniques (e.g., sonication and
461 HPH). The main constituents of the cell wall of microalgae are cellulose incorporated with
462 glycoprotein. Cellulases and protease are the most common enzymes combination used to disrupt
463 the cell wall effectively.

464
465 Wang et al. (2015) found with the almost equal amount of energy consumption, HPH can obtain
466 nearly double the cell disruption efficiency than sonication. Enzymatic hydrolysis and thawing
467 processes are relatively time-consuming process in comparison to sonication and HPH.

468 3.3. *Quantification of abiotic mechanism*

469 The direct photolysis of the PPCPs is calculated by adding a known amount of PPCP in ultrapure
470 water. Degrading under radiation is allowed for a certain time in the absence of microalgae or
471 any other microorganisms. Ultrapure water is used as a medium to avoid any other means of
472 degradation or removal of PPCP. Similarly, hydrolysis is assessed by adding a known amount of
473 PPCP in ultrapure water, where degrading is allowed under dark conditions and in the absence of
474 algal cells for a specific period. A sterile medium is used to confirm the contribution of the
475 hydrolysis pathway in wastewater. The volatilization is estimated by comparing the PPCP
476 present in aerated and non-aerated reactors. The evaporation of water during volatilization is
477 balanced by adding ultrapure water. However, due to the presence of microorganisms in real
478 wastewater, direct measurements of hydrolysis and direct photolysis are not possible. The
479 quantifications of hydrolysis and direct photolysis are conducted by indirect measurement, as
480 described at the beginning of the current section.

481 3.4. *Quantification of indirect photolysis and biodegradation mechanism*

482 The indirect photolysis by microalgae is estimated by comparing the concentration of PPCPs
483 present in the reactors fed with microalgae in wastewater under light and dark conditions. The
484 biodegradation (R_b) of PPCPs by microalgae is calculated according to the following equation
485 (Xiong et al., 2017a):

$$486 \quad R_b (\%) = (A_t - A_r - R_{ad} - R_{ab} - R_a - R_{inp}) \times 100/A_t$$

488
489 Where A_t is the initial amount of PPCP added to the medium, A_r is the residual amount in the
490 medium, R_{ad} is the amount of PPCP adsorbed on the microalgal cell surface, R_a is the amount
491 removed by abiotic processes, R_{inp} is the amount of PPCP removed by indirect photolysis, and
492 R_{ab} is the amount of PPCP accumulated in the algal cells.

493 The biodegradation of PPCPs is considered as the predominant or sole mechanism if it ceases at
494 the addition of nutrients due to the preference of microalgae to consume nutrients over micro-
495 contaminants when both are present in the medium (Matamoros et al., 2016).

496 4. Factors affecting the removal of PPCPs

497 The performance of a wastewater treatment system in terms of removal of PPCPs is considerably
498 dependent on abiotic and biotic factors. Hydraulic retention time, light intensity, temperature,
499 and seasonality are considered as abiotic factors, while phylogenetic diversity of microorganisms
500 is known as biotic factor that affects the removal of PPCPs from the wastewater treatment
501 system. It is anticipated that the optimum conditions of abiotic factors favor a higher specific
502 growth rate of microalgae, which induces the system to quickly and more efficiently uptake the
503 nutrients N & P and PPCPs (i.e., as a source of carbon).

504 4.1. *Temperature and seasonality*

505

506 Temperature and season are interrelated factors, where open and upscale plants come in direct
507 influence, while the temperature of a closed and small treatment system can be controlled.
508 Temperature regulates the metabolic process and enzymatic activity in microalgae. Any
509 fluctuation in temperature can affect the biodegradability of PPCPs, which is directly related to
510 the enzymatic actions. The optimal temperature for microalgae is reported in the range of 25-
511 30°C (Bamba et al., 2015; Chinnasamy et al., 2009). Higher than optimum temperature causes a
512 decrease in chlorophyll-*a* content in microalgae cells, which decreases the photosynthesis
513 process and consequently affects the growth. Thus, a high temperature is not suitable for those
514 PPCPs which undergo biodegradation and sorption; however, high temperature promotes indirect
515 photolysis up to some extent. Microalgae cells get injured at high temperatures (e.g. >30°C) and
516 consequently release low molecular organic acids into the culture media, which favor indirect
517 photolysis degradation of PPCPs. Similarly, Zhang et al. (2012) reported higher photolysis
518 degradation of norfloxacin at 35°C than at 25°C. Among many recalcitrant compounds,
519 carbamazepine is one of the most troublesome pharmaceuticals showing extremely low removal
520 at CWWTPs (Luo et al., 2014) as well as from algal photo-bioreactor (Xiong et al., 2016) during
521 winter. However, Matamoros et al. (2015) observed a 30% increase in the biodegradation of
522 carbamazepine in the presence of microalgae at warmer weather than cold conditions. Warmer
523 temperature (Mediterranean climate of average temperature 26°C) favors the removal of
524 biodegradable, hydrophobic, and photodegradable compounds that are associated with more
525 prolonged average solar radiation (Matamoros et al., 2015). Also, *Scenedesmus* sp. showed better
526 removal of NH₄-N at a warmer climate (Ruiz-Martínez et al., 2015). Microalgae produce excess
527 EPS in cold climates to withstand harsh weather, which could be beneficial for indirect
528 photodegradation. However, short and low irradiation does not favor photodegradation (Wang et
529 al., 2009). Gao et al. (2011) demonstrated that four species of *Chlorella*, i.e., *Chlorella vulgaris*,
530 *Chlorella* sp. (1uoai), *Chlorella* sp. (2f5aia), and *Chlorella miniata* biodegraded nonylphenol
531 more efficiently at elevated temperature (30°C) and high light intensity; thus, proving high
532 photosynthetic and metabolic activities at high temperature and intense light.

533 4.2. *Hydraulic retention time (HRT)*

534

535 The HRT is a key parameter that should be optimized for better performance of photobioreactors
536 in terms of removal efficiency of PPCPs from wastewater. In general, the HRT used for
537 wastewater treatment in photobioreactors and HRAP varies from 2-10 days (Matamoros et al.,
538 2015; Chu et al., 2015; Rasoul-Amini et al., 2014). Longer HRT increases the removal of PPCPs
539 during treatment by providing enough time for biodegradation, sorption, and indirect
540 photodegradation. On the other hand, longer HRT causes an increase in the biomass of

541 microalgae due to cell division, increasing the chance of micropollutants to be biodegraded and
542 sorbed by more cells. Matamoros et al. (2015) suggested that during warm or summer seasons,
543 longer HRT does not play a significant role. However, a remarkable difference in PPCPs
544 removal was observed during a cold season when the temperature was considered as limiting
545 condition. Four days of HRT is considered enough for removing a long list of PPCPs in HRAP.
546 This HRT is comparatively longer than that of CWWTPs, generally operating from 12-24h.

547 4.3. Light intensity

548

549 Light is a vital environmental factor for the survival of photoautotrophic and photoheterotrophic
550 microalgae. The microalgae culture system for metabolite production or wastewater treatment is
551 commonly designed to maximize the use of light by providing high surface/volume ratios. Light
552 intensity affects the growth of microalgae and, consequently, nutrients and pollutants removal
553 from wastewater. It has been demonstrated that increasing light intensity enhances the
554 production of biomass (Luo et al., 2017; Hena et al., 2018). The exposure to significantly high
555 illumination damages the photosystem II of chloroplast in microalgae; consequently, decreasing
556 the metabolic activities of microalgae and the efficiency of PPCPs removal. The damaged
557 photosystem II in chloroplast eventually gets repaired; nevertheless, cells take a longer time to
558 reach its exponential phase and hence decrease the efficiency of nutrients uptake as well as
559 micropollutants removal. It has also been reported that the maximum nutrients and organic
560 compounds removal occur during the exponential phase of cells. In the case of PPCPs removal,
561 high biomass of microalgae favors biodegradation and sorption; however, the photolysis
562 mechanism has a slightly different trend. Zhang et al. (2012) demonstrated the relation between
563 the biomass of *Chlorella vulgaris* and the photolysis of norfloxacin. They observed that
564 photodegradation increased from 35.9% to 40.9%, with increasing cell counts from $1.7 \times 10^6/L$ to
565 $1.7 \times 10^7/L$ within 60 mins. Clearly, more cells produce more hydroxyl radicals as
566 photosensitizers from dissolved organic matter excreted by microalgae under illumination.
567 However, a further increase in cell counts caused self-shading effects of algal cells, preventing
568 light from penetrating and hence decreased photodegradation. Conversely, microalgae have only
569 shown a 5% norfloxacin removal under dark conditions, possibly due to hydrolysis and
570 adsorption. However, direct photolysis in the presence of light and the absence of microalgae
571 attained a maximum removal of 9.1%. Hena et al. (2018) increased the intensity of light from
572 160 to 300 $\mu\text{mol photon/m}^2/\text{s}$ during the late exponential phase of *Arthrospira platensis* for
573 treating dairy farm wastewater to avoid the shading effect of cells. Garcia-Rodríguez et al. (2013)
574 studied the role of microalga *Spyrogira* sp. and aquatic plant *Zannichellia palustris* in photolysis
575 degradation and the contribution of light during the total removal of six antibiotics from
576 sulfonamides and tetracyclines families. The difference in antibiotic removal between covered
577 and uncovered conditions of wastewater showed a minimal decrease in the concentration of all
578 antibiotics studied, except for oxytetracycline. Oxytetracycline significantly degraded even in the
579 dark, possibly due to hydrolysis. The rest of the tested antibiotics showed better removal in the
580 presence of light and even higher removal in the presence of light and microalga. Out of the 20
581 days of the inoculation of microalgae and aquatic plants, the degradation rate remained higher
582 than under controlled conditions until the first 5 days (i.e., absence of microalga and aquatic
583 plants), followed by either decrease in degradation rate or remains constant in the presence of
584 vegetation. During the initial days of inoculation, both direct and indirect photolysis occurred.
585 However, with time, an increase in biomass caused hindrances in photodegradation, and

586 consequently, the rate of photolysis decreased in the presence of vegetation. Escapa et al. (2017)
587 observed a sharp decrease in the photodegradation of paracetamol and salicylic acid during the
588 exponential phase of *C. sorokiniana* due to an increase in biomass; subsequently, reducing the
589 irradiance availability in the culture. However, the semi-continuous culture increased the
590 photodegradation because of dilution in biomass concentration. Gomez et al. (2013) observed the
591 same trend of photolysis of pollutants in secondary treated wastewater by *Muriellopsis* sp.
592 Occasionally, the presence of microalgae causes a decrease in photodegradation because of the
593 adsorption of the targeted compounds; thus, reducing the availability of compounds for photo-
594 oxidation.

595

596 4.4. Phylogenetic diversity of microorganisms

597

598 Successful cultures of microalgae in varieties of wastewaters, including industrial, domestic, and
599 farming, all containing a considerable load of PPCPs, is clear evidence of algal tolerance towards
600 a range of pharmaceuticals. However, all microalgae cannot remove every kind of PPCPs from
601 wastewater. The selection of microalgal strain is an important step of wastewater treatment,
602 depending upon the type of PPCPs present. The removal of some PPCPs by microalgae is
603 compound-specific, while others are species-specific. Most of the antibiotics are compound-
604 specific; thus, showing a constant removal regardless of any microalgae used for
605 phycoremediation. For instance, 7-amino cephalosporanic acid can be completely removed by
606 different microalgae, such as *Chlorella* sp., *Chlamydomonas* sp., and *Mychonastes* sp.
607 Interestingly, the same mechanisms (i.e., hydrolysis, photolysis, and adsorption) were involved
608 in removing 7-amino cephalosporanic acid by different microalgae (Guo et al., 2016). Similarly,
609 diclofenac (i.e., NSAID), behaves as compound-specific with different species of *Chlorella* sp.
610 The two different species of *Chlorella* (i.e., *C. sorokiniana* and *C. vulgaris*) have shown an
611 almost equal removal of diclofenac (i.e., 29% and 21%, respectively) in 9 days (Escapa et al.,
612 2016).

613

614 Species-specific compounds show different removal efficiencies with different microalgae. For
615 example, green microalgae *Nannochloris* sp. can completely remove triclosan (Bai and Acharya
616 2016), while cyanobacteria *Microcystis aeruginosa* can remove only 46% (Huang et al., 2016)
617 from aqueous media within 7-8 days. Diclofenac also acts as species-specific for *Chlorella* sp.
618 and *Scenedesmus obliquus*, which removed 21-29% and 79%, respectively, in the same time
619 span (Escapa et al., 2016). Natural and synthetic hormones also behave differently during their
620 removal by microalgae. Progesterone is a natural hormone, while norgestrel is a synthetic
621 hormone. They have a similar structure and almost the same molecular weight; however, they are
622 biodegraded at different rates. Progesterone biodegrades faster than norgestrel by microalgal
623 strains *Scenedesmus obliquus* and *Chlorella pyrenoidosa*. Additionally, *Scenedesmus obliquus*
624 can biodegrade both hormones up to 95%, while *Chlorella pyrenoidosa* can biodegrade only
625 progesterone up to 95%. Nevertheless, norgestrel can only be removed up to 60% (Peng et al.,
626 2014). Briefly, progesterone is an example of compound-specific, while norgestrel is an example
627 of species-specific for *Scenedesmus obliquus* and *Chlorella pyrenoidosa*. A few interesting
628 comparative studies of PPCPs removal via microalgae have been listed in Table 3.

629 It is obvious from the above discussion that it is practically impossible to efficiently remove
630 different varieties of PPCPs from real wastewater using an axenic (mono) culture system of
631 microalgae. The phylogenetically diversified culture of microalgae also known as consortium

632 cultures or co-cultivation is defined as a mixed culture of two or more types of strains of
633 microalgae, or microalgae associated with other microorganisms in cultures such as bacteria or
634 fungi are more popular for the treatment of wastewater containing a range of PPCPs (Matamoros
635 et al., 2016; Liu et al., 2017; Munoz and Guieysse, 2006). Similar to microalgae, bacteria can
636 also bio-adsorb PPCPs on the surface of the cells, which is commonly made up of peptidoglycan,
637 teichoic acids, and lipoteichoic acids (Flemming and Wingender 2010). These chemicals offer
638 spots for the bioadsorption of PPCPs (Fomina and Gadd 2014). Simultaneously, bacterial EPS
639 also helps in adsorption of PPCPs with the same mechanism as microalgae do. During
640 wastewater treatment, bacteria perform metabolic as well as co-metabolic degradation (Table 4).
641 In co-metabolic degradation, the degradation of PPCPs depends on the presence of non-specific
642 enzymes catalyzing the metabolism of other substrates (Tiwari et al., 2017).

643 A comparison between a microalgal consortium and microalgae-bacterial consortium is
644 summarized in Table 5. A mixed culture of *Chlorella* sp. and *Scenedesmus* sp. was used for
645 removing a range of NSAIDs from water (Matamoros et al., 2016). The reason for the increased
646 nutrients and PPCPs removal efficiency of the co-cultures of microalgae is still not well
647 understood; nevertheless, it could be due to the competitive/inhibitive and cooperative
648 interactions between different strains of microalgae, as shown in Fig. 3. Mendes and Vermelho
649 (2013) postulated the concept of metabolites exchange between microorganisms for cooperative
650 interaction, enhancing the biomass and, consequently, the nutrients and micropollutants removal
651 efficiency. Xiong et al. (2017b) demonstrated the removal efficiency of monocultures of
652 *Chlorella vulgaris*, *Micractinium resseri*, *Scenedesmus obliquus*, *Ourococcus multisporus*, and
653 *Chlamydomonas mexicana* and their consortium for antibiotic enrofloxacin in aqueous media.
654 The removal efficiency of the consortium was comparable to the most efficient strains, although
655 the consortium showed the highest growth inhibition in the presence of enrofloxacin than an
656 individual culture of microalgae. The co-cultivation of microorganisms or microalgae produces
657 secondary metabolites known as allelochemicals, which might inhibit the growth of other
658 microorganisms (Cembella 2003; Gross 2003). According to Xiong et al. (2017b), the growth
659 inhibition would be due to allelochemicals excreted by microalgae or degraded products of
660 enrofloxacin performing as allelochemicals. *Raphidocelis subcapitata* showed inhibition in co-
661 cultivation with *C. vulgaris* caused by the production of allelochemicals chlorellin (fatty acid) by
662 the latter. The production of allelochemicals is controlled by abiotic and biotic factors. Ishika et
663 al. (2017) used a co-cultivation technique to culture marine, halotolerant, and halophilic
664 microalgae to increase biodiesel production and nutrients removal from wastewater. Although
665 the reason was not clear, it was referred to as an example of cooperative interactions between
666 different strains of microalgae.

