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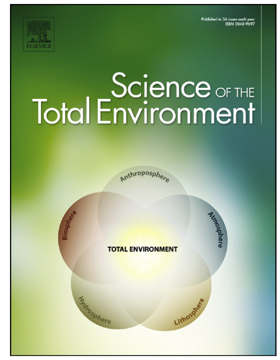

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Progress in microalgal mediated bioremediation systems for the removal of antibiotics and pharmaceuticals from wastewater

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Abstract

Worldwide demand for antibiotics and pharmaceutical products is continuously increasing for the control of disease and improvement of human health. Poor management and partial metabolism of these compounds result in the pollution of aquatic systems, leading to hazardous effects on flora, fauna, and ecosystems. In the past decade, the importance of microalgae in micropollutant removal has been widely reported. Microalgal systems are advantageous as their cultivation does not require additional nutrients: they can recover resources from wastewater and degrade antibiotics and pharmaceutical pollutants simultaneously. Bioadsorption, degradation, and accumulation are the main mechanisms involved in pollutant removal by microalgae. Integration of microalgae-mediated pollutant removal with other technologies, such as biodiesel, biochemical, and bioelectricity production, can make this technology more economical and efficient. This article summarizes the current scenario of antibiotic and pharmaceutical removal from wastewater using microalgae-mediated technologies.

Keywords: Antibiotics; bioadsorption; pharmaceuticals; microalgae; biodiesel; bioelectricity

1. Introduction

Anthropogenic activities along with irrational use of pharmaceuticals and antibiotics and their continuous release from their manufacturing industries have led to their persistent and increased concentrations in different wastewaters and aqueous ecosystems (A. Verma et al., 2014; A. K. Verma et al., 2014; W. Wang et al., 2018). Advances in the field of healthcare science have brought with them improved longevity and a better lifestyle for humans along with increased consumption and irrational use of antimicrobial and pharmaceutical products (Ahuja et al., 2021; Silva et al., 2019). Most of these compounds undergo metabolic reactions within the human body (hydroxylation and cleavages); however, pharmacokinetic studies have revealed that most are not fully metabolized and instead are excreted via feces/urine in original form or as degradation products. These products ultimately reach aquatic environments via wastewater effluents and can stress ecosystems and cause health hazards (Mohsenpour et al., 2021; Reddy et al., 2021). More than 3000 frequently used pharmaceutical compounds that have been detected and quantified in environmental samples are registered in the European Union market alone, and the number is increasing continuously. Australia is the only country that has formulated guidelines for pharmaceuticals in drinking water. Patel et al. (2019) has reviewed the top 100 most common pharmaceuticals found in wastewater. Various pharmaceutical compounds have been detected in the range of µg/L and ng/L in aquatic systems using LC-MS/MS and GC-MS with sewage water, such as ibuprofen and naproxen in Canada (Rogers et al., 1986), salicylic acid (1.83-95.62 µg/L), and clofibric acid (2.54-9.74 µg/L) in the United State (Hignite and Azarnoff, 1977), sulfonamides (6470 µg/L) in groundwater of Denmark (Holm et al., 1995), β-blockers and antibiotics (6 µg/L) in Germany (Hirsch et al., 1999). According to Behera et al. (2011), various antibiotics (sulfamethazine, sulfamethoxazole, trimethoprim, and lincomycin) are present in the effluent of wastewater treatment plants of industrial cities in South Korea.

