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Microalgae based wastewater treatment for the removal of emerging contaminants: A review of challenges and opportunities

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A B S T R A C T

Emerging contaminants (ECs) are attracting considerable attention due to their potential risk to human health and ecosystem. The past decade has seen a renewed importance in microalgae for bioremediating ECs from wastewater. Several proof of concept studies have been published to rationalize the use of microalgae for bioremediating ECs at laboratory conditions. However, there has been little discussion on real world application of microalgae for bioremediation purposes. This review paper sheds new light on obstacles faced in commercial use of microalgae for bioremediating ECs. The presence of multiple ECs and their affinity for microalgae raise some concern about the validity of laboratory findings. Dynamic changes of environmental conditions and accidental contaminations can significantly influence rate of bioremediation in large scale system. Appropriate pilot scale studies may bridge the gap between the laboratory scale studies and commercial scale applications. Considering the fate of ECs in microalgal cell, more research is needed in the direction of biodegradation assisted bioremediation due to end use of algal biomass. In fact, a wide range of extremophile microalgae species can be screened for selective removal of ECs. In-depth investigations are needed to characterize the quality of wastewater effluent after the separation of microalgal biomass. Notably, life cycle analysis related studies are needed to look at the viability of microalgae assisted bioremediation of ECs.

1. Introduction

Emerging contaminants (ECs) or "chemicals of emerging concern" are attracting considerable interest due to increased awareness of their risks to human health and aquatic biota [12,32]. The most prevalent ECs include, but not limited to pharmaceuticals and personal care products (PPCPs), endocrine disrupting compounds (EDCs), perfluorinated compounds (PFCs), surfactants, gasoline additives, disinfection by-products, algal and cyanobacterial toxins, organometallic compounds, brominated and organophosphate flame retardants, plasticizers and nanoparticles [80,81]. To date, the global consumption of pharmaceutical and personal care products is about 10,000 tons per year [120]. The adverse characteristics of ECs include high polarity, bioaccumulation and persistent to biodegradation that pose a serious threat to aquatic resources and to human health [109]. Several steroid pharmaceuticals and pesticides can act as endocrine disruptors, causing feminization and reproductive disruption in fish [76,124].

Most of the ECs lack any regulatory standards since many hypotheses regarding ECs appear to be unfounded [104]. Aquatic guidelines for priority pollutants including nitrophenols, Per- and polyfluoroalkyl substances (PFAS), carbamazepine and ibuprofen have been developed by European Union Water Framework Directive and the United States Environment Protection Agency (EU Directive 2013/39/EC [33]) [5,83,92].

At present, most of conventional wastewater treatment plants are not sufficiently designed to remove or bioremediate ECs. Various technologies, including activated sludge, constructed wetlands, chemical precipitation, solvent extraction, electrocoagulation, and anaerobic bed reactors have been trialed for the treatment and removal of ECs in wastewater [4,63,104]. However, characterization techniques for ECs are not well-grounded, especially in the presence of multiple contaminants in the wastewater [4,104,128].

Algae-based treatments have been found to be more efficient at removing nutrients and heavy metals from wastewater compared to chemical treatment [51,84]. Microalgae have received much attention in the past decade due to their ability for the removal of nutrient (Nitrogen, Phosphorus and Carbon) and heavy metals from wastewater [2,31,78,81]. Meanwhile, a growing body of literature has investigated the use of microalgae for the removal of ECs. Notably, a number of studies have witnessed the concomitant removal of nutrients and ECs from synthetic and domestic wastewater [85,104,124]. In the light of recent developments in bioremediation techniques, there is a growing interest for the use of microalgae for bioremediating pharmaceuticals in the wastewater effluent [31,98]. Thus, coupling nutrient removal with bioremediation of ECs offers cost-effective, innovative solution to the conventional wastewater treatment.

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Table 1
Percent removal efficiency of Pharmaceutical ingredients at laboratory scale by Microalgae.