667 In microalgae-bacteria consortium, both cooperative and inhibitive aspects are observed.
668 Metabolites produced by microalgae could be allelochemicals or growth inhibitors for bacteria.
669 Chlorellin performed as bactericidal for several bacteria, such as *Pseudomonas aeruginosa*,
670 *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli*. This is the reason why
671 microalgae-mediated treated wastewaters have been reported as free from the presence of active
672 *E. coli* or fecal coliform bacteria (Ansa et al., 2011). Besides, high pH and elevated temperature
673 of culture (i.e., caused by photosynthetic processes of microalgae) act as bactericides. On the
674 other hand, the counterpart bacteria also excrete metabolites, which would be algacides and
675 control the microalgal bloom naturally (Fuentes et al., 2016). Despite the competition between
676 microorganisms, the symbiotic relationships in many microalgae and bacteria have been
677 observed to biodegrade pollutants cooperatively. Bacteria capture the organic compounds and O₂

678 released by microalgae as electron acceptors, reducing photosynthetic oxygen stress among
679 photoautotroph microalgae (Park et al., 2008). However, in return, vitamin B₁₂ produced by
680 bacteria promotes the growth in microalgae (Kazamia et al., 2012). Besides, in iron-deficient
681 environments, microalgae uptake siderophores produced by some bacteria as iron substitutes for
682 growth (Amin et al., 2009). *Bacillus licheniformis* was found to enhance the content of
683 chlorophyll-a in *Chlorella vulgaris*, as well as the removal efficiency of nitrogen and phosphorus
684 from wastewater (Liang et al., 2013). Similarly, few freshwater microalgae and diatoms showed
685 better pollutant removal efficiency when cultured with bacteria *Neochloris oleoabundans*, and
686 have accumulated more cellular metabolites (lipid) than when cultured alone (Olguin et al.,
687 2013). *Chlorella* sp. with bacterial consortium was used to remove ketoprofen (Ismail et al.,
688 2016).

689
690 Another consortium microorganism used for PPCPs removal along with microalgae is fungi.
691 Bodin et al. (2016) cultivated microalgae *Chlorella vulgaris* with fungus *Aspergillus niger* to
692 remove ranitidine from water.

693 **5. Acclimatization of microalgae**

694 The improved response of microalgae in an extreme environment is crucial for wastewater
695 treatment, especially when the influent carries PPCPs. A slow exposure of PPCPs to microalgae
696 generally enhances their limit of tolerance and improves the removal capacity of PPCPs in
697 (WWTPs). Tolerant strains of microalgae are known as acclimated strains, while the process is
698 known as acclimatization. Extensive researches have been conducted on the acclimatization of
699 microalgal metabolisms to remove nutrients from wastewater. Several microalgae can adopt
700 different pathways of metabolisms while responding to the changes in the environmental
701 conditions for their survival and growth via exhibiting metabolic shift. Cultivating facultative
702 strains of microalgae in heterotrophic mode is a standard practice to eliminate nutrients from
703 wastewater while simultaneously favors high lipid accumulation, specific growth rate, and
704 minimize the light requirement (Perez-Garcia et al., 2011). However, a direct change from
705 photoautotrophic mode to heterotrophic mode may be fatal for some facultative strains of
706 microalgae. Azma et al. (2010) confirmed a long lag phase for *Tetraselmis suecica* when it was
707 transferred to heterotrophic mode after a photoautotrophic mode of cultivation for cell
708 enrichment. This strain was finally acclimated through a gradual photoperiod adaptation. Hena et
709 al. (2015b) introduced a photoheterotrophic mode of cultivation between photoautotrophic and
710 heterotrophic systems as a novel procedure of adaptation for *Chlorella sorokiniana* without
711 compromising the extended lag phase of cell adaptation. Yang et al. (2017) investigated the
712 compensatory response of green microalgae *Chlorella pyrenoidosa* towards the removal of
713 antibiotic ceftazidime after treating it under harsh or limiting conditions. *C. pyrenoidosa* was
714 cultured under limited light, nitrogen, and phosphorus for 6 h before exposure to ceftazidime;
715 consequently, the removal efficiencies were improved up to 99.15%, 98.57%, and 99.9%,
716 respectively. Hena et al. (2015c) observed that the bio-volume of microalgae in the consortium
717 varied during acclimatization in harsh conditions, while the fittest showed the highest % of bio-
718 volume after acclimatization. Hence, the other aspect of acclimatization is to maintain the bio-
719 volume of microalgal strains before treatment. Alteration in salinity of culture medium can easily
720 acclimatize microalgal cells through genetic and physiological adaptation. Xiong et al. (2017a)
721 acclimated wild strains of *Chlorella vulgaris* with several exposures from low to high

722 concentration ranges of levofloxacin at elevated salinity to improve the removal efficiency of
723 levofloxacin. Guo and Chen (2015) acclimated *Chlorella pyrenoidosa* in 100 mg/L of antibiotic
724 cefradine for two weeks before being introduced into activated sludge for enhancing the removal
725 efficiency of the system. Garcia-Rodríguez et al. (2013) acclimated *Spyrogira* sp. and
726 *Zannichellia palustris* simply by placing them into a fish tank for a month to remove
727 tetracyclines and sulphonamides from secondary effluent of Empuriabrava WWTP. Sole and
728 Matamoros (2016) acclimated the consortium of microalgae *Chlorella* sp. and *Nitzschia*
729 *acicularis* into secondary treated wastewater for 20 days before co-immobilizing the culture for
730 removing EE2, and OP from wastewater.

731 **6. Risk impact of PPCPs on microalgae**

732 Diverse microalgae actively participate in the removal of PPCPs in algal-mediated wastewater
733 plants. They can significantly withstand high concentrations of PPCPs in sewage wastewater
734 after adaptation or acclimatization. However, even adapted or acclimatized strains of microalgae
735 cannot completely remove PPCPs from the wastewater. In fact, the residual PPCPs and their by-
736 products remaining in the treated water, slip through the (WWTPs) as effluents and pose a
737 challenge to the existence of the microalgal community in the environment that are not adapted
738 or resistant towards the PPCPs. Generally, the cell density of microalgae decreases in the
739 presence of PPCPs due to the death of sensitive cells; nevertheless, continuous exposure of
740 PPCPs might allow them to grow again after adaptation. Guo et al. (2016) found that
741 pharmaceutical contaminants of the same class show different effects on microalgal species even
742 if they share the same evolutionary lineage. This statement was extended and explained by
743 Ramanan et al. (2016). Specifically, bacteria synergistically help in the growth of microalgae and
744 vice-versa; thus, including complex enzymatic interactions between them, which are of species-
745 specific association. The introduction of antibiotics harms bacteria as a targeted organism by
746 disturbing the enzymatic correlation between microorganisms and disrupting microalgal growth.
747 Fu et al. (2017) confirmed that the antibiotics florfenicol, doxycycline, oxytetracycline, and
748 azithromycin showing the highest bacterial growth inhibition, also evidenced high toxicity to
749 microalga *Pseudokirchneriella subcapitata*.

750 Although it is difficult to analyze the toxic effect of PPCPs to non-targeted microalgae in the
751 environment, the measurement of hazard or risk quotients can be used to depict the potential
752 ecological risk of a specific PPCP to microalgae (Gros et al., 2010). The hazard or risk quotient
753 is the ratio of measured environmental concentration (MEC) and predicted no-effect
754 concentration (PNEC) of a certain PPCP for a specific microalga (Gros et al., 2010). MEC
755 represents the maximum concentration level detected for each PPCP in water bodies (wastewater
756 effluents and surface waters) while the PNEC values are obtained by specifically dividing the
757 EC50 value of each PPCP by a safety factor of 1000 (Gonzalez-Pleiter et al., 2013). The value of
758 risk quotient of a particular PPCP equals to or higher than one indicates its potential toxicity for
759 an alga (Grung et al., 2008). The toxicological effect of a PPCP can be assessed by studying
760 different aspects such as growth rate and biochemical characteristics of the microalga, including
761 pigments (chlorophyll and carotenoid) content, and the activity of antioxidant enzymes, i.e.,
762 malondialdehyde (MDA), catalase (CAT), and superoxide dismutase (SOD). However, the most
763 common way for toxicity evaluation is to calculate the effective concentration (EC50) of the
764 stressor (PPCPs) at which 50% of the growth rate of an organism (microalgae) is inhibited. It has
765 been reported that the value of EC50 increased with an increasing period of cultivation; thus,

766 anticipating the adaptation of microalgae. According to the Commission of the European
767 Communities (1996), pollutants with EC50 >100 mg/L are classified as harmless substances,
768 those with EC50 from 10-100 mg/L are included under the harmful category, while those with
769 EC50 of toxic substances placed between 1-10 mg/L, and all pollutants having EC50 <1 mg/L
770 are considered as very toxic substances. The toxicological effect of PPCPs on the growth rate,
771 chlorophyll, and carotenoids content, and activity of antioxidant enzymes of microalgae are
772 summarised in Table 6. Under normal culture and environmental conditions, the generation and
773 consumption of reactive oxygen species (ROS) in microalgae are maintained in equilibrium.
774 However, the exposure of PPCPs tends to induce excess production of ROS in microalgal cells,
775 such as hydroxyl radicals ($\cdot\text{OH}$), superoxide radicals ($\text{O}_2^{\cdot-}$), and hydrogen peroxide (H_2O_2). ROS
776 are strong oxidants that can lethally damage the cell organelles by peroxidation of
777 polyunsaturated fatty acids and proteins present in membranes, causing an increase in the
778 permeability of the membrane (Ke et al., 2010; Tang et al., 2016). The polyunsaturated fatty
779 acids produce malondialdehyde (MDA) as a product after peroxidation, which can be analyzed in
780 the lab to confirm the degree of structural and functional damages in the cell. Once the
781 microalgae are exposed to the stressor or toxic compounds (PPCP), the cells start to counteract
782 the toxicity of excess ROS by initiating the synthesis of anti-oxidative enzymes such as
783 superoxide dismutase (SOD) as the first line of defense in the cell. SOD reacts with $\text{O}_2^{\cdot-}$ and
784 converts it to O_2 and hydrogen peroxide, which are less oxidative than $\text{O}_2^{\cdot-}$. Catalase (CAT), a
785 heme-containing enzyme produced at the chloroplast and cytoplasm along with SOD, interacts
786 with H_2O_2 and produces O_2 and H_2O (Jin et al., 2012; Huang et al., 2012). A steady decrease in
787 SOD and CAT activity during assay tests is a sign of adaptation of microalgal cells, which
788 gradually appears after a few days of exposure to stressors (PPCPs) (Xiong et al., 2017a).
789 Several microalgae show a low dose stimulation and high dose inhibition in growth in the
790 presence of particular stressors, known as hormesis. Freshwater diatom *Navicula* sp. and green
791 microalgae *C. vulgaris* exhibited better growth in the presence of low concentrations of
792 ibuprofen due to hermetic dose-response (Geiger et al., 2016; Ding et al., 2017). Among ROS,
793 superoxide ($\text{O}_2^{\cdot-}$) acts as a central factor of signal transduction, activating the gene expression to
794 encoding SOD (Liu et al., 2014; Liu et al., 2012). However, in a worst-case scenario, if the DNA
795 is damaged by oxidation, then the cell fails to organize its systems and is followed by cell death,
796 also known as programmed cell death (PCD).
797 Photosynthesis is an essential process for the survival of microalgae. This process is related to
798 the growth and several metabolic activities of microalgae. Thus, any alteration in growth in
799 microalgae during PPCPs (stressors) exposure is related to the changes in chlorophyll. PPCPs
800 damage thylakoid and chloroplast lipids by annihilating membranes functionally and structurally,
801 consequently destroying photosystem II (PSII) and the content of chlorophylls and carotenoids
802 (Nie et al., 2008). Low chlorophyll content as a stress response of PPCPs has been observed in
803 microalgae *Tetraselmis chui*, *Isochrysis galbana*, and *C. pyrenoidosa* in the presence of
804 thiamphenicol, florfenicol, and chloramphenicol (Lai et al., 2009). In 10 days, *C. vulgaris* started
805 showing stress response for metronidazole (Hena et al., 2020). In some cases, a gradual increase
806 in chlorophyll has been observed with an increase of PPCP dosage with time. *Chlorella*
807 *pyrenoidosa* and *Microcystis aeruginosa* showed an increase in chlorophyll in the presence of
808 antibiotics in media, such as spiramycin, cefradine, and amoxicillin (Chen et al., 2015; Liu et al.,
809 2014). Xiong et al. (2017b) reported an increment in chlorophyll by 38% to 19% in
810 *Chlamydomonas mexicana* with an increase in the concentration of ciprofloxacin from 60 mg/L
811 to 100 mg/L, respectively, compared to control culture. Chlorophyll was observed to act as a

812 protective mediator in the attenuation of excess ROS in the cell (Xiong et al., 2016). Carotenoids
813 play important roles during the initial reactions of photosynthesis and possess enough anti-
814 oxidative properties to quench the ROS produced during the exposure of pollutants (Jahns and
815 Holzwarth, 2012). Carotenoids increases in *C. mexicana* in the presence of enrofloxacin and
816 ciprofloxacin (Xiong et al., 2017b). Increased content of carotenoid has also been observed in
817 *Dunaliella bardawil*, *Dunaliella tertiolecta*, *S. obliquus*, and *C. mexicana* exposed to
818 carbamazepine (Xiong et al., 2016; Tsiaka et al., 2013; Salguero et al., 2003). The matrix of
819 water plays a significant role in toxicity upon microalgae. Some quinolones acquire antagonistic
820 characters in the presence of calcium and magnesium and decrease their effects on
821 microorganisms and toxicity (Li et al., 2000). Hagenbuch and Pinckney (2012) reported the same
822 effect of tylosin, lincomycin, and ciprofloxacin towards *C. closterium* and *N. ramosissima* (i.e.,
823 both are from marine habitats). Also, a higher EC50 value was observed in saline water culture
824 than those obtained in freshwater culture (Halling-Sørensen et al., 2003). On the other hand,
825 photodegradation products of sulfamethoxazole are more toxic and less biodegradable in
826 seawater; thus, increasing the toxicity of compounds, and decreasing the EC50 value for
827 microalgae (Teixeira and Granek, 2017).
828

829 **7. Conventional and improved hybrid microalgae culture techniques for efficient** 830 **removal of PPCPs from wastewater by microalgae** 831

832 *7.1. Conventional microalgae culture techniques* 833

834 Phycoremediation is considered a promising substitute for conventional biological treatments to
835 remove micropollutants and nutrients from wastewater, along with several other benefits of
836 biotechnological applications (Ruiz-Marin et al., 2010). Microalgae are considerably flexible in
837 adapting to different techniques of culture. The culture techniques are mainly discussed on the
838 basis of the motility of the cells in culture media and the degree of control of the abiotic factors
839 affecting the removal of PPCPs from wastewater.