Recently global attention has been drawn towards the preservation of freshwater resources from the discharge of emerging pollutants and treating wastewater. Various effects related to contaminated wastewater are now better understood due to the development of detection technologies (Rempel et al., 2021); however, the successful removal of such compounds from wastewater remains a major challenge in environmental biotechnology. To avoid deleterious effects on aquatic flora and fauna, wastewaters must be free from compounds rich in organic carbon, phosphorous, and nitrogen (Leslie Grady et al., 2011; Mohsenpour et al., 2021). Limited information is available on the effects of pharmaceuticals and their degradation products on humans and the environment. However, impaired development in frogs and behavioral effects in fish exposed to antidepressants, endocrine-disrupting diseases in fish exposed to estrogen, and development of antimicrobial resistance in bacteria due to excessive use of antibiotics have been reported (Celino-Brady et al., 2021; Gould et al., 2021; Wang et al., 2016). The process of treatment of domestic and industrial wastewater differs significantly and depends upon the complexity and toxic nature of the compound (Ahuja et al., 2022). Current technologies for wastewater treatment involve removing suspended solids and pathogenic microorganisms through primary (sedimentation, flocculation, and neutralization) and secondary (aerobic and anaerobic digestion) treatments, but these technologies are theoretically not designed to remove pharmaceuticals (Sonune & Ghate, 2004). This is evident from recent studies in which a substantial amount of various pharmaceutical compounds were detected in the effluent of wastewater treatment plants (WWTP) (Schoeman et al., 2017). The use of advanced treatment technologies such as ozonation, electrolysis, ion exchange, and reverse osmosis have demonstrated some potential in removing a variety of compounds but their large scale implementation is costly (Akagunduz et al., 2021; Altunterim and Vergili, 2020). Alternative solutions to explore include renewable biological systems, which are simple and easy to grow in complex wastewater (Q. Wang et al., 2020). Numerous researchers have explored the potential of microalgae for the successful removal of organic pollutants. *Nannochloropsis* sp. in the form of free cells remove olanzapine and in immobilized form can remove paracetamol and ibuprofen (Encarnação et al., 2020b). Xiong et al. (2020) explored *Scenedesmus obliquus* for the removal of doxylamine and reported 56% removal and the addition of bicarbonate increased the efficiency by up to 63%. Microalgal-based systems are recognized as an alternate method for wastewater treatment with the added advantage to nutrient removal being the generation of microalgal biomass which can be further used as raw material for bioenergy and biochemical productions. Research into microalgal-mediated wastewater technology has expanded recently. According to the Scopus database, 2204 published articles were found with keywords ‘microalgae and wastewater treatment.’ In terms of publication number, the top five countries were China (489), India (254), the United States (201), Spain (191), and Brazil (152) (Fig. 1). Recent literature has described the utilization of monoculture of microalgae and microalgae-bacterial consortia for the removal of a variety of compounds.

This review focuses on the different organic pollutants (antibiotics and pharmaceuticals) present in wastewater systems, their sources, details of processes and mechanisms used for their removal using microalgal systems, and integration of the system with other products.

2.0 Adverse effect of organic pollutants (antibiotics and pharmaceutical) residues on health and the environment

The exponential growth of the human population has brought with it an expansion of industrialization. Climate change due to emissions of carbon dioxide has been one consequence of this growth, as has been increased pollution due to greater effluent discharge, deforestation, and terrestrial pollution. Some contaminants are relatively new to ecosystems and thus have the potential to be more lethal. This class of pollutants is known as ‘emerging contaminants (ECs)’. U.S. Environmental Protection Agency (EPA) described emerging contaminants as “any compound/s or microorganisms or formulations that are non-known to be present in natural resources or were not present earlier and are detrimental to the environment, and ecosystem”. ECs mainly include cyanotoxins, brominated flame retardants (BFRs), microplastics, per-fluorinated compounds (PFCs), and pharmaceuticals and personal care products (PPCPs) (Oluwole et al., 2020). These compounds are new to the ecosystem and may have higher toxicity than conventional pollutants. Moreover, environmental accumulation, bioaccumulation, and bioactivity further increase the risk. Such general accumulation is evident from the high frequency of diabetes, cancer, impotency, and evolution of antibiotic-resistant microorganisms.