Active ingredients (% removal)	Micralgae species	Experimental condition	Reference
ciprofloxacin (100) sulfadiazine (54.53)	*Chlamydomonas* sp. *Tai-03*	Medium: synthetic wastewater, Temperature: 25 ± 1 °C, CO_2: 2%, Light intensity: 250 μmol m^{-2} s^{-1} (12/12 light/dark cycle), Duration: 5–6 days	[121]
Sulfamerazine, (84) sulfamethoxazole (74) sulfamonomethoxine (75)	*H. pluvialis*,	Medium: pre-sterilized synthetic wastewater, Temperature: 25 ± 1 °C, Light intensity: 12 h: 12 h dark/light cycle), Duration: 40 days	[58]
trimethoprim (37), clarithromycin, (76) azithromycin(78) roxithromycin(63) lomefloxacin (93)	*S.capricornutum*,		
levofloxacin and (60) flumequine(46) (Average removal efficiency by all microalgae)	*S. quadricauda and C. vulgaris*		
Acetaminophen (67)	*Chlorella sorokiniana*	Medium: Mann and Myers, Temperature: 25 ± 1 °C, pH (7.5 ± 0.5), Light intensity: 370 μE/m2/s (12/12 light/dark cycle), Duration: 144 h	[31]
Sulfamethazine (31.4–62.3) Sulfamethoxazole (27.7–46.8)	*Scenedesmus obliquus*	Medium: sterilized Bold's Basal Medium, Temperature: 27 °C, Light intensity: 45–50 μmol/m2/s (16/8 light/dark cycle), Duration: 14 days	[122]
Carbamazepine (<21), ibuprofen (60), gemfibrozil (<27)	*Chlorella vulgaris* *Scenedesmus obliquus*	Medium: synthetic wastewater, Temperature: 22 °C, Light intensity: 90–160 μmol m^{-2} s^{-1} (16/8 light/dark cycle), Duration: 25 days	[62]
Memantine (92) Hydroxyzine (96) Biperiden (86) Bupropion(94) Clomiprsmine (100) Amitriptyline (100) Diphenhydramine (95) Flecainide (74) Mitrazapine (89) Orphenadrine (94) Trihexyphenidyl (88)	*Coelastrum astroideum*	Medium: Bold's basal, Light intensity: 45–650 μmol m^{-2} s^{-1} (custom made white LED panel), Areation-1 L/min, CO_2: 3%. pH:7.2 ± 0.5. Temperature: 25 °C, Duration: 12 days	[43]
Tetracycline (100)	*Chlamydomonas* sp. *Tai-03*	Medium: BG-11, Temperature: 30 °C, Light intensity: 200 μmol m^{-2} s^{-1},CO_2 : 2.0%, Aeration: 0.2 vvm, Duration: 5–6 d.	[121]
Amitriptyline (74) Bupropion (60) Clomipramine (100) Ofloxacin (65) Caffein (68) Diphenhydramine (74) Flecainide (71) Hydroxyzine (77) Memantine (88) Mitrazapine (66) Orphenadrine (84)	*Chlorella sorokiniana*	Medium: Bold's basal, Light intensity: 45–650 μmol m^{-2} s^{-1} (custom made white LED panel), Areation-1 L/min, CO_2: 3%. pH:7.2 ± 0.5. Temperature: 25 °C, Duration: 12 days	[43]
Ofloxacin (61) Codeine (57) Tramadol (53) Memantine (100) Hydroxyzine (94) Biperiden (95) Bupropion(83) Clomiprsmine (100) Diphenhydramine (99) Flecainide (100) Mitrazapine (86) Orphenadrine (100) Trihexyphenidyl (100)	*Chlorella vulgaris*	Medium: Bold's basal, Light intensity: 45–650 μmol m^{-2} s^{-1} (custom made white LED panel), Areation-1 L/min, CO_2: 3%. pH:7.2 ± 0.5. Temperature: 25 °C, Duration: 12 days	[43]
Ofloxin (89) Codeine (59) Memantine (96) Hydroxyzine (99) Biperiden (95) Bupropion(96) Clomiprsmine (100) Amitriptyline (100) Diphenhydramine (96) Flecainide (94) Mitrazapine (90) Orphenadrine (97) Trihexyphenidyl (97)	*Scenedesmus obliquus*	Medium: Bold's basal, Light intensity: 45–650 μmol m^{-2} s^{-1} (custom made white LED panel), Areation-1 L/min, CO_2: 3%. pH:7.2 ± 0.5. Temperature: 25 °C, Duration: 12 days	[43]
Tramadol (91)	*Scenedesmus obliquus*	Medium: BG11, Temperature: 24 ± 2 °C on Light intensity: 33.8 μE/m2/s.	[4]
Diclofenac (98), Paracetamol (67)	*Chlorella sorokiniana*	Medium: Mann and Myers, pH = 7.5 ± 0.5,Irradiance: 370 μE m^{-2} s^{-1} (12:12 h light/dark) Temperature: 25 ± 1 °C.	[100]
Levofloxacin (>80)	*Chlorella vulgaris*	Medium: BBM +1% (w/v) sodium chloride, Temperature 27 °C, Light intensity: 45–50 Lmol photon m^{-2} s^{-1} (16/8 h light/dark cycle), Duration: 11 days.	[123]
salicylic acid (>99)	*Scenedesmus obliquus*	Medium: Mann and Myers, pH: 7.5 ± 0.5, irradiance: 370 μE m^{-2} s^{-1}(12:12 h light/dark cycle) Temperature: 25 ± 1 °C.	[100]
Carbamazepine (35)			[125]

(*continued on next page*)

Table 1 (*continued*)

Active ingredients (% removal)	Micralgae species	Experimental condition	Reference
	Chlamydomonas Mexicana	Medium: Bold's Basal, Temperature: 27 °C, Light intensity: 45–50 mmol photon m^{-2} s^{-1}(fluorescent light), Duration: 14 days	
Cephalosporin antibiotics 7-ACA (100)	*Chlamydomonas* sp	Medium: BM, BBM and BG-11(species specific) Light intensity: 200 μmol m^{-2} s^{-1} (12/12 light/dark cycle), Temperature of 26 ± 1 °C, CO_2: 2.5%, Aeration rate: 0.2 vvm, Duration:16 days	[46]
Cephalosporin antibiotics 7-ACA (100)	*Chlorella* sp.	Medium: BM, BBM and BG-11(species specific) Light intensity: 200 μmol m^{-2} s^{-1} (12/12 light/dark cycle), Temperature of 26 ± 1 °C, CO2: 2.5%, Aeration rate: 0.2 vvm, Duration:16 days	[46]
Diclofenac (>79)	*Scenedesmus obliquus*	Medium: Mann and Myers, Temperature: 25 ± 1 °C), Aeration: 0.3 v/v/min, CO_2:7% v/v	[32]
Salicylic acid (73)	*Chlorella sorokiniana*	Medium: Mann and Myers	[32]
Cefradine (76)	*Chlorella pyrenoidosa*	Medium: BG11, Temperature:25 ± 1 °C, Light intensity: 2000 lux (12 h:12 h light/ dark cycle), Duration: 96 h.	[18]

Limited reviews have published in the past to signify the use of microalgae for bioremediating ECs at laboratory conditions. However, those reviews call into question the validity of findings from laboratory scale systems. Notably, the commercial use of microalgae for bioremediating ECs remains unclear due to the conceptual gap between laboratory finding and real-world applications [83,93,98,110]. Therefore, this review for the first time explore the challenges and potential solutions in the perspective to bringing out the microalga-bioremediation of ECs to full scale/commercial scale system.