840 On the basis of the degree of control of the abiotic factors, the microalgal culture techniques are
841 broadly divided into two categories: closed or open culture techniques. The closed and open
842 culture techniques are further divided into two subcategories: suspended or immobilized culture
843 technique depending upon the motility of the cells in culture media (Fig. 4).
844

845 *7.1.1. Closed and open culture techniques* 846 847

848 Photo-bioreactors are closed systems where microalgae grow under controlled conditions. A
849 tubular photo-bioreactor is one of the most efficient and promising designs of closed photo-
850 bioreactor systems. The culture is circulated by pumping, and the system is incorporated with a
851 gas exchange unit where a CO₂ supply can be used by microalgae in photosynthesis and for
852 removing O₂ from the medium. Compared to open systems, closed systems are more efficient in
853 terms of volumetric productivity (such as lipid and biomass) and pollutant removal efficiency.
854 However, difficulties in upscaling, overheating, and construction cost are clear drawbacks for
855 implementing it as wastewater treatment in large scales unless the wastewater is containing

856 highly hazardous pollutants that cannot be remediated in open systems. Volatilization
857 mechanisms for PPCPs removal also get hindered by closed bioreactors. Kong et al. (2010)
858 reported higher wastewater treatment efficiency in closed systems rather than open systems with
859 *C. reinhardtii*. Closed culture system is more popular in the lab for small scale of real (Zhou et
860 al., 2011) or synthetic wastewater treatment to study the suitability of a particular microalgal
861 strain for a specific micro-pollutant in a controlled atmosphere (Xiong et al., 2017b; Hena et al.,
862 2020; Escapa et al., 2017). Zhou et al. (2011) autoclaved the wastewater to check the stability of
863 selected microalgal strains for particular wastewater, which is not feasible for real wastewater
864 treatment at large scales.

865
866 HRAPs are a modified form of conventional stabilization ponds used for the treatment of urban
867 wastewater. HRAPs are microalgal culture ponds with 0.2 to 1 m of depth, incorporating a
868 paddlewheel to homogenize the culture and helping in mixing the atmospheric CO₂ with media.
869 Generally, open systems are not equipped with air or a CO₂ supply. WWTPs incorporated with
870 HRAP for wastewater treatment are known as Advanced Pond System (APS). APS is comprised
871 of anaerobic digestion chamber, HRAP, and followed by algal settling pond, as shown in Fig. 5.
872 Anaerobic ponds are commonly 2-5 m in depth and receive wastewater with high biological
873 oxygen demand (BOD) and chemical oxygen demand (COD) values. In general, this pond is free
874 of microalgae and dissolved oxygen. The anaerobic bacteria are involved in the BOD removal by
875 anaerobic digestion, followed by a settling process. The treated wastewater is transferred to
876 HRAP for microalgal treatment, which is inoculum with single or consortium of microalgae or
877 microalgae-bacteria to remove COD, BOD, total nitrogen, phosphorus, and micro-pollutants (i.e.,
878 including PPCPs). The microalgal settling pond or microalgal biomass harvesting pond receives
879 treated wastewater from HRAP, where different techniques are used to separate biomass from
880 aqueous media. Since microalgae cannot settle by themselves as activated sludge or it may
881 partially settle due to gravity after a long time. A flocculant is added to speed up this process.
882 The separated microalgal biomass can be used as a fertilizer (Mulbry et al., 2005) or as feedstock
883 for the energy (Hena et al., 2018).

884
885

886 7.1.2. *Suspended and immobilized culture techniques*

887

888 Suspended culture technique is more popular than immobilized culture in WWTPs due to its
889 cost-effectiveness. Nevertheless, harvesting biomass of microalgae at the end of the process is
890 one of the main limitations for the development of this type of wastewater treatment system
891 worldwide. Suspended microalgae culture is being used in closed and open bioreactors for
892 different operational modes (batch, semi-batch, and continuous operation modes). Ciprofloxacin
893 (Hom-Diaz et al., 2017a) and tetracycline (de Godos et al., 2012) were efficiently removed from
894 HRAP by suspended algal cells. Escapa et al. (2017) cultivated suspended cells of *Chlorella*
895 *sorokiniana* for removal of paracetamol and salicylic acid in batch and semi-continuous mode of
896 operations, where semi-continuous showed better removal efficiency for both pharmaceuticals.
897 The advantages and limitations of the processes using suspended and immobilized cell culture
898 are listed in Table 7.

899

900 The suspended microalgae culture is well established in wastewater treatment; however, the
901 harvesting of microalgal cells is an extra step to finalize the treatment process. To overcome the
902 time and energy-consuming issues, the immobilized culture technique of microalgae has shown
903 as a promising alternative to suspended culture (Pires et al., 2013; He and Xue, 2010).
904 Immobilized cultures are capable of accomplishing two steps in a single stage: bioprocessing and
905 harvesting. Gonçalves et al. (2017) suggested a better microalgal growth in biofilm than
906 suspended culture. Xie et al. (2020) found that immobilized cell culture techniques are more
907 appropriate for treating antibiotic-containing water than suspended cell culture technique because
908 the former technique can inhibit the toxic effect of antibiotics on microalgae. Sole and
909 Matamoros (2016) suggested a light-blocking effect of free microalgae in the suspended cell
910 culture technique, which consequently prevents the photo-biodegradation mechanism of PPCPs.
911 In general, the immobilized technique is more effective in removing PPCPs than suspended
912 technique. An immobilized mono-culture of *C. vulgaris* on sodium alginate gel impregnated with
913 Al₂O₃ nanoparticles was capable of removing 89.6% of carbamazepine from water in four days
914 of treatment in a closed photo-bioreactor system, while only 48.5% was removed from the
915 suspended culture of *C. vulgaris* (constant cell density; 3.0×10⁶ cells/mL) (Wu et al., 2020). Sole
916 and Matamoros (2016) found that the removal rates of EE2 were significantly higher in
917 immobilized microalgae reactors than in free microalgae reactors.
918 There are two types of immobilizations: natural or passive immobilization and artificial or active
919 immobilization.

920
921 Natural immobilizations are more complex in character than artificial or active immobilization.
922 The examples of natural immobilization techniques are always mixed-culture, and
923 microorganisms behave symbiotically with each other. Natural immobilization is the innate
924 characteristics of microorganisms to anchor to the different surfaces. The attachments of the cells
925 on solid surfaces generally form biofilms due to the secretion of EPS by metabolically active
926 cells of microalgae and bacteria. The EPS of biofilm protects the immobilized cells from direct
927 contact with extreme conditions (e.g., pH, pollutants or toxic substrates, temperature). Also,
928 extracellular enzymes in EPS assist in the external biodegradation of pollutants (Hou et al., 2013).
929 In nature, microalgae-bacteria consortium is present as biofilms, which play an important role in
930 PPCPs removal from surface water. River biofilm (microalgae-bacteria reactors) are found
931 beneficial for degrading ibuprofen but not for clofibrac acid (Winkler et al., 2001). Writer et al.
932 (2011) identified a biofilm useful for the removal of steroidal hormones via biodegradation and
933 sorption mechanisms. Periphyton is a natural consortium of microalgae-bacteria used in lab-scale
934 to remove nutrients and five PPCPs mainly due to biodegradation processes (Kang et al., 2018).
935 Among those, nitrogen and phosphorus were removed up to 77% and 68%, respectively,
936 ibuprofen and hydrochlorothiazide were moderately removed up to 48.7%, while gemfibrozil
937 and carbamazepine were poorly removed (i.e., up to 20.6%). Interestingly, these removal trends
938 were similar to those of CWWTPs (Luo et al., 2014).

939
940 Artificial immobilization is an induced process to trap the metabolically active cells either by
941 adsorption on a solid surface, entrapment within an emulsion, polymers matrix, or semi-
942 permeable membrane (Hameed and Ebrahim 2007; Eroglu et al., 2015). The artificial
943 confinement of cells within polymers matrix and adsorption onto solid surfaces are the most
944 common techniques to immobilize cells. The most commonly used matrix is natural polymers
945 such as carrageenan, alginate, chitosan, and agar, which are non-toxic to microalgal cells. The

946 appropriate pore sizes of matrix allow substrates and products to diffuse into and from the matrix
947 of polymers, respectively, during the treatment process. However, immobilizing a microalgae
948 culture into biopolymers is a comparatively expensive technique; thus, restricting the application
949 at large scales. Ismail et al. (2016) co-cultured a strain of ketoprofen degrading bacteria with
950 *Chlorella* sp. for attaining higher biodegradation.
951

952 7.2. *Improved hybrid microalgae culture techniques*

953 Pharmaceuticals are only partially metabolized in animals and humans, while the rest is excreted
954 and end up in municipal WWTPs. The recalcitrant nature of PPCPs causes contaminants to slip
955 through the treatment plant and enter into the environmental subsurface and possibly the
956 drinking water treatment plants (Reemtsma et al., 2016). Among all persistent PPCPs, antibiotics
957 have received widespread attention due to their potentiality to induce antibiotic resistance
958 bacteria (ARB) in every compartment of the environment. These ARBs release antibiotic-
959 resistant genes (ARGs) into the environment, having a fair chance to be acquired by other
960 pathogenic bacteria (Berglund et al., 2017). On the other hand, microalgal treatment of
961 wastewater has been proven as competent as conventional wastewater treatment processes
962 (U'beda et al., 2017). The microalgae are not the targeted organism of antibiotics and have a
963 higher tolerance to contaminants than bacteria, including antibiotics. However, microalgae show
964 toxicity towards PPCPs, which inhibit their growth. Among all reported PPCPs, tetracycline is
965 the most toxic for microalgae with EC_{50} lower than 10 $\mu\text{g/L}$ (Wang et al., 2017). The concept of
966 hybrid techniques was developed to enhance the removal capacity of PPCPs from the WWTPs
967 and to reduce the risk impact of PPCPs on the ecosystem (outside the treatment plant), including
968 bacteria and microalgae. However, Hena et al. (2020) suggested that the biomass of microalgae
969 produced during the treatment of wastewater containing PPCPs could be used as a valuable
970 feedstock for biofuels production since the treated biomass is not suitable to be used for other
971 purposes such as fertilizers and animal feed. This way, the phycoremediation of wastewater and
972 concomitantly biomass production as feedstock for biofuels are a waste to worth paradigm. In
973 this section, some hybrid techniques are discussed.
974

975 7.2.1. *Hybrid microalgae-UV treatment technique*

976 Advanced oxidation processes such as UV, ozone, and H_2O_2 can efficiently disintegrate the
977 PPCPs from water; however, their by-products, high consumption of energy, and oxidants dose
978 are few drawbacks of these processes. The by-products of cefradine and sulfamethoxazole are
979 more toxic than their parent compounds after treating them with UV and ozone, respectively (Du
980 et al., 2015; Dantas et al., 2008). To minimize the above problems and to achieve an economical,
981 environmentally sustainable, and efficient process to remove PPCPs, the chemical process has
982 been combined with a biological method (Fig. 6). In association with the biological entities, the
983 intermediates of the recalcitrant compounds produced by chemical processes can biodegrade
984 more efficiently than individual processes. In combined or hybrid treatment, the chemical
985 processes are kept mild to produce biodegradable intermediates but not destined to induce the
986 total degradation of compounds, which save the costs as well as the environment. Microalgae are
987 well documented in the literature for its ability to biodegrade PPCPs and their intermediates (Gao
988 et al., 2011; Shao et al., 2002). Du et al. (2015) reported on the toxicity control of cefradine by a
989 hybrid UV-microalgae treatment system. Yang et al. (2017) demonstrated the removal of
990

991 antibiotics cefradine and amoxicillin by hybrid UV-green microalgae (*Chlorella pyrenoidosa*,
992 *Selenastrum capricornutum*, and *Scenedesmus obliquus*) system, where microalgae played a
993 major role in the biodegradation while UV triggered the treatment. *S. obliquus*, along with UV-
994 irradiation at 365 nm, showed the best possible removal (99.84%) of cefradine and amoxicillin
995 within 24 h of application. The bacteriostatic test for the bacteria *E. coli* and *S. aureus* reflected
996 insignificant toxicity after hybrid treatment. Liu et al. (2017) enhanced the removal efficiency of
997 the hybrid system by incorporating an additional step of microalgal treatment for ceftazidime
998 removal after treating it with UV-microalgae. The process was termed UV-
999 microalgae/microalgae treatment.

1000 7.2.2. Hybrid microalgae-activated sludge system technique 1001

1002 The exposure of high concentrations of antibiotics to the diversified bacterial population in
1003 activated sludge systems offer the most favorable condition for bacteria to develop resistance in
1004 WWTPs. Consortia have always been found more efficient in biodegradation of PPCPs than
1005 mono-culture of either microalgae or bacteria. However, the hybrid microalgae-activated sludge
1006 system is a relatively new concept, initially reported by Guo and Chen (2015), for treating
1007 cephalosporins (i.e., one of the most common antibiotics used by human beings, cattle, and
1008 aquaculture farming). Kümmerer (2009) stated that almost 60% of the total antibiotics used for
1009 therapeutic use belong to the cephalosporins family. The finding of Guo and Chen (2015) proved
1010 that antibiotics do not come in direct contact with bacteria if they have been pre-treated by
1011 microalgae. The proposed technique highly assists in avoiding ARB development.
1012 Simultaneously, the hybrid microalgae-activated sludge system showed an excellent removal
1013 capability (up to 97.9%), while the initial concentration of cephalosporins was 100 mg/L. This
1014 technique is a promising approach to treat wastewater in two steps (Fig. 7) to protect the
1015 bacterial community from acquiring resistance and developing ARB or releasing ARGs in the
1016 environment.

1017 7.2.3. Hybrid microalgae-membrane photo-bioreactor technique 1018

1019 Several studies have focussed on membrane bioreactor (MBR) combined with activated sludge
1020 for PPCPs removal from wastewater (Kovalova et al., 2012; Tadkaew et al., 2011; Radjenovic et
1021 al., 2009; Alvarino et al., 2016). Spring et al. (2007) suggested that an MBR is more efficient in
1022 removing PPCPs than conventional treatment due to following reasons:

- 1023
- 1024 1. Many compounds adhered to the surface of the sludge during treatment are also retained in the
1025 sludge by membrane filtration.
- 1026 2. In many cases, the membrane surfaces also capture the compounds.
- 1027 3. Longer sludge retention time enhances the biodegradation of recalcitrant compounds in MBR.
- 1028

1029 Similar to MBR, the membrane photo-bioreactor technology (MPBR) is a bioreactor equipped
1030 with light and membrane units, which assist microalgae to grow and harvest complete biomass
1031 (Fig. 8). Currently, comprehensive studies have been conducted on MPBR; nevertheless, most of
1032 these studies revolved around the removal of nitrogen and phosphorus from wastewater and
1033 synthetic culture media (Honda et al., 2012; Bilad et al., 2014; Marbelia et al., 2014; Gao et al.,

1034 2015; Boonchai and Seo, 2015; Gao et al., 2016; Lee et al., 2018). Few studies are available on
1035 the MPBR system for PPCPs removal (Derakhshan et al., 2018).

1036 7.2.4. *Hybrid microalgae-constructed wetland technique*

1037 Constructed wetlands (CW) have been proven as an operational technique for PPCPs removal
1038 (Dordio et al., 2010; Matamoros et al., 2008; Zhang et al., 2011; Hijosa-Valsero et al., 2011;
1039 Hussain et al., 2012). The shallow bed of CW contains free-floating plants or plants with
1040 rudimentary kinds of roots (Cole 1998), which are capable of producing water of quality enough
1041 for disposal into natural water bodies (Garcia-Rodríguez et al., 2013). Regarding nutrients
1042 removal, the nitrification process in nitrogen removal is a rate-limiting step due to oxygen
1043 deficiency (Xiong et al., 2018b). This drawback can be overcome by incorporating microalgae
1044 into the system, which produces oxygen during photosynthesis. The configuration of the
1045 expected hybrid microalgae-constructed wetland techniques is illustrated in Fig. 9. Zhang et al.
1046 (2013) reported 74% removal of carbamazepine and almost complete removal of naproxen in a
1047 wetland system containing *Scirpus validus*. On the other hand, carbamazepine could only be
1048 removed by 32.7% by activated sludge in conventional wastewater treatment (Postigo et al.,
1049 2010).