The pharmaceutical industry is one of the biggest industries in terms of production capacity and thus the largest effluent discharging enterprise as well. In the last few decades, the use of PPCPs has increased exponentially and so production has increased in an equivalent trend to meet the demand. PPCPs include substances such as therapeutic drugs, nutraceuticals, deodorants, musks, perfumes, shampoos, body lotions, hair sprays, dyes, sunscreens, creams, nail paints, and lipsticks that can be used to improve personal health or appearance. Most of the PPCPs are formulated with bioactive compounds with a natural or synthetic origin that is active even at low concentration and can modulate the metabolic pathways in living beings (Shraim et al., 2017). An estimated 100,000 to 200,000 tons of pharmaceutical products are consumed globally annually. Besides industrial effluents, non-metabolized drug traces and their byproducts (5%-90%) are discharged from the body via feces and urine which are also added to various water bodies. In 1999, U.S. Geological Survey has confirmed the presence of PPCP traces (hormones, sterols, antibiotics, pesticides, and nonprescription drugs) in surface and groundwater (Table. 1). However, the concentrations measured were too low at that time to affect human health, but continuous accumulation has become a global challenge. The solubility in the aqueous phase followed by a high response from the cell membrane for pharma products and active pharmaceutical ingredients (APIs) and the ability to persist in biological systems has increased the risk for non-target organisms (Ahuja and Bhatt, 2018; Oluwole et al., 2020). Some studies have focused on the adverse effects of pollution on aquatic organisms and have included suppressed development in frogs and frog metamorphosis, increased female population in fishes, and alteration in metabolic, physiological behavior, and reproduction (Shraim et al., 2017). The evolution of antibiotic-resistant microorganisms is one of the well-known and common examples of the adverse effect of the continuous discharge of antibiotics in the environment. The ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species*) are antimicrobial-resistant pathogens that require urgent attention (Rani et al., 2021). Evolved microorganisms are harder to treat and thus are more lethal in comparison to wild strains (Vumazonke et al., 2020). Another problem related to these contaminants is bioaccumulation in food chains. Various antibiotics and pharmaceuticals along with their use and potential hazards are summarized in the Table. 2.

3.0 Process of organic pollutant removal using the microalgal system

The identification, management, and removal of pharmaceuticals and antibiotics from wastewaters hold an important role in dealing with the problems of pollution. Analysis of 32 secondary and final treated wastewater samples from Beijing, Tianjin, and Wuxi in China has shown the presence of aromatic hydrocarbons such as pyrene and naphthalene and flame retardants such as tributyl phosphate, and phthalates such as bis-2-ethylhexyl phthalate (Wang et al., 2018). These studies warrant the use of advanced remediation techniques for the removal of organic pollutants, including membrane processes, UV irradiation, ozonation, photon-fenton treatment, and bioremediation processes using different microorganisms such as bacteria, fungi, microalgae, and enzymes released from them (Ahmed et al., 2017; Bhatia et al., 2021a). Fungi-produced enzymes like laccases, peroxidases, and peroxygenases are more effective. Laccases have a broad substrate specificity and exhibit fast reactions. Recently, microalgae-based technologies have gained more attention mainly because of their low operational costs, ability to fix CO_2, and easier growth requirements. Algae can switch from a heterotrophic to autotrophic mode, depending on experimental conditions, and thus can remediate a large number of organic pollutants (Mohsenpour et al., 2021). They are also known to degrade xenobiotic compounds and remove heavy metals. *Chlorella* sp., *Chlamydomonas* sp., and *Scenedesmus* sp., have the potential to remove various organic pollutants from municipal wastewater (Alemu et al., 2018).