2. Removal efficiency of various ECs by microalgae

Table 1 summarizes the laboratory scale studies that aimed for bioremediating pharmaceutical compounds using microalgae. It could be observed that *Chlorella, Chlamydomonas and Scenedesmus Sp.* are the most frequently reported and extensively studied species in these proof of concept studies. This was mainly due to robustness and adaptability of those microalgae at stressful environmental conditions. Considering the high diversity of microalgae species, it can be noted that only few species were sufficiently studied for their ability for bioremediating ECs. Thus, screening programs are needed to test and validate the selective removal of ECs by wide range of microalgae species [104]. Thus, the extensive diversity of microalgae provides a research opportunity for bioprospecting microalgae species that can remove wide range of contaminants efficiently [104]. There is still considerable uncertainty regarding the operation of batch reactors at long hydraulic retention time (Tables 1 and 2). Obviously, commercial scale algal bioreactors are operated under semi-continuous or continuous mode with short HRTs. Thus, a major stumbling block exists for validating the removal efficiencies of ECs achieved at laboratory conditions into full-scale system. Limited studies have explored the removal efficiency of various ECs in real wastewater (Table 3).

3. Toxicity of wastewater

Wastewater medium can be toxic to some of the microalgae species especially in the largescale real-world applications. This is the foremost challenge faced by microalgae based WWTS. Wastewater toxicity depends on the source of waste and the type of wastewater [93]. Notable factors such as predatory zooplankton, high ammonium concentration, heavy metals (Cadmium, Mercury) and high oxygen concentration can cause significant toxicity in municipal wastewater [85]. For instance, treatment of olive mill wastewater was challenging due to antibacterial properties and phytotoxicity of high (poly) phenolic content.

Acclimation or adaptation of microalgae to the wastewater system is primarily studied to overcome this challenge. It was observed that the genetic adaptation helped microalgae to tolerate severe doses of antibiotics, herbicides and mine waste [38,55]. Further, microalgae have been shown to acclimate to a variety of sub-lethal stresses such as heavy metals, singlet oxygen, salinity and high light [85,124]. When microalgae are exposed to extreme environments, it induces the production of toxic degrading enzymes [44,109]. A study by Ref. [18] revealed that the pre-exposed microalga could remove antibiotic cefradine more effectively than its wild species. In another work [85], demonstrated that the growth rate of acclimated strains in untreated wastewater was significantly higher than that of non-acclimated strains. It was observed that the *Chlorella luteoviridis and Parachlorella kessleri* were well acclimated to secondary-treated municipal wastewater medium within a acclimation period of 8 weeks. Further, it was observed that the acclimation to wastewater tolerance was correlated with higher accumulation of carotenoid pigments and increased ascorbate peroxidase activity [85].

Microalga *P. kessleri* which is isolated from wastewater effluent showed great potential to grow in saline, high temperature, oxidative, acidic and alkaline conditions while accumulating radionuclide particles [85]. A core problem of conventional wastewater treatment in handling the ECs is that the presence of pharmaceutical, personal care products, pesticides etc. at extremely low concentration [15,17]. It is interesting to note that EC50 (concentration of ECs at which 50% of algal growth is inhibited) of most of microalgae species are several orders of magnitudes higher than that of typical ECs concentration in real wastewater system [65]. The growth of *Chlorella vulgaris* was significantly inhibited by diazinon (insecticide) above the concentration of 40 mg/L. However, maximum removal efficiency of 94% was observed at the concentration of 20 mg/L [61].

4. Nutrient deficiency

One downside factor regarding the microalgae mediated EC bioremediation is that the deficiency of essential nutrients in wastewater medium. Microalgae growth was limited by carbon availability in few studies that attempted to remove ECs from domestic wastewater [2,98]. Nitrogen and Phosphorus limitation was likely to affect the microalgae growth in palm oil mill effluent medium, thus slowed down the bioremediation of ECs. It is plausible that deficiency of micro-nutrients such as iron, manganese, zinc, sulfur, copper, potassium, and magnesium can limit the microalgal growth and further complicate the bioremediation process. This requirement differs among taxa and in some cases excess amounts could cause toxic effects [20,98].

[94] postulated that the biodegradability of ECs correlates well with C: N: P ratio of the wastewater in the absence of inhibitory or recalcitrant compounds. It was found that the optimum biodegradability was achieved at C: N: P ratio of 100: 18: 2. Number of studies have stressed the importance of nutrient deficiency that could indirectly affect the bioremediation process [98,101,102].

Supplementation of essential nutrient would impose additional cost to bioremediation process. Thus, co-addition of nutrient rich wastewater such as piggery wastewaters, food wastewater, and anaerobic effluents would be beneficial [35,72,101,102].

Table 2
Percent removal efficiency of ECs (excluding pharmaceuticals) at laboratory scale by Microalgae.