1050 8. **Comparative removal efficiency of PPCPs between microalgae and conventional** 1051 **wastewater treatment**

1052 The removal efficiency of PPCPs depends upon the physicochemical properties (Table 1) of the
1053 compounds as follows;

- 1054
- 1055 1. The higher the K_{ow} , the higher is the removal efficiency of the compound from WWTPs via
1056 sorption processes.
 - 1057 2. The higher the tendency of the compound towards the sludge phase, the higher is the solid-
1058 aqueous distribution coefficient; therefore, the better is the removal of the compound via
1059 sorption.
 - 1060 3. The negative charge of the functional group of the compound repels the negative charge of
1061 the microbial cell membrane; thus, hindering the removal of compounds via external
1062 biodegradation.
 - 1063 4. The complexity of the structure also regulates the biodegradability of compounds. A
1064 compound with linear, unsaturated, and electron-donating groups was found as more
1065 biodegradable than compounds possessing cyclic structure, saturated long linear carbon chain,
1066 and electron-withdrawing groups in their structure.

1067

1068 Wastewater is extremely complex, and for many PPCPs, the removal efficiencies do not follow
1069 the above-discussed rules. Also, in most cases, the removal efficiency is lower than expected. In
1070 brief, conventional wastewater treatment systems are not completely able to remove PPCPs from
1071 urban wastewater, and hence, more efficient and specific treatments are required. However, no
1072 available specific treatment is capable of removing all PPCPs from wastewater due to their wide
1073 varieties. A conclusion on comparative efficiency between conventional and microalgae-
1074 mediated treatment systems is a difficult task since most of the studies have been conducted on
1075 different influent concentrations of PPCPs. Nevertheless, Zhou et al. (2014) compared activated
1076 sludge systems with microalgae-mediated systems for a broad range of PPCPs. They found that
1077 microalgal systems can remove, in general, antibiotics and antimicrobial agents (e.g.,

1078 sulfamethazine, clarithromycin, sulfamethoxazole, sulfapyridine, roxithromycin, and triclocarban)
1079 more efficiently than activated sludge systems. However, it is difficult to draw conclusions on
1080 the comparative efficiency of the systems without treating the same wastewater. In this section,
1081 the results from different CWWTPs and microalgae-mediated wastewater treatment plants were
1082 collected, compared, and shown in Table 8.

1083 Microalgae-based wastewater treatment systems can competently remove many types of PPCPs,
1084 such as NSAIDs, antibiotics, and stimulants. The lower retention time of conventional activated
1085 sludge processes is one of the major reasons for the low removal capacity of highly polar
1086 pharmaceuticals (Buttiglieri and Knepper, 2008; Le-Minh et al., 2010). Ahmed et al. (2017)
1087 claimed that the general pattern of PPCPs removal in microalgae-based wastewater treatment
1088 systems and activated sludge system follow the next trend: pharmaceuticals > PCPs > EDCs and
1089 EDCs > PCPs > pharmaceuticals, respectively.

1090
1091 As long as phycoremediation is concerned, microalgae and cyanobacteria have more advantages
1092 over bacterial treatment since they can grow in various modes of cultivation, i.e., phototrophic,
1093 heterotrophic, and mixotrophic (Delrue et al., 2016). Microalgae have numerous potential
1094 applications. Remarkably, the most promising future objective on a large scale is their use for
1095 bioremediation of wastewater. Microalgae are being used to bioremediate numerous pollutants of
1096 different characteristics and properties released from the domestic, industrial, agricultural, and
1097 farm sectors (Hena et al., 2018; Chinnasamy et al., 2010). Additionally, CO₂ mitigation during
1098 culture and the use of biomass as feedstock for biodiesel or biofuel production are other benefits
1099 of microalgae-mediated treatment over CWWTPs (U'beda et al., 2017; Cuellar-Bermudez et al.,
1100 2016).

1101 **9. Concluding remarks and perspectives**

1102 Pharmaceuticals and personal care products are micro-pollutants that, even at low doses, can
1103 induce physiological effects in humans and other organisms in the environment. Their stable
1104 structure resists disintegration and consequently induce longer persistence in the environment;
1105 thus, remaining biologically active. The main sources of PPCPs into the aquatic environment are
1106 the effluents of WWTPs, runoff water from agriculture and farmlands, and the sipping of landfill
1107 leachate and their continuous exposure to microalgal life; consequently, exerting harmful effects.
1108 Globally, WWTPs are unable to completely remove PPCPs from wastewater. Therefore, there is
1109 an urgent need for more effective and advanced technologies to remove this wide range of
1110 emerging pollutants. There are numerous systems currently used to remove bio-refractory
1111 organic and inorganic pollutants from aqueous media (e.g., advance oxidation processes,
1112 adsorption, and liquid-liquid extraction); nevertheless, these systems have yet to be improved to
1113 be applied on an industrial scale. Besides recent breakthroughs in physical and chemical
1114 technologies, the development and further exploration of the potentiality of microalgae to
1115 efficiently bio-transform or bio-adsorb micro-pollutants is a promising approach. This review
1116 highlights the feasibility of microalgae in removing PPCPs from wastewater and toxicological
1117 effect of PPCPs on microalgae. However acclimatization and the improved hybrid microalgae
1118 culture techniques are the keys to increase the removal efficiency of PPCPs from wastewater and
1119 reduce the toxicological effect of PPCPs on bacteria and microalgae present in ecosystem
1120 Additionally, the recovered biomass would be used in other sectors. Despite comprehensive
1121 studies, there are still many WWTPs around the world where PPCPs have not been thoroughly
1122 analyzed. Therefore, it is highly required to study treatment performance, which could expand

1123 the current understanding of the fate of PPCPs and might breakthrough some strains for
1124 bioremediation.

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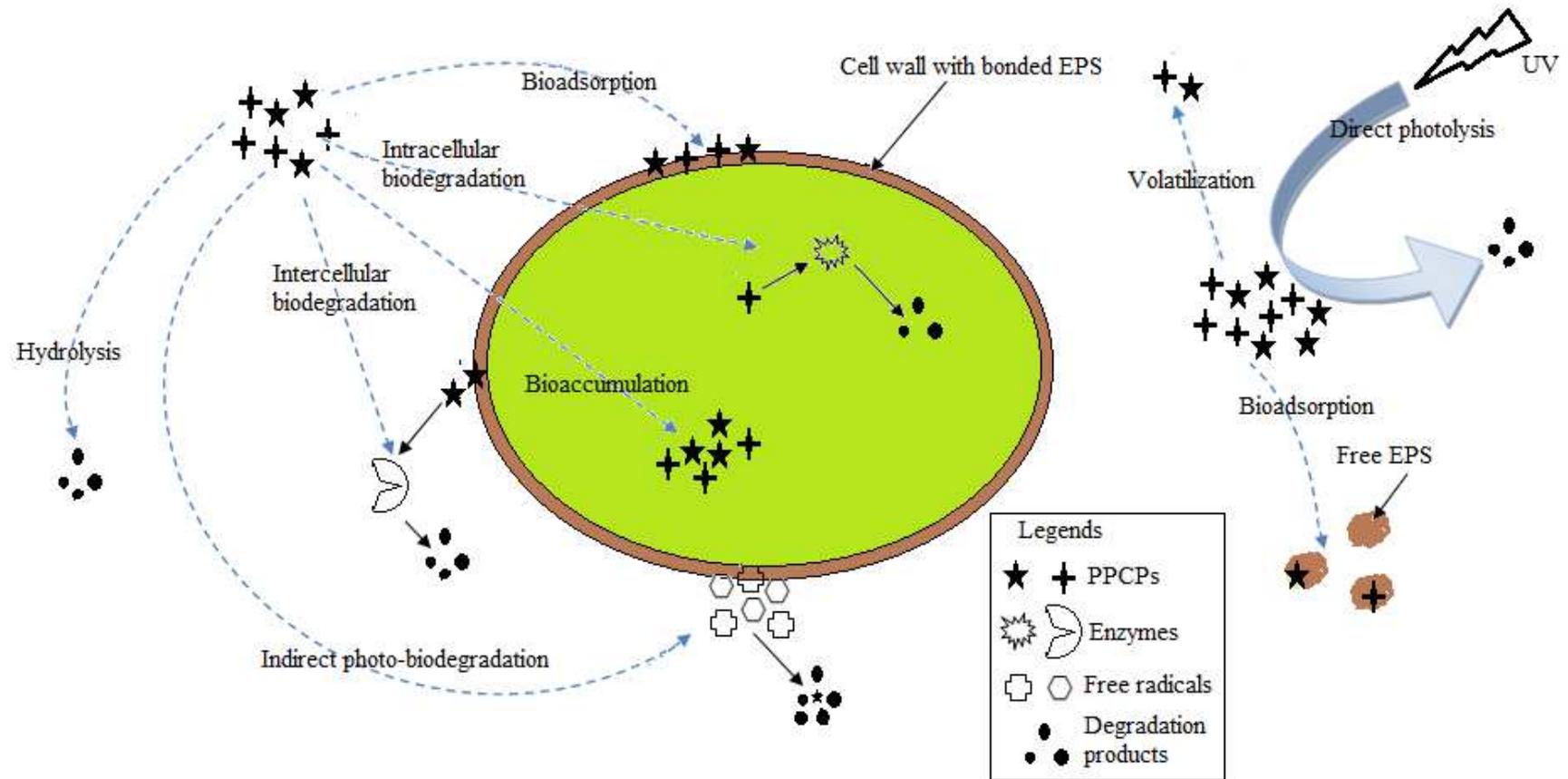


Figure 1: Mechanisms involved in the removal of PPCPs by microalgae

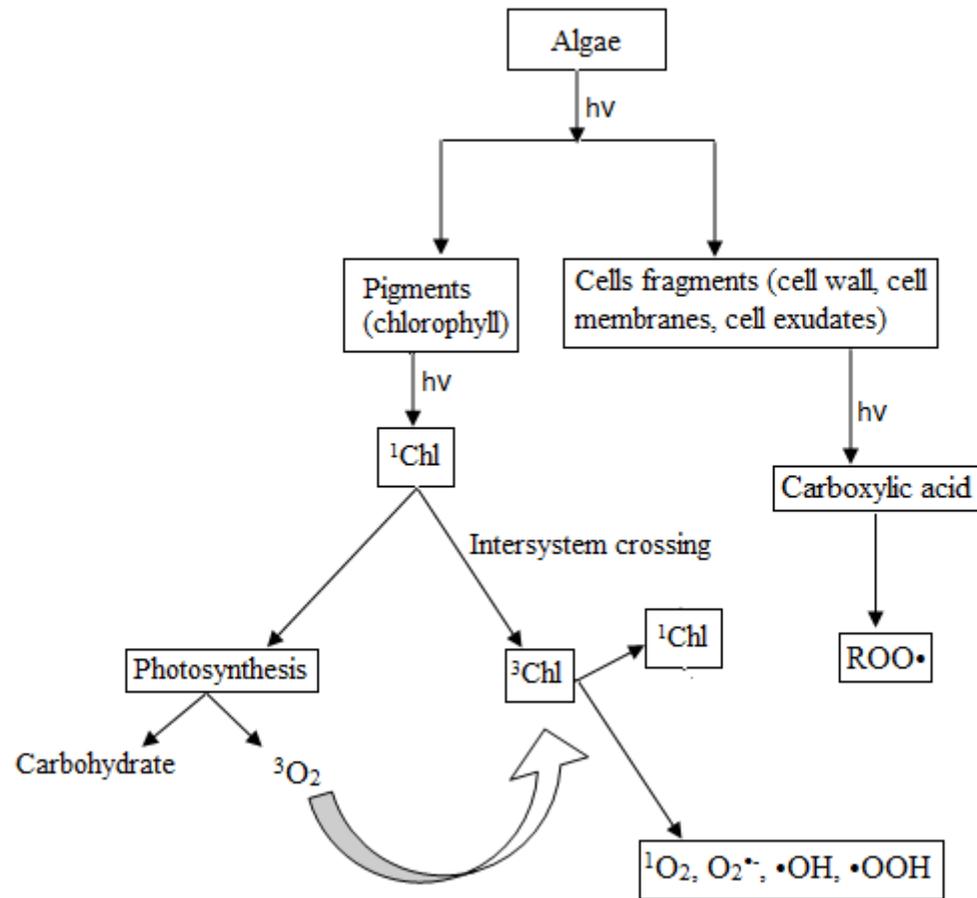
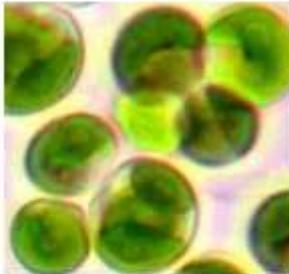


Figure 2: Mechanism of microalgal photo-degradation of pollutants in water

Cooperative Interaction

Vitamin B₁₂ Consumption
Siderophores Consumption
EPS Production
O₂ Production
CO₂ Consumption



Microalgae

Bactericides or Allelochemicals Production

High pH

Vitamin B₁₂ Production
Siderophores Production
EPS Production
O₂ Consumption
CO₂ Production



Bacteria

Algicides or Allelochemicals Production

Competitive Interaction

Figure 3: Cooperative and competitive interactions between microalgae and bacteria