3.1 Antibiotics removal: Incomplete metabolism of antibiotics inside human beings and secretion of these antibiotics and their byproducts through urine and feces has led to their emergence as major contaminants of wastewater (Anh et al., 2021; Manaia et al., 2020). This uncontrolled discharge is also responsible for the rapid dissemination of antibiotic resistance genes in environmental microorganisms (Krzeminski et al., 2019). Different antimicrobial resistance mechanisms have been reported, such as mutation resistance, horizontal gene transfer, modification of antibiotic molecule, decreased permeability, and change in efflux pump and target sites (Munita and Arias, 2016). Thus, their efficient removal from wastewaters is a serious concern. Traditional wastewater treatment processes are expensive due to high operational costs, and energy requirements. A cost comparison of various micropollutant treatment methods reported 0.17 €/m^3 for traditional methods, 0.65 €/m^3 for reverse osmosis, 0.48 €/m^3 for activated carbon, 0.30 €/m^3 for UV, and 0.23 €/m^3 for ozonation method (Bui et al., 2016). Microalgal-based technologies have therefore been explored as possible alternatives (Table 3). These processes are inexpensive, sustainable, and assist in nutrient recycling and extraction of valuable products (Zhu et al., 2019).

Kiki et al. (2020) studied four algae *Haematococcus pluvialis*, *Selenastrum capricornutum*, *Scenedesmus quadricauda*, and *Chlorella vulgaris* against ten types of antibiotics and reported a higher affinity of *S. capricornutum* and *C. vulgaris* for the macrolides and fluoroquinolones than for sulfonamides, while *H. pluvialis* and *S. quadiricauda* showed a relatively higher preference for sulfonamide. In another study, different algae *Scenedesmus obliquus*, *Chlamydomonas mexicana*, *C. vulgaris*, *Ourococcus multisporus*, *Micractinium resseri* and *Chorella pyrenoidosa* were studied in monoculture form and in consortium form for the removal of enrofloxacin (ENR), and individual microalgae and consortium were able to remove ENR by 18-26% in 11 days (Xiong et al., 2017a). Khan et al. (2020) studied a combination of algal treatment and oxidation processes to improve antibiotic removal from wastewater. Algal pretreatment makes the wastewater alkaline and removes antibiotics that are resistant to oxidation. Alkaline water is more favorable for the removal of clopidol with ultraviolet C treatment and also promotes degradation of florfenicol with ozonation (Khan et al., 2020). Guo et al. (2016) evaluated *Chlorella* sp. Cha-01, *Chlamydomonas* sp. Tai-03 and *Mychonastes* sp. YL-02 for cephalosporin 7-ACA removal from wastewater. Cephalosporin has a slight growth inhibitory effect but there is no effect on lipid accumulation and the mechanism involved in antibiotic removal includes adsorption, hydrolysis, and photolysis reactions (W.-Q. Guo et al., 2016). Ciprofloxacin (CIP) and sulfadiazine (SDZ) elimination routes in *Chlamydomonas* sp. Tai-03 were investigated by Xie et al. (2020) who reported that CIP was mainly removed through the biodegradation route (65.05%) whereas SDZ was removed via photolysis (35.60%). Antibiotics also affect microalgal-bacterial community structure. Wang et al. (2021) investigated the influence of tetracycline on the nonaerated microalgal-bacterial granular sludge of wastewater. Tetracycline reduced chlorophyll production in microalgae and decreased ammonia-N removal which further induce decoupling of symbiosis in microalgal-bacterial granular sludge. Jiang et al. (2019) used *Chlamydomonas reinhardtii* for removal of first-generation cephalosporin cefradine from wastewater and reported hydrolysis, desorption, and photoisomerization as the main mechanism involved. Hom-Diaz et al. (2017) used high-rate algal ponds (HRAP) to investigate ciprofloxacin removal from wastewater. The reactor was operated under various durations of artificial illumination and hydraulic retention time, and it was reported that CIP removal occurs by photodegradation during daytime and by adsorption to biomass during nighttime. Photodegradation of CIP is mainly attributed to ring-opening reactions followed by substitution and loss of functional groups which modulate the structure for microbial degradation (Fig. 2a). Earlier reports proposed six structures as photodegradation products out of Metb-01, and Metb-02 have resulted from degradation of piperazine ring while in Metb-03 molecule undergone ring degradation along with functional group substitution (F with H). In Metb-04, 05, and 06, molecules undergo functional group substitution and addition (Cardoza et al., 2005). Ciprofloxacin can be removed by a freshwater microalga *Chlamydomonas mexicana* and the addition of sodium acetate as an electron donor to the culture significantly increases its removal (Xiong et al., 2017c). Acclimation of *C. vulgaris* to levofloxacin increases the rate of biodegradation of the antibiotic. Also, the addition of sodium chloride (1% w/v) enhances this process through bioaccumulation (Xiong et al., 2017b). An increase in salinity reduces microalgae toxicity of different antibiotics due to altered biochemical characteristics and extracellular polymeric substance (EPS) production which is provoked by osmotic stress (Mishra et al., 2008; Pancha et al., 2015).