Type of ECs	Compound (% removal)	Micralgae species	Experimental condition	Reference
Personal care products (PCP)	Methylisothiazolinone (100)	*Scenedesmus* sp. *LX1*	Medium: BG11 medium, Temperature: 25 °C ± 1 °C, Light intensity:55–60 μmol m^{-2} s^{-1} (14:10 h light/dark cycle), Duration:4 days.	[117]
	Bisphenol A (100)	*Chlamydomonas* sp. *Tai-03*	Medium: BG-11, Temperature: 30 °C, Light intensity: 200 μmol m^{-2} s^{-1},CO_2 : 2.0%, Aeration: 0.2 vvm, Duration: 5–6 days	[121]
	Climbazole (>88)	*Scenedesmus obliquus*	Medium: BG-11, Temperature: 30 °C, Light intensity: 3000 lux (12 h:12 h light/dark cycle), Duration: 12 days	[87]
	Triclosan (100)	*Nannochloris*	Medium: Milli-Q water, 12 h light/12 h dark cycle, Duration: 7 days	[9]
	Triclosan (77.2%)	*Chlorella pyrenoidosa*	Medium: Acetate carbon source, Temperature: 22 °C, light intensity: 4000 lux (16/8 h light/dark cycle),	[116]
Hormones	β-estradiol (E2) 17a-ethinylestradiol (EE2) (100)	*Chlamydomonas reinhardtii*	Medium: P49 (species specific), Temperature: 25 ± 1 °C, Light intensity:172 ± 18 μmol m^{-2} s^{-1}, Duration: 10 days	[53]
	β-estradiol (E2) (88) 17a-ethinylestradiol (EE2) (60–95)	*Selenastrum capricornutum*	Medium: P49 (species specific) Light intensity: 172 ± 18 μmol m^{-2} s^{-1}, Temperature: 25 ± 1 °C, Duration: 10 day	[53]
	Progesterone (95)	*Chlorella pyrenoidosa*	Medium: BG11, Temperature: 25 °C, Light intensity: 3000 lux (12 h:12 h light/dark cycle)	[91]
	17 α –Estradiol (85) 17 β-estradiol (95) Estrone (85) Estriol (95)	*Scenedesmus dimorphus*	Medium: Proteose-Peptone(PPM) and modified bold 3N medium (MB3N), light/dark cycle of 12 h:12 h, Duration: 8 days.	[127]
	17 α-Ethynylestradiol (68)	*Desmodesmus subspicatus*	Medium: M4, Temperature: 20 ± 2 °C, Light intensity:15 μE m^{-2} s^{-1} (16/8 h light/dark cycle), Duration: 72 h.	[74]
Surfactant	Nonylphenol (83.77%)	*Ankistrodesmus acicularise*	Medium: BG11 medium, Light intensity: 90 μmol m^{-2} s^{-1} (cool white fluorescent tubes), 12 h:12 h light/dark cycle, Areation-35 ml/min, Temperature: 25 ± 2 °C, Duration: 120 h	[48]
	Nonylphenol (>80)	*Chlorella vulgaris*	Medium: Bristol, Temperature: 25 °C, light intensity:40 lmol $s^{-1}m^{-2}$ (16/8 h light/dark cycle), Duration:168 h,	[37]
Pesticide	Trichlorfon (TCF) (100)	*Chlamydomonas reinhardtii*	Medium: sterilized Bold's basal medium, Temperature: 25 °C ± 1 °C, Light intensity:6000 lux (12:12 h light/dark cycle), Duration:10 days.	[113]
	2,4-dichlorophenol (2,4-DCP) (100)	*Chlorellar pyrenoidosa*	Medium: BG11 medium, Temperature: 25 °C ± 1 °C, Light intensity: 4000 lux (12:12 h light/dark cycle), Duration:10 days.	[66]
	Propamocarb (50)	*Chlorella vulgaris*	Medium: Z8, Temperature: 20 °C, Light intensity: 100 μmol m-2 s-1 (16:8 h light/dark cycle)	[7]
	2,6-dichlorophenol (50)	*Scenedesmus obliquus*	Medium: Glucose carbon source, Temperature: 30 °C, light intensity: 54–60 $mols^{-1}m^{-2}$ (24 h light)	[88]
	Isoproturon (54)		Medium: mineral growth medium, Temperature: 23 ± 2 °C, Light intensity: (65 μmol m^{-2} s^{-1}, Duration: 96 h	[27]
	α-endosulfan (95–99)	Scenedesmus sp	Medium: Sterilized Bold's basal, Temperature: 22 °C, Light intensity: 2000 lux(24 h light),Duration:30 days.	[103]
Flame retardant	Polybrominated diphenyl ethers (>80)	*Chlorella* sp.	Medium: Bristol medium, Temperature: 22 ± 1 °C, Light intensity: 40 μmol m^{-2} s^{-1} (16 h:8 h light/dark cycle) Duration: 7days	[25]
	Tetrabromobisphenol-A (TBBPA) (85)	*Coelastrum sphaericum*	Medium: BG11, Temperature: 25 °C, Light intensity: 3000 lux (12 h:12 h light/dark cycle) Duration: 240 h	[91]
	Tetrabromobisphenol-A (TBBPA) (90)	*Scenedesmus quadricauda*	Medium: BG11, Temperature: 25 °C, Light intensity: 3000 lux (12 h:12 h light/dark cycle) Duration: 240 h	[91]
Industrial chemicals (aromatic hydrocarbons)	Para-xylene (100)	*Rhodomonas* sp. *JZB-2*	Medium: F/2 medium, Light intensity: 60 μmol m^{-2} s^{-1}, 14 h:10 h light/dark cycle, Temperature: 20 °C, Duration: 6days	[67]
	19 different chlorinated phenolic compounds (9-90)	*Scenedesmus obliquus*	Medium: liquid culture medium, Light intensity: 50–60 μmol m^{-2} s^{-1}, 12 h:12 h light/dark cycle, Temperature: 30 °C, Duration: 6days	[89]
	Phenanthrene (70) (PHE), Fluoranthene (FLA) and Pyrene (PYR) (>70)	*Rhodomonas baltica*	Medium: Conway medium, Light intensity: 2500Lux, 12 h:12 h light/dark cycle, Temperature: 18 °C, Duration: 6days	[8]
plasticizers	Diethyl phthalate (DEP) (81.2%), di-n-butyl phthalate (DBP) (93.1%)	*Cylindrotheca closterium,*	Medium: sterile F/2 medium, Light intensity: 300Lux (cool white fluorescent tubes), 16 h:8 h light/dark cycle, Temperature: 25 ± 1 °C, Duration: 216 h	[36]
PCP, Pesticide	α-naphthol (71) β-naphthol (53)	*Chlorella vulgaris*	Medium: Sterile Bold's Basal, Temperature: 25 ± 1 °C, pH 7.0, Light intensity of 5000 lux	[30]

5. Multiple contaminants and fate of contaminant inside the algal cell

In most of laboratory scale studies, only target ECs were tested under controlled conditions (Tables 1 and 2). However, wastewater contains various contaminants that can result in competition for the binding sites and changes in the stability of the EC-microalgae interactions. Many past literatures have overlooked the interference amongst contaminants and microalgal cell due to antagonistic, synergistic and additive effect of toxicity by multiple contaminants [97,104,127].