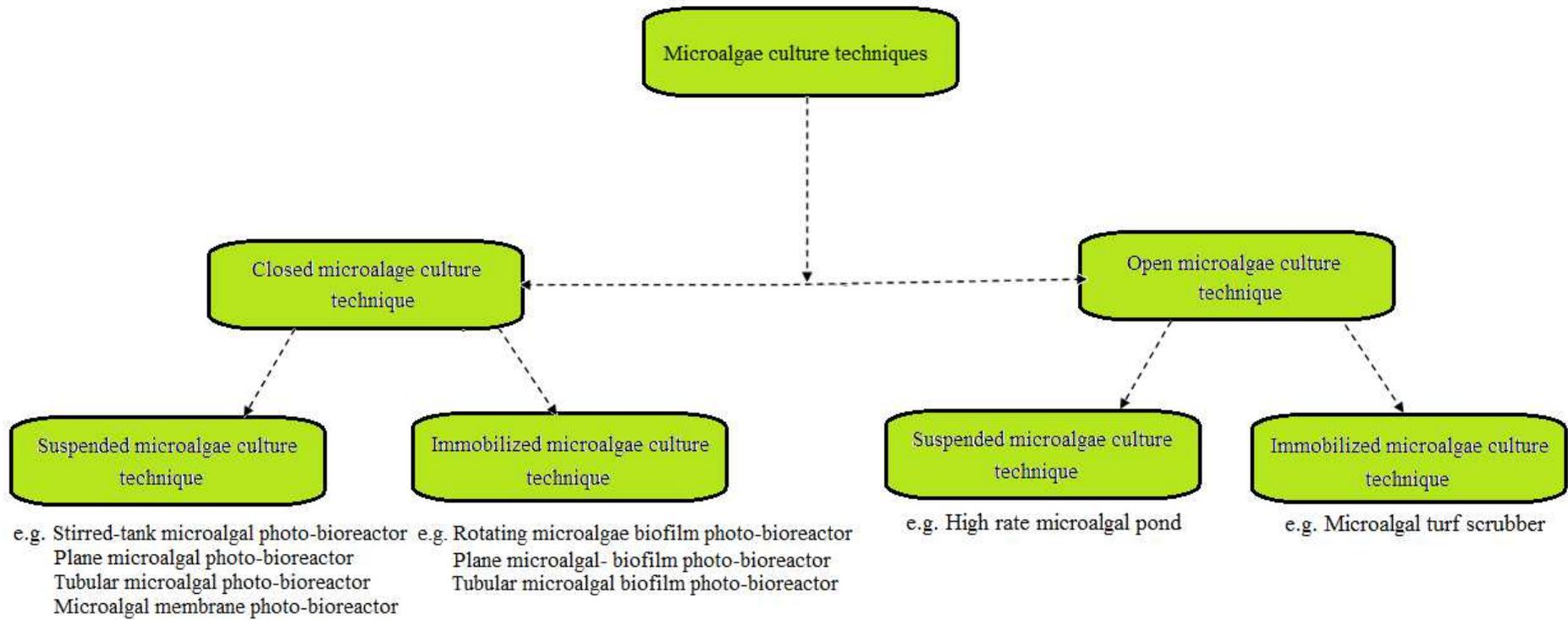


Figure 4: Microalgae culture techniques and examples

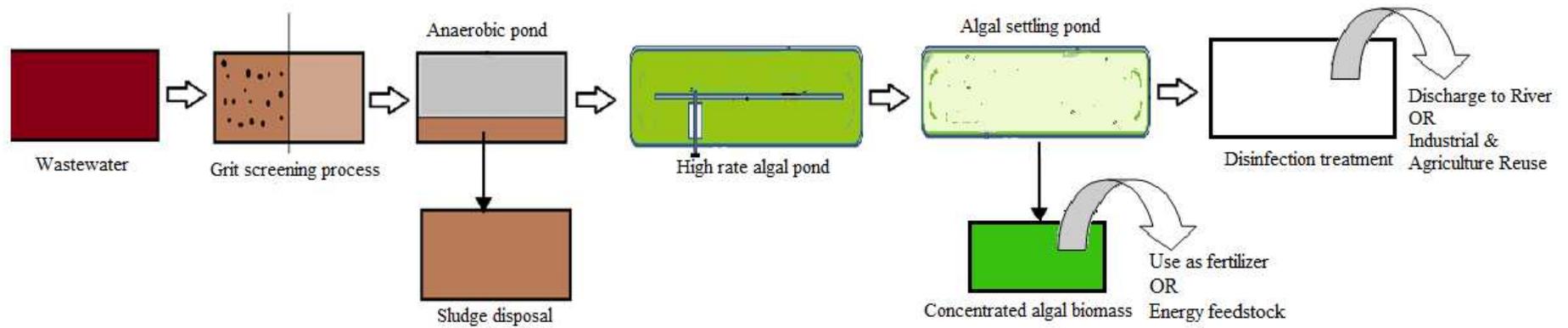


Figure 5: Scheme for wastewater treatment through HRAP

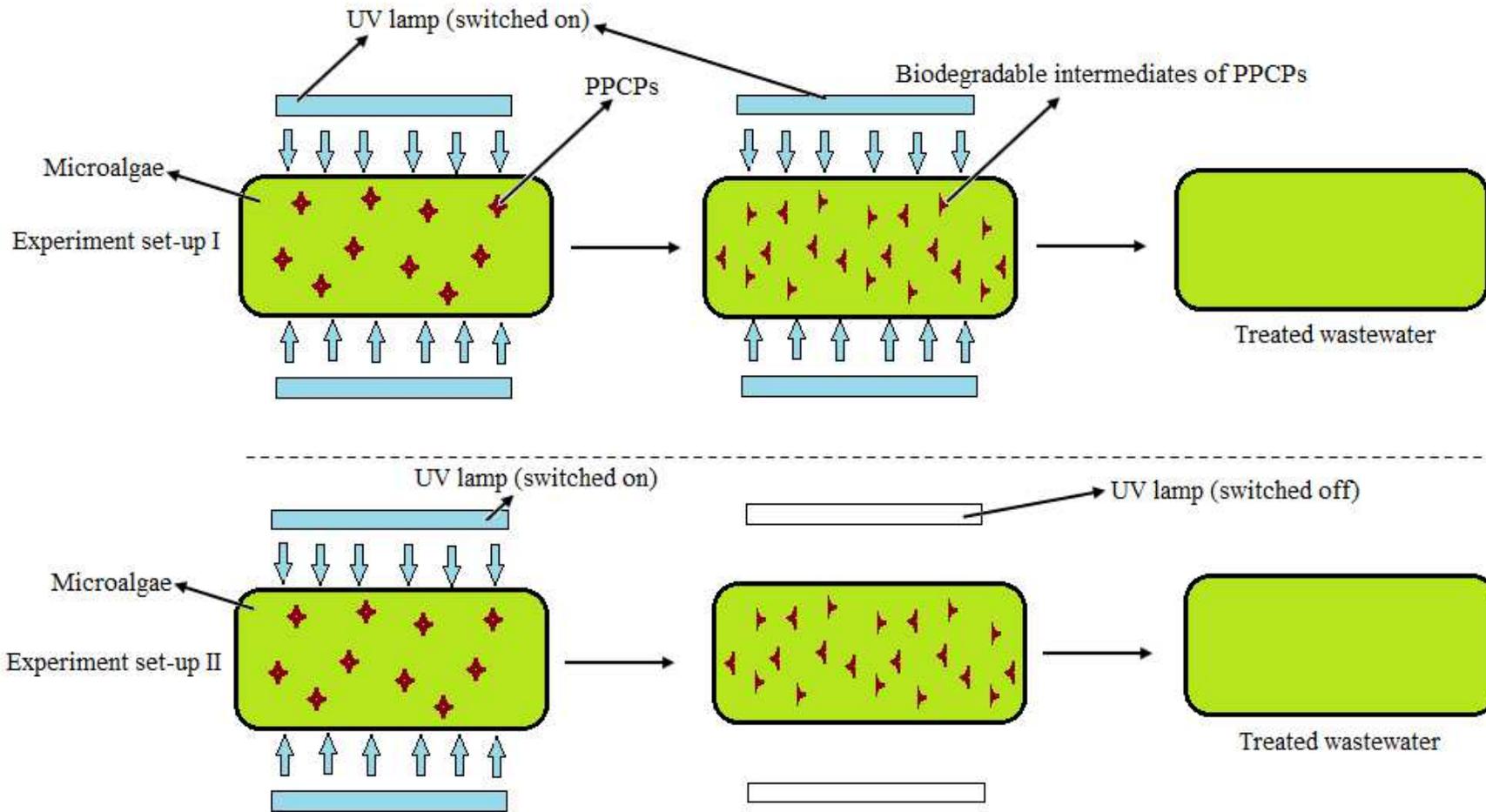


Figure 6: Hybrid microalgae-UV treatment system technique. In experiment set-up I, the UV lamps are switched on during the whole treatment process, while in experiment set-up II, the UV lamps are switched on only for certain period of time (depending upon the PPCPs removal efficiency of the coupling UV irradiation and microalgal treatment).

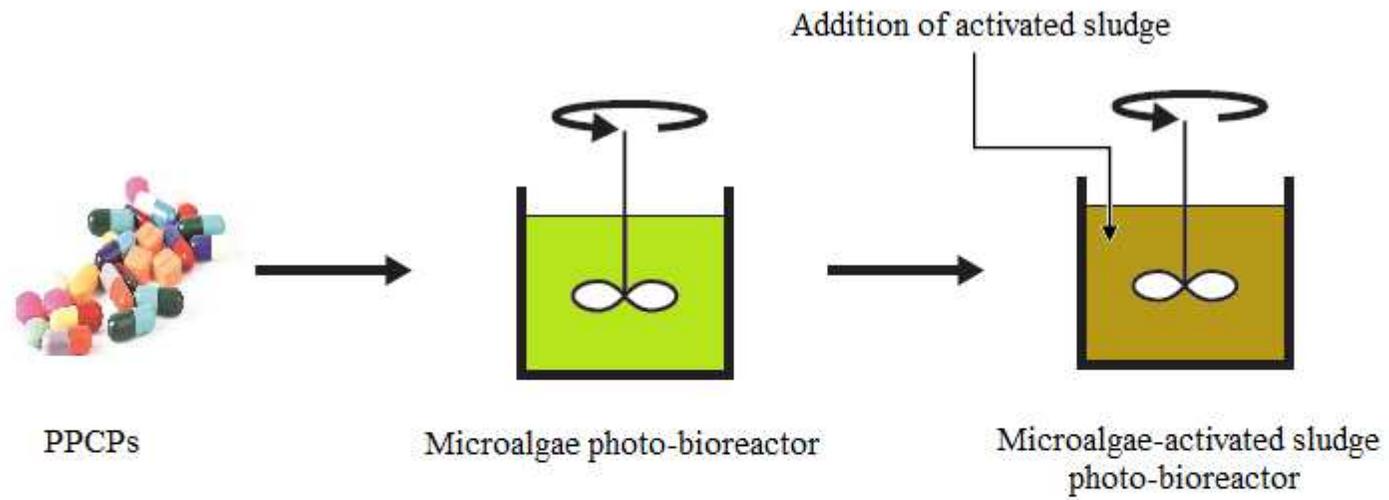


Figure 7: Hybrid microalgae-activated sludge system

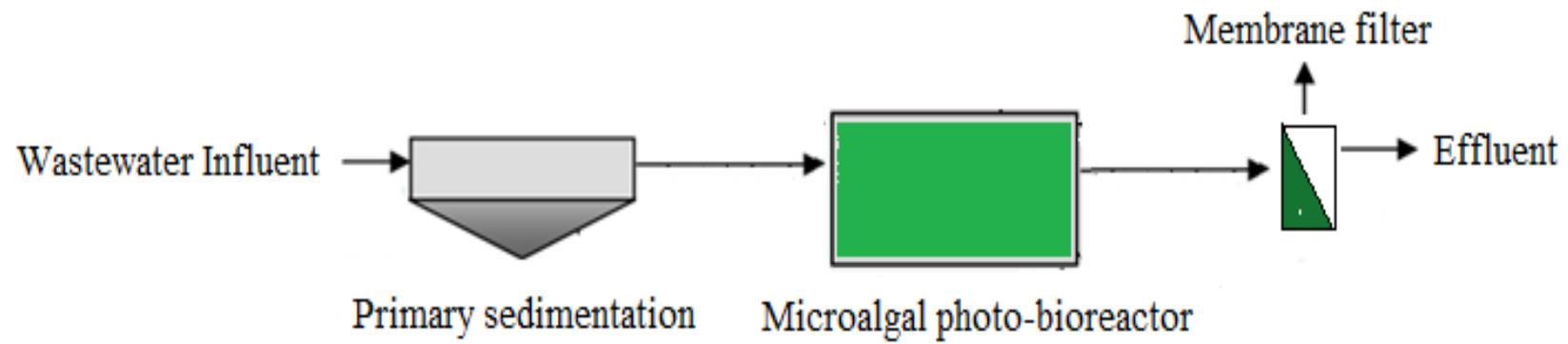


Figure 8: Hybrid microalgae-membrane photo-bioreactor technique

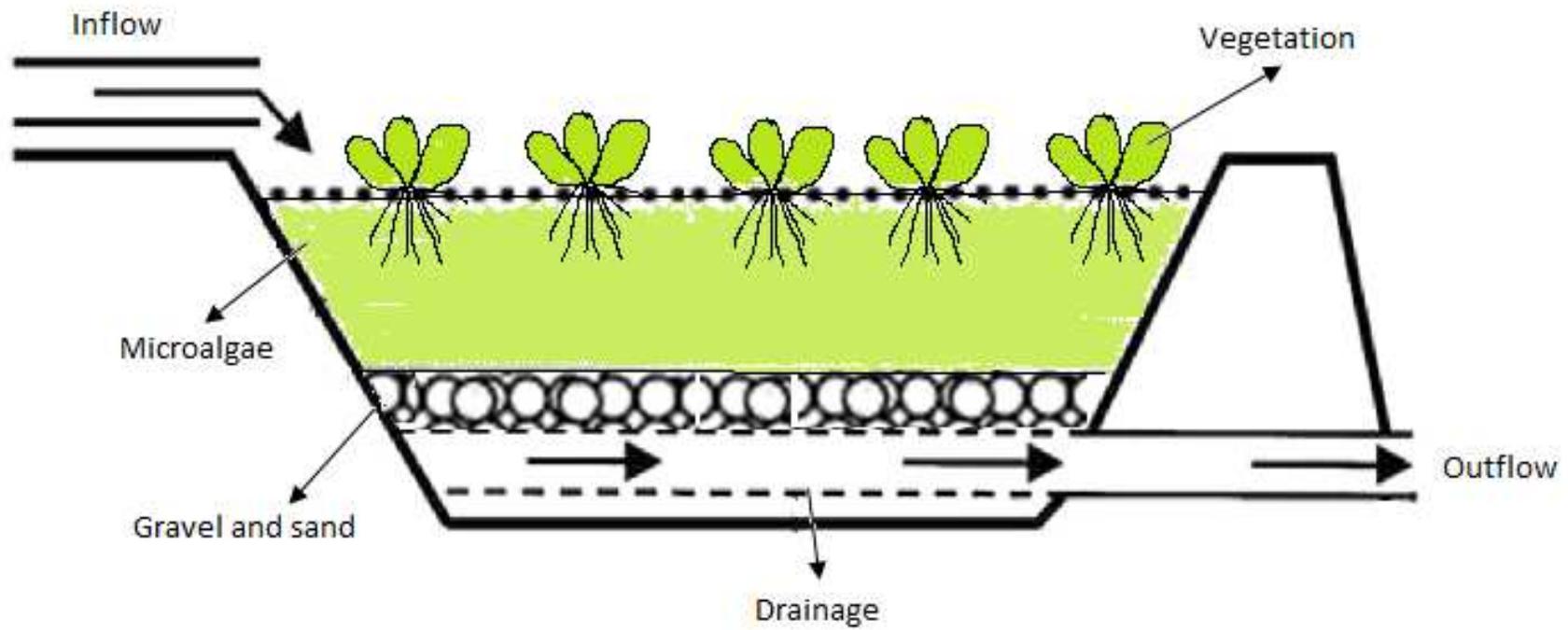


Figure 9: Hybrid microalgae-constructed wetland technique

Table 1: Physicochemical properties of PPCPs

PPCPs	Log Kow	pKa	Kd	Reference
17 α -Ethinylestradiol	3.67	10.4	13820	Xue et al., 2010
17 β -Estradiol	4.01	10.4	24350	Xue et al., 2010
Acetaminophen	0.27	9.4	6.7 \pm 6.2	Radjenović et al., 2009
Atenolol	0.1-0.57	9.4	95 \pm 60	Radjenović et al., 2009
Carbamazepine	2.25	7	314 \pm 205	Radjenović et al., 2009
Clofibrac acid	2.57	3.18	4.8 \pm 2.5	Ternes et al., 2004
Diazepam	2.83	3.3	44 \pm 26	Ternes et al., 2004
Diclofenac	4.02	4.51	459 \pm 32	Ternes et al., 2004
Erythromycin	2.48	8.88	309 \pm 271	Radjenović et al., 2009
Estrone	2.25	10.4	20240	Xue et al., 2010
Galaxolide	5.9	-	4920 \pm 2080	Ternes et al., 2004
Gemfibrozil	4.77	4.75	23 \pm 23	Radjenović et al., 2009
Ibuprofen	3.79	4.91	9.5 \pm 3.1	Radjenović et al., 2009
Ketoprofen	3	4.45	226 \pm 180	Radjenović et al., 2009
Naproxen	3.1	4.15	35.5 \pm 18.4	Fernandez-Fontaina et al., 2013
Sulfamethoxazole	0.48	5.5	3.2 \pm 4.5	Radjenović et al., 2009
Tonalide	5.7	-	5300 \pm 1900	Ternes et al., 2004

Table 2: Microalgal removal of PPCPs from different matrixes of water and mechanisms involved