Presence of multiple contaminants in wastewater may enhance the toxicity of wastewater compared to the presence of single EC. A recent study with *Chlorella vulgaris* claims that the EC50 values for erythromycin, enrofloxacin, and erythromycin-enrofloxacin mixture were 85.7, 124.5 and 39.9 mg/L, respectively. The lowest EC50 value for the mixture indicates the synergistic effect of the two antibiotics [65,114,115]. Interestingly, presence of some specific contaminants seemed to influence and increase the removal rate of other contaminants. In a study by Ref. [122]; removal efficiency of sulfamethazine (SMZ) was increased by 3.4-fold from its initial removal percentage (17.3%) when SMZ

Table 3
Percent removal efficiency of ECs in real wastewater by Microalgae.

Medium and Experimental condition	Micralgae species	Type of ECs	Compound (% removal)	Reference
Medium: Agricultural runoff Hybrid photobioreactor with open tanks and closed tubular reactor	Mixed microalgae culture	Pesticides	Alachlor (100), linuron(100), cybutrine(100), deisopropyl atrazine(100), terbuthylazine(100), azynphos ethyl(100), chlorfenvinphos(100), malaoxon(100), fenthion oxon(100), fenthion sulfoxide(100)	[40]
Medium: Domestic wastewater from waste water treatment plant in polypropylene 21 L HRAPs Duration: 7.0 ± 0.2 days	Consortium of microalgae formed mainly by *Scenedesmus* sp	Surfactant	Mixture of surfactant (90–97%)	[101]
Medium: Domestic wastewater HRAP with volume of 470 L	Mixed microalgae culture	Pharmaceutical	Metronidazole (89–91) N, N-didismethyl venlafaxine (85–88.6) acetaminophen (100) diclofenac (51.3–54.8) ibuprofen (78–79) sulfamethoxazole (50.5–85.3)	[39]
Medium: Ultrafiltration autoclaved wastewater effluent, Duration: 7 days	*Desmodesmus subspicatus*	Hormones	17 β-Estadiol,17 α-Ethynylestradiol (60)	[11]
Medium: Domestic wastewater HRAP Duration: 6 month	Mixture of algae-bacteria consortia (dominated by *Coelastrum* sp.)	Pharmaceutical	Antibiotic mixtures (average removal rates between 89.4 and 99.8)	[112]
Medium: Sterile, filtered Sewage treatment plant wastewater, Temperature: 25 °C, Light intensity: 60 mmol m^{-2} s^{-1} (of 12 h: 12 h dark/light cycle), Duration: 7 days	*Scenedesmus obliquus*	Pharmaceutical	clarithromycin, roxithromycin and triclocarban (>80)	[100]
Medium: Toilet wastewater Pilot scale microalgal photobioreactor	Mixed microalgae culture	Pharmaceutical	Acetaminophen (>99) Ibuprofen (>98) Ketoprofen(36) Naproxen (69) Salicylic acid (33–100) β-blocker atenolol (>80) lorazepam (30–57) hydrochlorothiazide (44–84)	[52]
Medium: Domestic wastewater HRAP	Mixture of algae-bacteria consortia	Pharmaceutical	Ciprofloxacin (20.1)	[54]
Medium: Municipal wastewater influent Open pond type Photobioreactor (650 L) Duration of photobioreactor operation: 3 years, removal efficiency are measured for duration of 7 days	Mixed population of freshwater green algae	Pharmaceutical	Beta-blockers atenolol, bispropol, metoprolol, clarithromycine, bupropion, atracurium, diltiazem, terbutaline (>90%) 14 pharmaceutical showed moderate removal (50–90%)	[42]
Medium: Filtered and autoclaved lake water, Duration: 7 days	*Nannochloris*	Pharmaceutical	Ciprofloxacin (100) Sulfamethoxazole (<40) Triclosan (100)	[10]
Medium: Sterile, filtered Sewage treatment plant wastewater, Temperature: 25 °C, Light intensity: 60 mmol m^{-2} s^{-1} (of 12 h: 12 h dark/light cycle), Duration: 7 days	*Scenedesmus obliquus*	Pharmaceutical	clarithromycin, roxithromycin and triclocarban (>80)	[100]
Medium: Urine, synthetic urine and anaerobically treated black water, Temperature: 35°, Light intensity: 68 μmol m^{-2} s^{-1}, CO_2:3% (v/v), Duration: 31 days	*Chlorella sorokiniana*	Pharmaceutical	Diclofenac, Ibuprofen, Paracetamol, and Metoprolol (60–100) Trimethoprim (60)	[23]
Medium: Urban wastewater in pilot high rate algae pond (HRAP)	Mixed microalgae culture (Primarily of Phylum *Chlorophyta*)	Mixture of Emerging organic contaminants (Pharmaceutical, pesticide, personal care products ets.)	caffeine, acetaminophen, ibuprofen, methyl di hydro jasmonate and hydrocinnamic acid (>90) oxybenzone, ketoprofen, 5-methyl/benzotriazole, naproxen, galaxolide, tonalide, tributyl phosphate, triclosan, bisphenol A and octylphenol (60–90) diclofenac, benzotriazole, OH-benzothiazole, triphenyl phosphate, cashmeran, diazinon, benzothiazole, celestolide, and atrazine (40–60) carbamazepine, methyl paraben, tris(2-chloroethyl) phosphate, 2,4-D (<40)	[75]
Medium: River water, Temperature: 25 °C, Light intensity: 3000 lux (12 h:12 h light/ dark cycle) Duration: 168 h	*Scenedesmus quadricauda*	Flame retardant	Tetrabromobisphenol-A (TBBPA) (88)	[91]
Medium: Influent wastewater (sterilized), Light intensity: 60 mmol m-2 s-1 (dark–light cycle of 12 h: 12 h condition). Duration: 7 days	*Chlorella vulgaris Chlorella Pyrenoidosa Scenedesmus Obliquus Chlamydomonas rheinhardii*	Pharmaceutical and PCP	Mixture of selected 50 organic contaminants-Average removal (>50)	[128]

combined with sulfamethoxazole (SMX) (Table 1). However, they found out that the presence of SMZ has negligible influence on the removal of SMX in all conditions. It was suggested that the SMX encouraged the induction of related catalytic enzymes. Similarly [44], found that the co-existence of tetrahydrofuran improved the degradation of benzene, toluene, ethylbenzene and m-xylene.