Contaminant (PPCPs)	Microalgae	Water matrix and technique specifications	Mechanisms involved	Removal (%)	Reference
Metronidazole	<i>C. vulgaris</i>	Culture medium (BG 11) was spiked with 5µM metronidazole for 18 days	Adsorption	100	Hena et al., 2020
Florfenicol	<i>Chlorella</i> sp.	Culture medium (BG 11) was spiked with 46 mg/L of Florfenicol	Bioaccumulation, Biodegradation and adsorption	97	Song et al., 2019
Ciprofloxacin	Algae-bacterial consortium	Wastewater spiked with 2 mg/L of ciprofloxacin. Experiments were conducted for 7 days at HRAP with a suspended culture of an algae-bacterial consortium	Photodegradation and sorption	97.46	Hom-Diaz et al., 2017a
Acetaminophen	Microalgae	Experiments were conducted with toilet wastewater for total 20 days.	Biodegradation, photo-biodegradation	>99	Hom-Diaz et al., 2017b
Ibuprofen				>98	
Naproxen				69	
Salicylic acid				72	
Enrofloxacin	<i>Scenedesmus obliquus</i>	Experiments were conducted with five pure strains and consortium of them separately in BBM culture medium spiked with 1mg/L enrofloxacin for 11 days incubation, while the consortium was prepared with an equal amount of all microalgae with final OD ₆₈₀ of ~1.0	Bioaccumulation, bioadsorption, and/or biodegradation	23	Xiong et al., 2017b
	<i>Chlamydomonas mexicana</i>			25	
	<i>Chlorella vulgaris</i>			26	
	<i>Ourococcus multisporus</i>			18	
	<i>Micractinium resseri</i>			20	
	Microalgal consortium			26	
Tetracycline	Microalgae-bacterial consortium	Artificial wastewater was treated with a microalgae-bacterial consortium in HRAP for 7 days	Indirect photodegradation and sorption	99	Norvill et al., 2017
Methyl parathion	<i>Fischerella</i> sp.	Culture medium (BG 11) was spiked with 20 mg/L methyl parathion for 4 days	Sorption and biodegradation	>80	Tiwari et al., 2017
Trimethoprim	<i>Nannochloris</i> sp.	F/2 algal culture media was spiked with target compound and treated with <i>Nannochloris</i> sp. for 14 days.	Non-degradable	0	Bai and Acharya 2017
Sulfamethoxazole			Photodegradation	32	
Triclosan			Sorption and photodegradation	100	
Diclofenac	<i>Chlorella sorokiniana</i>	Anaerobically treated wastewater spiked with	Biodegradation, photolysis, and sorption	45	De Wilt et al., 2016
Ibuprofen				99	
Paracetamol				99	
Metoprolol				38	
Carbamazepine				30	
Trimethoprim				55	
7-amino cephalosporanic acid	<i>Chlorella</i> sp.	The experiments were conducted in a synthetic medium; BM, BBM, and BG-11, respectively, for 24h spiked with 100mg/L 7-amino cephalosporanic acid.	Hydrolysis, photolysis, and biosorption	76.2	Guo et al., 2016
	<i>Chlamydomonas</i> sp.			69.3	
	<i>Mychonastes</i> sp.			64.9	
Cefradine	<i>Chlorella pyrenoidosa</i> and activated sludge	Water was spiked with 100 mg/L of antibiotics in separate flasks and incubated with microalgae later combined with activated sludge from wastewater treatment plant. Total time span for experiments	Sorption, hydrolysis, and photodegradation	89.9	Guo and Chen 2015
Cefalexin				94.9	
Ceftazidime				89.7	
Cefixime				100	

		were 48h. The experiments were conducted at lab scale				
β - estradiol	<i>Selenastrum capricornutum</i>	Microalgae were cultured in anaerobic digester centrate wastewater spiked with both hormones and incubate for 7 days.	Biodegradation and adsorption	100	Hom-Diaz et al., 2015	
17 α -ethinylestradiol	<i>Selenastrum capricornutum</i>			95		
β - estradiol	<i>Chlamydomonas reinhardtii</i>			100		
17 α -ethinylestradiol	<i>Chlamydomonas reinhardtii</i>			76		
17 α -estradiol	<i>Scenedesmus dimorphus</i>	Artificial wastewater was incubated with microalgae for 8 days	Biodegradation	85	Zhang et al., 2014	
17 β -estradiol				95		
Estrone				85		
Estriol				95		
17 α -ethinylestradiol	<i>Desmodesmus subspicatus</i>	Artificial wastewater was incubated with microalgae for 3 days	Adsorption and biodegradation	68	Maes et al., 2014	
Progesterone	<i>Scenedesmus obliquus</i>	Artificial wastewater spiked with 1.6 μ M hormones incubated separately with microalgae for 5 days	Biodegradation	95	Peng et al., 2014	
Progesterone				<i>Chlorella pyrenoidosa</i>		95
Norgestrel				<i>Scenedesmus obliquus</i>		95
Norgestrel				<i>Chlorella pyrenoidosa</i>		60
Sulfathiazole	<i>Spyrogira</i> sp.	Secondary effluent wastewater spiked with a mixture of six antibiotics with a final concentration of 200 μ g/L. The experiments were conducted with 20 days incubation of suspended cells of Spirogyra in secondary treated wastewater at lab-scale.	Biodegradation and indirect photodegradation	36	Garcia-Rodríguez et al., 2013	
Sulfapyridine				37		
Sulfamethazine				15		
Sulfamethoxazole			14	Photodegradation		
Tetracycline			89			
Oxytetracycline			93			
Norfloxacin	<i>Chlorella vulgaris</i>	Water spiked with 20 mg/L of norfloxacin. Experiments were conducted in lab-scale	Photodegradation	36.9	Zhang et al., 2012	

Table 3: Comparison between microalgal strains for removing PPCPs

PPCPs	Microalgae	Specific conditions	Removal (%)	References
Enrofloxacin	<i>Scenedesmus obliquus</i>	Cultures were developed in sterilized Bold's Basal Medium for 11 days under 40-50 $\mu\text{mol photon/m}^2\cdot\text{s}$ light intensity, at 27°C temperature, shaking with 150 rpm and light/dark cycle of 16:8h. The initial concentration of enrofloxacin was 1 mg/L. The consortium was prepared with an equal amount of all microalgae with final OD ₆₈₀ of ~1.0	23	Xiong et al., 2017b
	<i>Chlamydomonas mexicana</i>		25	
	<i>Chlorella vulgaris</i>		26	
	<i>Ourococcus multisporus</i>		18	
	<i>Micractinium resseri</i>		20	
	Consortium		26	
Naproxen	<i>Cymbella sp.</i>	The freshwater algae <i>Cymbella sp.</i> and <i>Scenedesmus quadricauda</i> were cultured in sterile D1 and BG11 medium and spiked with 1mg/L naproxen. The inoculum size was maintained with 1×10^5 cells mL. The culture was maintained for 30-day incubation.	97.1	Ding et al., 2017
	<i>Scenedesmus quadricauda</i>		58.8	
Salicylic acid	<i>Chlorella vulgaris</i>	Microalgal strains were cultured in Mann and Mayers medium with an initial inoculum size of about 3×10^6 cells mL, for 24h under 175 $\mu\text{mol photon/m}^2\cdot\text{s}$ light intensity, at 25°C temperature, with 7% CO ₂ and 250 rpm with 12:12 photoperiods. The initial concentration of each targeted compound was 25 mg/L.	>25	Escapa et al., 2017
	<i>Tetradesmus obliquus</i>		>93	
Paracetamol	<i>Chlorella vulgaris</i>		>21	
	<i>Tetradesmus obliquus</i>		>40	
7-amino cephalosporanic acid	<i>Chlorella sp.</i>	<i>Chlorella sp.</i> , <i>Chlamydomonas sp.</i> , and <i>Mychonastes sp.</i> , were developed in a synthetic medium; BM, BBM and BG-11 respectively for 24h under 200 $\mu\text{mol photon/m}^2\cdot\text{s}$ light intensity, at 26°C temperature, with 2.5% CO ₂ aeration. The initial OD ₆₈₀ of inoculum was 0.1, and the initial concentration of 7-amino cephalosporanic acid was 100 mg/L.	76.2	Guo et al., 2016
	<i>Chlamydomonas sp.</i>		69.3	
	<i>Mychonastes sp.</i>		64.9	
Carbamazepine	<i>Chlamydomonas mexicana</i>	The microalgae were cultured in Bold Basal Media in two different flasks at 27°C and 150 rpm, under 45-50 $\text{mmol photon/m}^2 \text{ s}$ for 10 days. The initial OD ₆₈₀ of inoculum was 1, and the initial concentration of carbamazepine was 1mg/L.	37	Xiong et al., 2016
	<i>Scenedesmus obliquus</i>		30	
Diclofenac	<i>Chlorella sorokiniana</i>	The cultures were cultivated in synthetic media at 25°C, under 175 $\mu\text{mol photon/m}^2 \text{ s}$, shaking with 250 rpm and light/dark cycle of 12:12h. The inoculum was maintained as 3×10^6 cells/mL, and the initial concentration of diclofenac was 25 mg/L.	70.01	Escapa et al., 2016
	<i>Chlorella vulgaris</i>		78.42	
	<i>Scenedesmus obliquus</i>		20.9	
Nonylphenol	<i>Chlorella vulgaris</i>	The cultures were cultivated in Bristol medium at 25°C, under 40 $\mu\text{mol photon/m}^2 \text{ s}$, shaking with 160	99	Gao et al., 2011
	<i>Chlorella sp. (1uoai)</i>		92	
	<i>Chlorella sp. (2f5aia)</i>		94	

	<i>Chlorella miniata</i>	rpm and light/dark cycle of 16:8 h for 7 days. The inoculum size corresponded to 1 mg/L chlorophyll a and the initial concentration of nonylphenol was 1 mg/L.	93			
Progesterone	<i>Scenedesmus obliquus</i>	The microalgae were cultivated in BG-11 medium at 25°C, under 3000 lux, shaking with 150 rpm and light/dark cycle of 12:12h for 5 days. The inoculum was maintained as 10 ⁶ cells/mL, and the initial concentration of target compounds was 1.6 µM.	>95	Peng et al., 2014		
	<i>Chlorella pyrenoidosa</i>		>95			
Norgestrel	<i>Scenedesmus obliquus</i>		~100			
	<i>Chlorella pyrenoidosa</i>		~60			
Acetaminophen (340 µg/L)	<i>Chlorella sorokiniana</i>		<i>Chlorella sorokiniana</i> was inoculated with 1.66×10 ⁶ cells/mL for the treatment of anaerobically treated wastewater at 35°C for 10 days under 68 µmol photon/m ² s with continuous illumination.		99	De Wilt et al., 2016
Carbamazepine (117 µg/L)					33	
Diclofenac (150 µg/L)		45				
Ibuprofen (320 µg/L)		100				
Metoprolol (180 µg/L)		38				
Trimethoprim (200 µg/L)		55				
Carbamazepine (0.130 µg/L)	<i>Chlamydomonas reinhardtii</i>	Filtered raw wastewater cultured with microalgae separately with inoculum size corresponding to 0.05 mg/L chlorophyll a, with 150 rpm, at 25°C under 60µmol photon/m ² .s light intensity for 12:12h light/dark cycle till 7 days.	12.3	Zhou et al., 2014		
	<i>Scenedesmus obliquus</i>		5.38			
	<i>Chlorella pyrenoidosa</i>		3.84			
	<i>Chlorella vulgaris</i>		10			
Ciprofloxacin (0.029 µg/L)	<i>Chlamydomonas reinhardtii</i>		79.3			
	<i>Scenedesmus obliquus</i>		79.3			
	<i>Chlorella pyrenoidosa</i>		75.86			
	<i>Chlorella vulgaris</i>		79.3			
Erythromycin (1.025 µg/L)	<i>Chlamydomonas reinhardtii</i>		85.95			
	<i>Scenedesmus obliquus</i>		63.90			
	<i>Chlorella pyrenoidosa</i>		74.43			
	<i>Chlorella vulgaris</i>		67.02			
Estrone (0.091 µg/L)	<i>Chlamydomonas reinhardtii</i>		84.61			
	<i>Scenedesmus obliquus</i>		87.91			
	<i>Chlorella pyrenoidosa</i>		87.91			
	<i>Chlorella vulgaris</i>		86.81			
Norfloxacin (0.032 µg/L)	<i>Chlamydomonas reinhardtii</i>	53.12				
	<i>Scenedesmus obliquus</i>	40.62				
	<i>Chlorella pyrenoidosa</i>	43.75				
	<i>Chlorella vulgaris</i>	50				
Ofloxacin (0.053 µg/L)	<i>Chlamydomonas reinhardtii</i>	52.83				
	<i>Scenedesmus obliquus</i>	45.28				

	<i>Chlorella pyrenoidosa</i>	45.28
	<i>Chlorella vulgaris</i>	43.39
Paracetamol (1.673 µg/L)	<i>Chlamydomonas reinhardtii</i>	88.46
	<i>Scenedesmus obliquus</i>	89.06
	<i>Chlorella pyrenoidosa</i>	93.54
	<i>Chlorella vulgaris</i>	93.06
Progesterone (0.011 µg/L)	<i>Chlamydomonas reinhardtii</i>	81.81
	<i>Scenedesmus obliquus</i>	81.81
	<i>Chlorella pyrenoidosa</i>	83.63
	<i>Chlorella vulgaris</i>	86.36
Roxithromycin (0.049 µg/L)	<i>Chlamydomonas reinhardtii</i>	93.87
	<i>Scenedesmus obliquus</i>	86.94
	<i>Chlorella pyrenoidosa</i>	92.04
	<i>Chlorella vulgaris</i>	89.80
Salicylic acid (62.510 µg/L)	<i>Chlamydomonas reinhardtii</i>	97.76
	<i>Scenedesmus obliquus</i>	98.28
	<i>Chlorella pyrenoidosa</i>	98.96
	<i>Chlorella vulgaris</i>	97.50
Sulfadiazine (0.028µg/L)	<i>Chlamydomonas reinhardtii</i>	73.92
	<i>Scenedesmus obliquus</i>	53.57
	<i>Chlorella pyrenoidosa</i>	57.14
	<i>Chlorella vulgaris</i>	66.07
Sulfadimethoxine (0.006 µg/L)	<i>Chlamydomonas reinhardtii</i>	50
	<i>Scenedesmus obliquus</i>	75
	<i>Chlorella pyrenoidosa</i>	60
	<i>Chlorella vulgaris</i>	68.33
Sulfametoxydiazine (0.027 µg/L)	<i>Chlamydomonas reinhardtii</i>	81.48
	<i>Scenedesmus obliquus</i>	87.03
	<i>Chlorella pyrenoidosa</i>	81.11
	<i>Chlorella vulgaris</i>	81.85
Sulfamethazine (0.056 µg/L)	<i>Chlamydomonas reinhardtii</i>	48.21
	<i>Scenedesmus obliquus</i>	17.85
	<i>Chlorella pyrenoidosa</i>	23.21
	<i>Chlorella vulgaris</i>	33.92
Triclocarban (0.057 µg/L)	<i>Chlamydomonas reinhardtii</i>	82.63
	<i>Scenedesmus obliquus</i>	98.59
	<i>Chlorella pyrenoidosa</i>	82.63
	<i>Chlorella vulgaris</i>	80.70
Triclosan (0.041 µg/L)	<i>Chlamydomonas reinhardtii</i>	57.56

	<i>Scenedesmus obliquus</i>		30.24	
	<i>Chlorella pyrenoidosa</i>		41.46	
	<i>Chlorella vulgaris</i>		52.19	
Trimethoprim (0.027 µg/L)	<i>Chlamydomonas reinhardtii</i>		37.03	
	<i>Scenedesmus obliquus</i>		18.51	
	<i>Chlorella pyrenoidosa</i>		29.62	
	<i>Chlorella vulgaris</i>		0.0	