In recent years, co-metabolism mechanism is explored to improve the removal efficiency of various ECs. Co-metabolism is the transformation of a non-growth substrate in the presence of a growth substrate [81]. In other words, co-metabolism facilitate the degradation of a given compound by the combined biochemical effects of several organisms [124]. It was reported that the removal efficiency of ciprofloxacin by *Chlamydomonas Mexicana* was increased from 13 ± 1% to 56 ± 1.8% after the addition of Sodium acetate (electron donor) [65,123]. On the contrary, removal efficiency of few contaminants could be negatively affected due to the interference of some organic substrates [124].

Bioremediation of ECs by microalgae can be explained by three key pathways such as bioadsorption, bio-uptake or bioaccumulation, and biodegradation [78,104,124]. Microalgal bioadsorption involves the adsorption of ECs on microalgal cell wall, or onto extracellular polymeric substances (EPS). EPS are generally excreted by the cells and released into bulk medium in the form of proteins, lipids, polysaccharides and nucleic acids [97,118]. There is a non-metabolic interaction between the contaminant (positively charged) and the negatively charged microalgal cell wall, or secretions [47]. Therefore, heavy metals and lipophilic, cationic ECs are successively removed by this pathway.

During bio-uptake or bioaccumulation, pollutants are transferred through cell wall into the interior of living algal cells where it binds to intracellular proteins and other substances. Unlike bioadsorption, bio-uptake of ECs is only viable in living microalgal cells [78,104]. The bioadsorption potential of microalgae is governed by the chemical structure of the EC. However, the area and chemical characteristic of the cell surface determine the amount of EC that can be adsorbed by microalgae [96,104]. The rate of both adsorption and biouptake processes are regulated by the environmental factors such as temperature, redox and pH [83,104].

Inevitably, binding sites of microalgae may be saturated with non-target contaminants since selective removal of ECs is not feasible in real world application [40]. Therefore, pilot scale studies are needed to validate the laboratory findings to field conditions. Notably, *Chlorella* and *Scenedesmus* are known as 'hyper accumulators' and 'hyper-adsorbents' due to their high affinity for heavy metals [16]. Similar research can be encouraged to explore 'hyper accumulators' for ECs.

Triclosan, trimethoprim, and sulfamethoxazole were shown to bioaccumulate in microalgae [10,124]. However, bioaccumulation of ECs by microalgae may results in overproduction of reactive oxygen species. This may lead to oxidative damage to biomolecules, cellular dysfunction, and ultimately cell death. Consequently, unbound ECs may be released back to environment [96,104]. Although such phenomenon can be controlled at laboratory conditions, it is not practical to prevent such aspects in commercial scale application.

6. Fate of contaminants inside the algal cell

Despite the advantages of bioaccumulation process, several studies fail to take into account of the fate of ECs inside the algal cell. There is still considerable controversy surrounding the safe disposal of toxic algal biomass after bioaccumulation [43,128]. [43] examined 8 microalgae species for their ability to remove 19 pharmaceuticals. It was reported that the removal efficiency of Biperiden and Trihexypenidyl by *Coelastrella* sp. were 92% and 94%, respectively. Report by Ref. [43] further confirmed that more than 90% removal efficiencies were achieved with *Chlorella vulgaris* and *Chlorella saccharophila*.

Biodegradation or biotransformation involves the transformation and breakdown of complex compounds into simpler molecules. The breakdown of compounds can occur intracellularly and/or extracellularly [43, 118]. Compared to bioadsorption or bio-accumulation processes, biodegradation has the potential to reduce the toxicity of ECs inside algal cells and in bulk medium. Notably, microalgae biomass can be further converted into value added products. Biodegradation can occur via two principle mechanisms such as metabolic degradation and co-metabolism. EC serves as the carbon source for microalga during metabolic degradation. In co-metabolism process, degradation of EC is mediated by enzymes that catalyze the substrates in the bulk medium [83,106].

Extensive literatures have examined the removal of pharmaceuticals and personal care products in wastewater by microalgal biodegradation (Tables 1 and 2) [78,81]. It was reported that estrogenic hormones were predominantly removed by microalgal biodegradation [118]. It was noted that enzymes are responsible for biodegradation and activation of enzyme is determined by the concentration of EC in the bulk medium. Thus, threshold concentration of the EC is crucial to trigger enzyme activity as well as microalgal biodegradation [83,104]. Biotransformation of these persistent and robust ECs by microalgae is complex. There is still considerable disagreement with regard to the role of enzymes and their role in biodegradation process [124]. Further research is needed to explore the role of enzymes and their degradation mechanism in wastewater medium.

It is also important to note that not all ECs are 'readily biodegradable' and they can be toxic to the microalgal cell [112]. reported that some of the non-biodegradable pharmaceutical contaminants were found to be resistant to photolysis (e.g: carbamazepine) in high rate algal ponds. It is suggested that microalgal strains can be pre-acclimated to sub-toxic concentrations of target EC. This is an important initial step for efficient remediation of toxic substances. Studies have proved that metabolic functions and cellular processes can be enhanced when microalgae are well acclimated to contaminants. Tolerances of microalgae to ECs seemed to increase in response to their chronic exposure to target EC. This is based on the fact that the enzymatic pathways are induced to counteract the toxic effects of ECs [21,83]. [18] reported that the removal efficiency of the antibiotic cefradine by *Chlorella pyrenoidosa* increased when it was pre-exposed to the antibiotic.

EC biodegradation is influenced by number of factors such as characteristic of pollutants, type of microalgae species, enzymatic pathway and environmental conditions. Microalgae may also enhance the biodegradation process indirectly via symbiotic relationships with bacteria [2]. It was postulated that photosynthetically mediated pH changes and high oxygen production could enhance the formation of reactive oxygen species during photosynthesis [46,83]. Reduced toxicity of algal biomass after biodegradation allows the end use of microalgae biomass for various purposes including biofuel. However, there is a likelihood that accumulation and sorption may leave certain amount of ECs after bioremediation [17].

7. Effluent quality

The goal of wastewater treatment is to meet stringent effluent quality standard. In microalgae mediated bioremediation studies, the effluent quality has been overlooked as most of those studies were confined to laboratory conditions. In a study by Ref. [40]; concentration of imidacloprid, diuron and terbutryn in the effluent were found to be higher than that observed in the influent. Similar observations were reported by Refs. [128] when four freshwater green microalgae species *Chlamydomonas reinhardtii, Scenedesmus obliquus, Chlorella pyrenoidosa* and *Chlorella vulgari* were tested for the removal of Diclofenac, Gemfibrozil, Ibuprofen, and Sulfamonomethoxine. For instance, concentration of ibuprofen in the influent increased from 70.3 to 977.3, 7875.6,4197.1, 4486.9 mg/L after bioremediated with *Chlamydomonas reinhardtii, Scenedesmus obliquus, Chlorella pyrenoidosa* and *Chlorella vulgaris,* respectively [128]. It is important to note that more than 79% removal efficiency was reported with Diclofenac at laboratory conditions (Table 1) [23,32,100]. This is presumably due to the de-conjugation and/or back-transformation of metabolites in the influent into their original compounds occurs during

the treatment process. However, further research is needed to rationalize this observation [40,111].

Formation of secondary products during substrate metabolism and biomass decay may become more toxic compared to primary compounds [65,101,102]. For instance, bioremediation of textile wastewater is typically characterized by decolorization and COD reduction [29,69]. In these studies, microalgae species such as *Chlorella vulgaris*, *Chlorella pyrenoidosa* and *Oscillatoria tenuisin* degrade azo dyes into simple aromatic amines and decolorize the dye wastewater. However, these aromatic amines are persistent organic pollutant and carcinogenic [34,101, 102]. In a study by Ref. [57]; the hydrolysis products of the oxytetracycline and tetracycline were found to be more toxic than that of their parent antibiotics. However, characterizing and quantifying the secondary products in the effluent is practically impossible.

In addition, presence of soluble algal products (SAPs) in the effluent also a concern even though they have been overlooked. SAPs are defined as Soluble organic matter is released by the microalgae into the culture medium. There are three main sources, including the extracellular organic matter secreted from living cells, the surface-retained organic matter desorbed under a given condition and the intracellular organic matter released from the dead and disrupted cells [95,129]. They include carbohydrates, protein, lipid, enzymes, vitamins, hormonal substances, pigment, inhibitors and toxins. The production of SAPs could be as high as 70 mg/L in terms of dissolved organic carbon (DOC), causing substantial environmental issues [130]. They could support bacterial growth as carbon sources, and cause odor and taste problems in the effluent. Could increase the amounts of the pre-cursor of disinfection by-products (DBPs) and inhibit microalgal growth, thus reducing the remediation efficiency [71,129]. Therefore, when ensuring the effluent quality, the presence of SAPs couldn't be ignored especially in the largescale systems.

These indicate the need for standard method to ensure the final quality of the effluent. To date, bio-assays and hazard quotients methodologies are used by some researches [31]. demonstrated the removal of Acetaminophen by *Chlorella sorokiniana* (67%) with 62% of total abnormalities reduction on the exposed zebrafish embryo. However, exposure to effluents caused a significant increase in total abnormalities of zebrafish embryo compared to the control [40]. evaluated the environmental risk associated with the compounds present in the effluent of photobioreactor using hazard quotients. Moderate risk was found for 2, 4-D, diazinon and terbutryn while high risk was observed with imidacloprid. Systematic studies are needed to look at the quality of effluent after microalgae assisted bioremediation of EC.

8. Need of pre and/or post treatment

Pre-treatment has become crucial for some of the bioremediation processes. For example, color of olive mill effluent may prevent the photosynthetic activity of microalgae and its growth [101,102]. [50] proposed a pretreatment process consist of physical separation and photolysis to remove bigger particles and reduce the organic load using *C. pyrenoidosa* [98].

Similarly, post treatment also suggested to improve effluent quality. Technologies such as activated carbon adsorption, filtration, ozonation, and ultrasound treatments were recommended as potential post-treatment options [65,98,101]. Apparently, both pretreatment and post treatment would result in additional cost and energy demand for the wastewater treatment process [101,102]. Few researches have suggested the coupling of constructed wetland treatment system [124] or activated sludge method [45] with microalgae treatment. Compared to other methods, these methods could be cost effective. However, a complete life cycle assessment is needed to validate the economic and technical viability of these systems.

9. Control of operational conditions/physicochemical factors

In laboratory conditions, physical chemical conditions can be easily controlled (Tables 1 and 2). However, commercial scale microalgae cultivation incorporates photobioreactors and high rate algal ponds (HRAPs) [40,112]. Optimizing physical chemical characteristics for large scale production is a challenging task especially in HRAP.