Table 4: PPCPs removal by bacterial strains and mechanisms involved

Bacterial strain	PPCPs	Mechanisms involved	Reference
<i>Alcaligenes xylosoxidans</i> subsp. <i>denitrificans</i> TR1	Triclosan	Metabolic degradation	Meade et al. (2001)
<i>Pseudomonas putida</i> TriRY	Triclosan	Metabolic degradation	Meade et al. (2001)
<i>Pseudomonas aeruginosa</i> TJ1	17 β -estradiol	Metabolic degradation	Zeng et al. (2009)
<i>Delftia tsuruhatensis</i>	Acetaminophen	Metabolic degradation	De Gusseme et al. (2011)
<i>Pseudomonas aeruginosa</i>	Acetaminophen	Metabolic degradation	De Gusseme et al. (2011)
<i>Stenotrophomonas</i> sp. f1	Acetaminophen	Metabolic degradation	Zhang et al. (2013)
<i>Pseudomonas</i> sp. f2 and fg-2	Acetaminophen	Metabolic degradation	Zhang et al. (2013)
<i>Pseudomonas aeruginosa</i> HJ1012	Acetaminophen	Metabolic degradation	Hu et al. (2013)
<i>Pseudomonas</i> sp. CBZ-4	Carbamazepine	Metabolic degradation	Li et al. (2013)
Ammonia-oxidizing bacteria	Atenolol	Co-metabolic degradation	Sathyamoorthy et al., 2013
<i>Stenotrophomonas maltophilia</i> KB2	Naproxen	Metabolic degradation	Wojcieszyn´ska et al. (2014)
<i>Pseudomonas</i> sp. I-24	Iopromide	Co-metabolic degradation	Xu et al. (2014)
<i>Pseudomonas psychrophila</i> HA-4	Sulfamethoxazole	Metabolic degradation	Jiang et al. (2014)
<i>Variovorax</i> Ibu-1	Ibuprofen	Metabolic degradation	Murdoch and Hay (2015)
<i>Bacillus thuringiensis</i> B1	Ibuprofen	Co-metabolic degradation	Marchlewicz et al. (2016)
<i>Bacillus thuringiensis</i> B1	Naproxen	Co-metabolic degradation	Marchlewicz et al. (2016)
<i>Nitrososphaera gargensis</i>	Mianserin	Co-metabolic degradation	Men et al., 2016
<i>Nitrososphaera gargensis</i>	Ranitidine	Co-metabolic degradation	Men et al., 2016
<i>Ochrobactrum</i> sp. MC22	Triclocarban	Metabolic degradation	Sipahutar and Vangnai (2017)
Ammonia-oxidizing bacteria	Acyclovir	Co-metabolic and Metabolic degradation	Xu et al., 2017
Ammonia-oxidizing bacteria	Atenolol	Co-metabolic degradation	Xu et al., 2018
Ammonia-oxidizing bacteria	Sulfadiazine	Co-metabolic degradation	Wang et al., 2019
Ammonia-oxidizing bacteria	Tetracycline	Bioadsorption on bacterial EPS	Lengbehn et al., 2020
Ammonia-oxidizing bacteria	Sulfadiazine	Co-metabolic degradation	Wang et al., 2020
Ammonia-oxidizing bacteria	Cephalexin	Co-metabolic degradation	Wang et al., 2020

Table 5: Comparison between microalgal and microalgae-bacterial consortiums

	Microalgal consortium	Microalgae-bacterial consortium
Interactions	Cooperative and competitive interactions occur between different strains of microalgae	Cooperative and competitive interactions occur between different strains of microalgae as well as bacteria
Robustness	It shows more resistance to environmental fluctuations and invasion of foreign species than monoculture but less than microalgae-bacterial consortiums.	It shows more resistance to environmental fluctuations and invasion of foreign species than microalgal consortiums.
Specificity	It shows a broader spectrum of contaminants removal efficiency than mono-algal culture, but less efficient than microalgae-bacterial consortiums.	It shows better and broader removal efficiency of PPCPs than microalgal consortium
System substitution	It can substitute the tertiary treatment step of a wastewater treatment plant	It can substitute secondary and tertiary steps of a wastewater treatment plant
Space requirement	It is generally less compact than microalgae-bacterial consortiums since it substitutes tertiary step of wastewater treatment plant with microalgae mediated reactor.	Microalgae-bacterial consortiums are more compact than conventional mono-algal and microalgal consortium mediated wastewater treatment plant since it replaces two steps by one component.
Cost	Although it can mitigate the atmospheric CO ₂ , aeration needs an extra cost.	This combination reduces the oxygenation and CO ₂ supply cost for bacteria and microalgal growth, respectively.
Feedstock	The harvested biomass can be used for fertilizers, biofuel production, and land rehabilitation.	The harvested biomass is not fit for biofuel production but can be used in land rehabilitation more efficiently than microalgae consortium.

Table 6: Toxicity of PPCPs on microalgae

PPCPs	Microalgae	EC50	Observation	Reference
Sulfadiazine	<i>Selenastrum capricornutum</i>	2.19 mg /L	-	Eguchi et al., 2004
Chloramphenicol	<i>Isochrysis galbana</i>	-	<i>Isochrysis galbana</i> was not remarkably affected by erythromycin and chloramphenicol up to 12 mg/L; however, furazolidone inhibited the growth even at 0.5 mg/L	Campa-Córdova et al., 2006
Erythromycin	<i>Isochrysis galbana</i>	-		
Furazolidone	<i>Isochrysis galbana</i>	<0.5 mg/L		
Chloramphenicol	<i>Chaetoceros gracilis</i>	>3 mg/L		
Erythromycin	<i>Chaetoceros gracilis</i>	>0.5 mg/L	<i>Chaetoceros gracilis</i> was found more sensitive towards chloramphenicol and erythromycin than <i>Isochrysis galbana</i> .	
Furazolidone	<i>Chaetoceros gracilis</i>	<0.5 mg/L		
Ibuprofen	<i>Navicula</i> sp.	>10 mg/L	0.1–1 mg/L cause an increase in growth rate, chlorophyll a, and carotenoids; however, as high dose as 10 mg/L ibuprofen causes a decrease in growth, chlorophyll, and carotenoids.	Ding et al., 2017
Ibuprofen	<i>Chlorella vulgaris</i>	82.25 mg/L	EC50value was tested for 48 h; however, the EC50 value increased with an increase in exposure time.	Geiger et al., 2016
Carbamazepine	<i>Dunaliella tertiolecta</i>	53.2 mg/L	EC50value was observed for 24 h. Concentrations of more than 50 mg/L caused a significant increase of MDA content after exposure of 24 h. 10 mg/L and more carbamazepine after 24 h of exposure caused increased in carotenoids through a decrease in chlorophyll a.	Tsiaka et al., 2013
Sulfadiazine	<i>Scenedesmus obliquus</i>	81.6 mg/L	At EC50 concentration SOD, CAT and MDA increased by 1.2, 3.8, and 5 fold respectively to its control culture.	Wang et al., 2017
Sulfamethoxazole	<i>Isochrysis galbana</i> ,		Sulfamethoxazole was noticed more toxic than trimethoprim for all three marine algae, while <i>Nannochloropsis oculata</i> was the most sensitive species of three. Photo-degradation products of sulfamethoxazole are more toxic and less biodegradable in seawater than the products of trimethoprim.	Teixeira and Granek (2017)
Sulfamethoxazole	<i>Chaetoceros neogracile</i>			
Sulfamethoxazole	<i>Nannochloropsis oculata</i>			
Trimethoprim	<i>Isochrysis galbana</i> ,			
Trimethoprim	<i>Chaetoceros neogracile</i>			
Trimethoprim	<i>Nannochloropsis oculata</i>			
Carbamazepine	<i>Trebouxia</i> TR9		<i>Trebouxia</i> TR9 and <i>Asterochloris erici</i> were isolated from lichen. The toxicity of tested analgesics was analyzed by cell aggregation and optical dispersion. <i>Trebouxia</i> TR9 shows large aggregation, while <i>Asterochloris erici</i> exhibited either no or two cell	Domínguez-Morueco et al., (2014)
Carbamazepine	<i>Asterochloris erici</i>			
Diclofenac	<i>Trebouxia</i> TR9			
Diclofenac	<i>Asterochloris erici</i>			

			aggregation. The observed least effective concentration for both microalgae in optical dispersion was 0.005µg/L for carbamazepine and 0.01µg/L for diclofenac.			
Tylosin	<i>Cylindrotheca closterium</i>	0.27 mg/L	Tylosin had the most negative effect, followed by lincomycin and ciprofloxacin. The EC50 values are obtained when treated as a single pollutant in culture. In binary mixture, 1.0 TU (0.5 EC50 of each compound) showed additive toxicity, less than 1.0 was synergistic, and higher than 1.0 was antagonistic in their mode of action.	Hagenbuch and Pinckney (2012)		
Lincomycin	<i>Cylindrotheca closterium</i>	14.2 mg/L				
Ciprofloxacin	<i>Cylindrotheca closterium</i>	55.43 mg/L				
Tylosin	<i>Navicula ramosissima.</i>	0.96 mg/L				
Lincomycin	<i>Navicula ramosissima.</i>	11.1 mg/L				
Ciprofloxacin	<i>Navicula ramosissima.</i>	72.12 mg/L				
Amoxicillin	<i>Pseudokirchneriella subcapitata</i>	>1500 mg/L	In general, <i>Anabaena</i> sp. CPB4337 was found more sensitive towards most of the antibiotics studied except tetracycline, which has a long record of being more toxic to green algae. However, erythromycin was the most toxic among all five antibiotics for both species. In mixed toxic effect, the combination of erythromycin and tetracycline presented more than 1 risk quotient, reflecting a potential ecological risk for microalgae.	Gonzalez-Pleiter et al., 2013		
Erythromycin	<i>Pseudokirchneriella subcapitata</i>	0.35 mg/L				
Levofloxacin	<i>Pseudokirchneriella subcapitata</i>	120 mg/L				
Norfloxacin	<i>Pseudokirchneriella subcapitata</i>	80 mg/L				
Tetracycline	<i>Pseudokirchneriella subcapitata</i>	3.31 mg/L				
Amoxicillin	<i>Anabaena</i> sp. CPB4337	56.3 mg/L				
Erythromycin	<i>Anabaena</i> sp. CPB4337	0.022 mg/L				
Levofloxacin	<i>Anabaena</i> sp. CPB4337	4.8 mg/L				
Norfloxacin	<i>Anabaena</i> sp. CPB4337	5.6 mg/L				
Tetracycline	<i>Anabaena</i> sp. CPB4337	6.2 mg/L				
Azithromycin	<i>Pseudokirchneriella subcapitata</i>	0.005 mg/L			Protein synthesis inhibitors antibiotics such as florfenicol, doxycycline, oxytetracycline, and azithromycin in bacteria inhibit the growth of microalgae due to disturbance in the synergistic effect of bacteria and microalgae. In contrast, the cell wall inhibitors antibiotics such as amoxicillin and cefotaxime showed relatively less toxicity towards microalgae. All EC50 values were calculated for 48 h exposure of compounds.	Fu et al., 2017
Doxycycline	<i>Pseudokirchneriella subcapitata</i>	0.846 mg/L				
Florfenicol	<i>Pseudokirchneriella subcapitata</i>	3.047mg/L				
Oxytetracycline	<i>Pseudokirchneriella subcapitata</i>	1.608 mg/L				
Sulfamonomethoxine	<i>Pseudokirchneriella subcapitata</i>	2.691 mg/L				
Ciprofloxacin	<i>Pseudokirchneriella subcapitata</i>	9.210mg/L				
Metronidazole	<i>Pseudokirchneriella subcapitata</i>	152.403 mg/L				
Norfloxacin	<i>Pseudokirchneriella subcapitata</i>	56.457 mg/L				
Ofloxacin	<i>Pseudokirchneriella subcapitata</i>	6.878 mg/L				
Rifampicin	<i>Pseudokirchneriella subcapitata</i>	96.694 mg/L				
Cefotaxime	<i>Pseudokirchneriella subcapitata</i>	488.110 mg/L				

Amoxicillin	<i>Pseudokirchneriella subcapitata</i>	539.874 mg/L		
Quinocetone	<i>Pseudokirchneriella subcapitata</i>	2.321mg/L		
Ciprofloxacin	Marine periphytic algae and bacteria	0.162mg/L	Sulfamethoxazole stimulated 75% increase in total pigment content at 0.001 mg/L concentration, which decreased with increasing concentration and restored again at 0.759 mg/L. It was noticed that there was an increase in algal biomass with an increase of pigment without any major shifts in the microbial community.	Johansson et al., 2014
Sulfamethoxazole	Marine periphytic algae and bacteria	0.271mg/L		
Ibuprofen	<i>Chlorella vulgaris</i>	<100mg/L	All compounds showed EC50 less than 100 mg/L after exposure for 96h. 2,4-di- chlorophenol exhibited the highest toxicity towards <i>C. vulgaris</i> and followed by ciprofloxacin, 3-chlorophenol, and ibuprofen. Ibuprofen has shown the least toxic effect on <i>C. vulgaris</i> . A mixture of compounds showed higher toxicity than individuals.	Geiger et al., 2016
Ciprofloxacin	<i>Chlorella vulgaris</i>	<100mg/L		
Clotrimazole	Natural microalgal communities (periphyton)	<0.003mg/L	Clotrimazole hinders in 14 α -demethylase-dependent sterol synthesis and causes to accumulate precursors (31-norlanosterol and obtusifoliol) in cells, which are not found in control culture. 1.74 μ g/L clotrimazole can cause 64% attenuation in total sterol formation and chlorophyll a in microalgae. However, 0.003-0.034 mg/l caused a severe reduction in microalgal community growth.	Porsbring et al., 2009
Ampicillin	<i>Pseudokirchneriella subcapitata</i>	PNEC till 2000 mg/L	The binary mixtures showed synergism at concentrations below 10 mg/L. EC50 of all binary mixtures come in between 0.48-5.95 mg/L. Ampicillin and amoxicillin do not show any significant changes with green algae up to 2000 mg/L; however, these have been reported as toxic for cyanobacteria.	Magdaleno et al., 2015
Amoxicillin	<i>Pseudokirchneriella subcapitata</i>	PNEC till 2000 mg/L		
Cephalotin	<i>Pseudokirchneriella subcapitata</i>	>600 mg/L		
Ciprofloxacin	<i>Pseudokirchneriella subcapitata</i>	11.3 mg/L		
Gentamycin	<i>Pseudokirchneriella subcapitata</i>	19.2 mg/L		
Vancomycin	<i>Pseudokirchneriella subcapitata</i>	724 mg/L		
Carbamazepine	<i>Scenedesmus obliquus</i>	54.60 mg/L	The EC50 values are reported after 6 days of exposure. Carbamazepine has been proved to be less toxic for a short duration (0-144 h) on both green algae; however, exposure for a longer time (5-30 days) demonstrated higher toxicity.	Zhang et al., 2012
Carbamazepine	<i>Chlorella pyrenoidosa</i>	33.11 mg/L		