However, the major concern is the dynamics of operational conditions in the real-world system and how it affects the removal efficiency of ECs by microalgae [112]. Observed maximum concentration for analgesics, anti-inflammatories and antibiotics in the influent during winter while these levels decreased two and three-fold in summer. To date, limited studies have investigated the removal of ECs using HRAP with real wastewater condition [22,76,112]. Temperature is one of the primary factors that affects the removal of ECs as higher temperatures typically increases kinetics and impact productivity [76]. reported that the removal of ECs using HRAP in a mild climate was very low (10–20%) (Table 3). Another study by Ref. [112] proved that higher temperature resulted in an increase in the removal efficiency of pharmaceutical contaminants such as mefenamic acid, naproxen and other analgesics and anti-inflammatories [112]. Suggested that the analgesics and anti-inflammatories such as ketoprofen and diclofenac showed relatively higher removal efficiencies in summer due to increased microbial activity. However, high temperature led to photoinhibition and microalgae growth almost ceased after midday.

Light intensity seemed to exert a stronger effect on algal productivity. In a study by Ref. [52,53] ciprofloxacin removal efficiency in the HRAP system was compared at indoor (Laboratory scale) and outdoor conditions. The limited light supply in the HRAP system resulted in reduced rate of pollutant photo-degradation (Table 3).

pH was reported to affect EC structure, sorption, and removal kinetics. It was observed that elevated pH during algae photosynthesis can reduce the sorption of acidic pharmaceuticals [118]. In fact, extreme pH can inhibit microbes [77,79]. In a study by Ref. [40]; high photosynthetic activity during summer led to elevated pH in the mixed liquor and promoted the desorption of terbutryn from the algal biomass. This resulted in higher concentration of this contaminants in effluent than that observed in the influent. CO_2 concentration in the system play major role in the variation of pH in the system. Dissolved Oxygen (DO) influence microbiology and thus biodegradation and biosorption of ECs. Mixing indirectly influence various other factors including temperature, pH, DO fluctuations and retention times. Hydraulic retention time influences the time available for the degradation of soluble pollutants [83].

Understanding and optimization of these factors would help us to increase the biomass concentration and productivity of microalgae. Subsequently, this would increase and optimize the bioremediation process of the treatment system [4,11,43].

10. Challenges associated with contaminations

Contaminations are of great concerns for microalgae cultivation in open reactors (raceways or HRAPs). Herbivorous protozoa and zooplankton (rotifers and cladocerans; Daphnia) grazing can reduce algal concentrations significantly (as high as 90% algal biomass) in just a few days. Considering the difficulty in controlling contaminants in HRAPs, mixed cultures are allowed although it does not favor algal productivity (Table 3). In laboratory conditions, contamination can be avoided by using closed photobioreactors. However, cost-effectiveness of this large scale photobioreactor due to the installation and operational costs. Cultivation of extremophile algae at harsh environmental conditions (light, temperature, pH) seemed to be promising option. In this case, microalgae can thrive in very low pH, temperature conditions where other organisms cannot survive. However, how this would affect the overall efficiency of bioremediation is also important [49].

Co-culture of microalgae with other organism such as bacteria or fungi may be a cost-effective option. Such organism also can remove ECs such as antibiotics, pesticide etc [2,52,53]. Further microalgae could be easily harvested after co-culturing with bacteria or fungi [18]. Bioremediation of ECs would make the end use of microalgae biomass more

critical. In fact, thermal treatment of microalgae such as hydrothermal liquefaction, pyrolysis will result in concentrating ECs in aqueous phase again.

11. Conclusion and future perspective

- It can be noted that most of the proof of concept studies were done in batch reactors under controlled laboratory conditions. Apparently, dynamics of operational conditions such as pH, temperature, dissolved oxygen, HRT, bacteria-microalgae interactions, light limitation/inhibition and mixing conditions in the real-world reactor system may significantly deviate from the laboratory conditions. Thus, pilot scale studies are needed to look at the challenges associated with the removal of ECs in continuous flow reactors under dynamic environmental conditions.
- Effects of multiple ECs in wastewater in real world application is unpredictable. In such cases, a pre-treatment unit prior to microalgae-based system may be needed to selectively remove the contaminants in conventional system followed by microalgae-based system.
- Despite the promising use of microalgae for the removal of ECs, bioadsorption or biouptake of microalgae do not provide the sustainable solution. Bioadsorption and biouptake processes facilitates the transformation of contaminant from one form to another form. Thus, it leaves the toxicity of ECs in the final algal biomass and prevents the ultimate use of microalgae such as biofuel, biocrude, animal feed, biofertilizer. It may make the entire process unsustainable/uneconomical. Thus, more research is needed to explore the sustainable pathways for biodegradation of ECs while reducing the toxicity of ECs in the microalgae consortium. Moreover, microalgal biomass after bioremediation should be disposed safely and special consideration is needed at large scale application.
- Quality of wastewater effluent after separation of microalgae biomass is poorly reported in the literature. Future research must focus on identifying and characterizing the byproducts formed during bioremediation process. Especially, relative toxicity of such by products and their presence might prevent the ability of reusing such wastewater.
- LCA is a sophisticated tool that can effectively evaluate and discuss the environmental consequences as well as economic feasibility of the entire bioremediation process. No significant contributions were made in the directions of LCA analysis. Thus, in-depth LCA analysis are needed to validate the promising outcomes of microalgae-bioremediation processes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

COD: Chemical oxygen demand
DBP: Disinfection by-product
DO: Dissolved Oxygen
DOC: Dissolved organic carbon
ECs: Emerging contaminants
EDCs: Endocrine disrupting compounds
EPS: Extracellular polymeric substances
HRAP: High rate algal pond
HRT: Hydraulic retention time
LCA: Life cycle assessment
PFAS: Polyfluoroalkyl substances
PFCs: Perfluorinated compounds
PPCPs: Pharmaceuticals and personal care products
SAP: Soluble algal product
SMX: Sulfamethoxazole
SMZ: Sulfamethazine
WWTS: Wastewater treatment system