			With time the chlorophyll content decreased even at as low as 0.5 mg/L of carbamazepine. CAT activity of <i>Scenedesmus obliquus</i> was found sensitive towards carbamazepine than <i>C. pyrenoidosa</i> , whereas it was opposite in the case of SOD, where <i>C. pyrenoidosa</i> demonstrated its vulnerability than <i>S. obliquus</i> .	
5-Fluorouracil	<i>Pseudokirchneriella subcapitata</i>	0.13 mg/L	5-Fluorouracil shown the highest toxicity to <i>Pseudokirchneriella subcapitata</i> among all four studied anti-cancer drugs, while cisplatin inhibited the growth of <i>Synechococcus leopoliensis</i> most as an individual pollutant. However, the toxicity of binary mixture 5-Fluorouracil and cisplatin was found more than expected due to their synergistic interaction. 5-Fluorouracil interferes with repairing DNA adducts and cross-links induces by cisplatin. Cisplatin with etoposide behaves antagonistically with both microalgae due to the interaction of cisplatin with etoposide, which decreases the toxicity of cisplatin towards microalgae.	Brezovsek et al., 2014
Cisplatin	<i>Pseudokirchneriella subcapitata</i>	1.52 mg/L		
Etoposide	<i>Pseudokirchneriella subcapitata</i>	30.43 mg/L		
Imatinib mesylate	<i>Pseudokirchneriella subcapitata</i>	2.29 mg/L		
5-Fluorouracil	<i>Synechococcus leopoliensis</i>	1.20 mg/L		
Cisplatin	<i>Synechococcus leopoliensis</i>	0.67 mg/L		
Etoposide	<i>Synechococcus leopoliensis</i>	PNEC till 351 mg/L		
Imatinib mesylate	<i>Synechococcus leopoliensis</i>	5.36 mg/L		
Ciprofloxacin	<i>Chlamydomonas mexicana</i>	65 mg/L	The EC50 values are reported after 96 h of exposure. SOD and MDA significantly increased in the exposure of ciprofloxacin.	Xiong et al., 2017a
Enrofloxacin	<i>Scenedesmus obliquus</i>	9.86 mg/L	The EC50 values are reported after 96 h of exposure. The chlorophyll content of <i>Micractinium resseri</i> and <i>Chlamydomonas mexicana</i> steadily increased with an increase in the concentration of enrofloxacin; however, <i>O. multisporus</i> , <i>Scenedesmus obliquus</i> , and <i>Chlorella vulgaris</i> showed opposite effect. The carotenoid of all microalgae increased with an increase of enrofloxacin concentration, while in <i>C. vulgaris</i> it increased first and followed by decrement. The high concentration of enrofloxacin (50-100 mg/L) induced the MDA in <i>M. resseri</i> and <i>C. vulgaris</i> significantly, whereas <i>S. obliquus</i> and <i>C. mexicana</i> showed an insignificant increase and in <i>O. multisporus</i> MDA decreased with increase in enrofloxacin	Xiong et al., 2017b
Enrofloxacin	<i>Chlamydomonas mexicana</i>	10.76 mg/L		
Enrofloxacin	<i>Chlorella vulgaris</i>	12.20 mg/L		
Enrofloxacin	<i>Ourococcus multisporus</i>	14.98 mg/L		
Enrofloxacin	<i>Micractinium resseri</i>	12.03 mg/L		

			concentration.	
7-amino cephalosporanic acid	<i>Chlorella sp.</i>	--	At 100 mg/L concentration, the biomass of <i>Chlorella sp.</i> , <i>Chlamydomonas sp.</i> , and <i>Mychonastes sp.</i> , were decreased by 12, 11.7, and 9.6% in comparison with control culture, which concluded that the antibiotic 7-amino cephalosporanic acid was least toxic for <i>Mychonastes sp.</i> The toxicity was also determined in terms of lipid accumulation. The results confirmed that even at 100 mg/L concentration of antibiotics, there were no changes in lipid content.	Guo et al., 2016
7-amino cephalosporanic acid	<i>Chlamydomonas sp.</i>	--		
7-amino cephalosporanic acid	<i>Mychonastes sp.</i>	--		
Carbamazepine	<i>Chlamydomonas mexicana</i>	797 mg/L	The EC50 values were reported for 96 h of exposure. The total chlorophyll and carotenoids content of <i>Chlamydomonas mexicana</i> increase with an increase in the concentration of carbamazepine while chlorophyll decreases but carotenoids slightly increase in <i>Scenedesmus obliquus</i> with an increase in the concentration of target compound. At high concentrations (above EC50), the SOD activity decreases in both microalgae.	Xiong et al., 2016
Carbamazepine	<i>Scenedesmus obliquus</i>	149 mg/L		
Naproxen	<i>Cymbella sp.</i>	102.76 mg/L	The EC50 values were reported for 72 h of exposure. Chlorophyll a and carotenoids almost remain the same till 50 mg/L concentration of naproxen; however, it decreases significantly at 100 mg/L. SOD increases till 1mg/L then followed by gradual low enzyme activity for both microalgae, while CAT increased for <i>Cymbella sp.</i> from 10mg/L and onwards, though <i>S. Quadricauda</i> showed consistency till 50 mg/L but decrease at high concentration of 100 mg/L.	Ding et al., 2017
Naproxen	<i>Scenedesmus quadricauda</i>	101.45 mg/L		

Table 7: Advantages and limitations of techniques used for suspended and immobilized microalgal mediated wastewater treatment

Suspended culture technique			Immobilised culture technique		
	Advantages	Limitations		Advantages	Limitations
High rate algal pond	<ul style="list-style-type: none"> * It costs less in installation, scaling-up, as well as maintenance with simple operational steps. * Volatilization mechanism of PPCPs removal is high. 	<ul style="list-style-type: none"> * Light can only be utilized from top of the surface; to increase the light utilization efficiency pond should be shallow and large in area, which uses large land area and paddlewheel to circulate the culture. * Since it is an open system, it has a high risk of contamination, high evaporation, and culture parameter cannot be controlled. * Harvesting is the most energy-consuming step. 	Algal turf scrubber	<ul style="list-style-type: none"> * It costs less in installation, scaling-up, as well as maintenance with simple operational steps. * High evaporation favors the volatilization mechanism of PPCPs removal. * Harvesting is easy. 	<ul style="list-style-type: none"> * Only surface cells can utilize light efficiently, and those which are embedded inside, start losing the capability to take part in indirect light photodegradation. * To increase the efficiency of the technique, the turf is supposed to be thin and large in area, which consequently covers a large area of land.
Stirred-tank Algal Photo-bioreactor	<ul style="list-style-type: none"> * Optimization and maintenance of culture parameter is easy. * Since contamination is low so biomass productivity is high. * It requires less space than high rate algal pond. 	<ul style="list-style-type: none"> * It costs more in installation, scaling-up, and maintenance. * Operation is complicated. * Poor light utilization efficiency. * Harvesting is not cost-effective. 	Rotating algae biofilm photo-reactor	<ul style="list-style-type: none"> * It requires small space and can work with a deep tank since every rotational disk gets a chance to be exposed in light periodically. * Harvesting is easy. * It has high gas transfer efficiency. * Scaling-up and maintenance are easy. 	<ul style="list-style-type: none"> * It consumes high energy in rotating disk. * Poor in controlling species; since the system is open hence contamination is high. * Gradual increase in biomass causes complexity in the rotational pattern, which needs to supervise constantly.
Plane algal Photo-bioreactor	<ul style="list-style-type: none"> * The closed system of plane algal photo-bioreactor facilitates high light utilization efficiency, * Better control on culture conditions, * Low risk of 	<ul style="list-style-type: none"> * Expensive installation * Required optimization of parameters during scaling-up causes complication in operation and makes it unsuitable for wastewater treatment. * Harvesting is not 	Plane algal-biofilm photo-reactor	<ul style="list-style-type: none"> * It possesses high light utilization efficiency. * It shows better control of culture conditions. * Low risk of contamination. * High biomass production. 	<ul style="list-style-type: none"> * Expensive installation. * Required optimization of parameters during scaling-up causes complication in operation and makes it unsuitable for wastewater treatment.

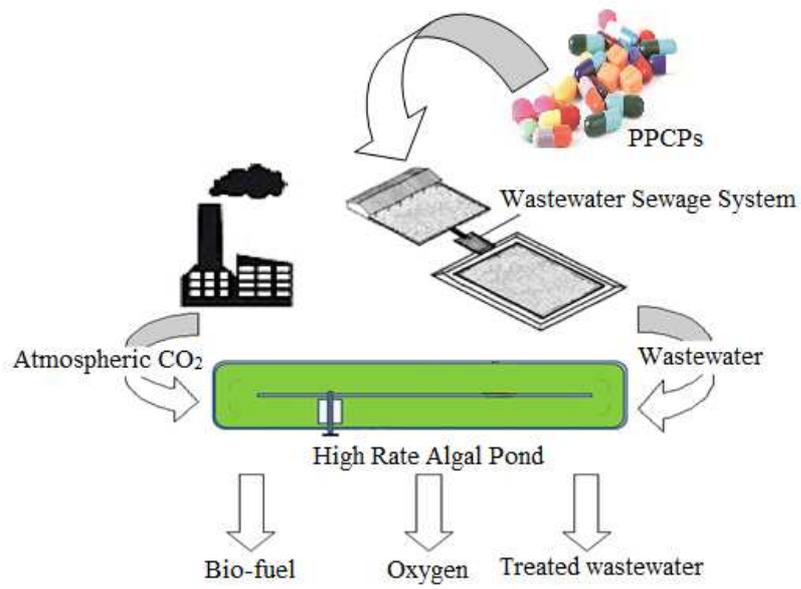
	contamination. * High biomass production.	cost-effective.		* It is more suitable for the production of valuable biomass products. * Harvesting of biomass is easy.	* Requires a large space.
Tubular algal Photo-bioreactor	* The closed system of tubular algal photo-bioreactor makes it possible for better control on culture parameters. * High biomass production is due to low risk of contamination.	* Installation is expensive. * Aeration decrease with the length of tubes, which requires multiple aeration ports. * Cleaning and scaling ups are challenging. * Harvesting is costly.	Tubular algal biofilm Photo-reactor	* Developed biofilm on tubular wall causes light to get utilized efficiently by microalgae. * Closed system prevents it from getting contaminants.	* It causes a high cost for installation. * This system inhibits the direct photodegradation. * Cleaning of the tube is difficult.
Algal membrane Photo-bioreactor	* Harvest and scaling-up of the system are easy. * Suitable for wastewater treatment. * Membrane provides a second line of PPCPs removal from wastewater. * High biomass production is due to the membrane.	* Installation is costly and complicated to operate. * Membrane fouling is a serious problem.			

Table: 8. Comparative study between algae mediated WWTPs and CWWTPs

Contaminants (mg/L)	Microalgae mediated WWTPs			CWWTPs		
	Influent (µg/L)	Removal (%)	References	Influent (µg/L)	Removal (%)	References
Antibiotics						
Erythromycin	0.12-1.03	37 to 86	Zhou et al., 2014; Ruhmland et al., 2015	0.12 – 10.0	0 to 82.5	Zhou et al., 2014; Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Santos et al., (2009); Terzić et al., (2008)
Sulfamethoxazole	0.051-0.32	-31 to 30	Zhou et al., 2014; Ruhmland et al., 2015	0.003 – 0.98	-91 to 88.9	Zhou et al., 2014; Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Santos et al., (2009); Terzić et al., (2008)
Trimethoprim	0.027-200	-3 to 93	De-Wilt et al., 2016; Zhou et al., 2014; Ruhmland et al., 2015	0.027 – 6.80	0 to 83.7	Zhou et al., 2014; Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Santos et al., (2009); Terzić et al., (2008)
Anti-inflammatory						
Acetaminophen	1.67- 340	88-99	Zhou et al., 2014; Matamoros et al., 2016; De-Wilt et al., 2016	1.6-56.9	98.7-100	Zhou et al., 2014; Behera et al., (2011); Gracia-Lor et al., (2012); Santos et al., (2009); Terzić et al., (2008)
Carbamazepine	0.13-117	0 - 62	Ruhmland et al., 2015; Matamoros et al., 2016; De-Wilt et al., 2016; Matamoros et al., 2015; Zhou et al., 2014	0.04-3.78	0 – 62.3	Behera et al. (2011); Kasprzyk-Hordern et al. (2009); Loos et al., (2013); Santos et al., (2009); Terzić et al., (2008)
Diclofenac	0.36 - 150	21 - 92	Ruhmland et al., 2015; Matamoros et al., 2015; Matamoros et al., 2016; Hijosa-Valsero et al., 2010; De-Wilt et al., 2016	0.001-94.2	0- 81.4	Behera et al., (2011); Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Loos et al., (2013); Santos et al., (2009); Stamatis and Konstantinou (2013)
Ibuprofen	2.42- 320	55-100	Matamoros et al., 2016; Hijosa-Valsero et al., 2010; De-Wilt et al., 2016	0.004-603	72-100	Behera et al., (2011); Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Loos et al., (2013); Santos et al., (2009); Stamatis and

						Konstantinou (2013); Stamatis et al., (2010)
Ketoprofen	0.82 – 4.25	50-95	Matamoros et al., 2015	0.004 – 8.56	10.8 -100	Behera et al., (2011); Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Loos et al., (2013); Terzić et al., (2008)
Naproxen	0.05 – 10.58	32 - 85	Matamoros et al., 2016; Hijosa-Valsero et al., 2010	0.002-52.9	43.3-98.6	Behera et al., (2011); Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Terzić et al., (2008); Zorita et al., (2009).
Salicylic acid	0.82 – 77.80	92 - 99	Zhou et al., 2014; Hijosa-Valsero et al., 2010; Matamoros et al., 2016	0.58-63.7	89.6-100	Zhou et al., 2014; Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Stamatis and Konstantinou (2013)
Lipid regulator						
Bezafibrate	0.21 – 0.50	24 - 79	Ruhmland et al., 2015	0.05 – 1.39	9.10 – 70.5	Behera et al., (2011); Gracia-Lor et al., (2012); Kasprzyk-Hordern et al., (2009); Loos et al., (2013); Santos et al., (2009); Terzić et al., (2008)
Clofibrilic acid	0 – 21.0	-1 to 30	Zhou et al., 2014	0 – 21.0	0 – 93.6	Zhou et al., 2014; Behera et al., (2011); Kasprzyk-Hordern et al., (2009); Loos et al., (2013); Santos et al., (2009); Terzić et al., (2008)
Stimulant						
Caffeine	3.66 – 18.4	15 - 99	Matamoros et al., 2016; Matamoros et al., 2015; Hijosa-Valsero et al., 2010	0.22 - 209	49.9 – 99.6	Behera et al., (2011); Loos et al., (2013); Santos et al., (2009)
β- Blocker						
Atenolol	0.02 – 0.21	43 - 95	Ruhmland et al., 2015	0.1 – 33.1	0 – 85.1	Alder et al., (2010); Behera et al., (2011); Kasprzyk-Hordern et al., (2009); Santos et al., (2009); Terzić et al., (2008)
Metoprolol	1.8 - 180	38 - 92	Ruhmland et al., 2015; De-Wilt et al., 2016	0.002 – 1.52	3 – 56.4	Alder et al., (2010); Behera et al., (2011); Kasprzyk-Hordern et al., (2009); Santos et al., (2009)
Hormones						
Estrone	0.042-1	52-84	Shi et al., 2010; Hom-Diaz et al.,	0.01-0.17	74.8-90.6	Behera et al., (2011); Janex-Habibi et al., (2009); Nie et al., (2012); Zorita et al.,

			2015			(2009).
Estradiol	0.03-1	54- 100	Shi et al., 2010; Hom-Diaz et al., 2015	0.002- 0.05	92.6-100	Behera et al., (2011); Janex-Habibi et al. (2009); Nie et al., (2012); Zorita et al., (2009)
17 α -Ethinylestradiol	0.01-5000	76-95	Shi et al., 2010; Hom-Diaz et al., 2015	0.001- 0.003	43.8-100	Janex-Habibi et al., (2009); Nie et al., (2012); Zorita et al., (2009)
<i>Fragrance</i>						
Galaxolide	1.47-1.58	47-97	Matamoros et al., 2016	0.03-25	87.8	Santos et al., (2009); Terzić et al., (2008)
Tonalide	0.84-0.86	51-90	Matamoros et al., 2016	0.05-1.93	84.7	Santos et al., (2009); Terzić et al., (2008)
<i>Disinfectant</i>						
Triclosan	0.042-0.28	31-95	Matamoros et al., 2016; Zhou et al., 2014	0.03-23.9	71.3-99.2	Behera et al., (2011); Kumar et al., (2010); Martin et al., (2010); Loos et al., (2013); Pothitou and Voutsas (2008)
<i>Surfactant</i>						
Nonylphenol	0-1.79	-54 to 80	Gao et al., 2011; Matamoros et al., 2016	0.03-101.6	21.7-99	Janex-Habibi et al., (2009); Martin et al., (2010); Nie et al., (2012); Rosal et al., (2010); Pothitou and Voutsas (2008); Terzić et al., (2008)
Octylphenol	0.05-5	58-99	Zhou et al., 2014	0.2-8.7	0-96.7	Janex-Habibi et al., (2009); Kasprzyk-Hordern et al., (2009); Martin et al., (2010); Nie et al., (2012); Pothitou and Voutsas (2008); Terzić et al., (2008)



Graphical Abstract