Various microalgal species have been reported to remove different antibiotics e.g. *Nanochloris* sp. for trimethoprim and sulfamethoxazole, *S. obliquus* for sulfamethazine, and *C. vulgaris*, *C. mexicana*, *Chlamydomonas pitschmannii*, *Ourococcus multisporus*, *Micractinium resseri*, and *Tribonema aequale* for levofloxacin (Leng et al., 2020). Polyculture mixtures and genetically modified algal species have also been employed to remove antibiotics from complex mixtures. Integration of algae-based remediation systems with other techniques like UV radiations, oxidation processes, algae–bacteria consortia, and algae–fungal coculture have been explored for the treatment of antibiotic-containing wastewaters (Leng et al., 2020).

3.2 Pharmaceutical removal: A mixture of pharmaceutical products is present in wastewaters and these compounds can accumulate in the food web via biomagnification, affecting the environment, wildlife, and humans (Wang et al., 2020). Various microalgae have been reported to remove pharmaceuticals from wastewater (Table. 3). Manganese (Mn) oxide is present in the natural environment and Mn(II)-oxidizing microorganisms are involved in its formation. Biogenic Mn oxides (Bio-MnOx) have higher oxidation capacities and require milder reaction conditions to remove pharmaceutical compounds. Wang et al. (2021) isolated forty strains of Mn-oxidizing microalgae and found three strains (*Chlamydomonas* sp. WH1–1, *Chlamydomonas* sp. WH1–4, and *Chlorella* sp. WH2–5) were able to oxidize Mn^{2+} by increasing pH and secreting Mn oxidation factor. Use of MnOMs and Bio-MnOx in combination results in carbamazepine removal of up to 80.12% (Wang et al., 2021).

García-Galán et al. (2020) evaluated a high-rate algae pond (HRAPs) to eliminate 12 pharmaceuticals and their main metabolites. The removal rate for most of the compounds was in the range of 40-60% except for the psychiatric drugs carbamazepine, metoprolol, and its metabolite. The main mechanism involved was bioadsorption/bioaccumulation. Gojkovic et al. (2019) isolated different microalgal species from Northern Sweden and studied these for the removal of 19 pharmaceuticals using a photobioreactor. Generally, microalgae are more efficient to remove lipophilic compounds (>70%) and show significant removal of biperiden, trihexyphenidyl, clomipramine, etc. *C. vulgaris* 13-1 and *Chlorella saccharophila* RNY, were found more efficient for removal of all the investigated pharmaceuticals with a small accumulation of compounds in biomass and can be further used for other applications. In another study, Hom-Diaz et al. (2017) investigated a 1200 L outdoor pilot-scale microalgal photobioreactor for removal of pharmaceutically active compounds from the toilet wastewater during two periods: September-October and October-December. Nutrients (ammonia nitrogen and phosphorus) and the demand for chemical oxygen were efficiently removed up to >80%. Process able to remove pharmaceutically active compounds by 30-80% and microalgal biomass was harvested with the use of ligninolytic fungi *Trametes versicolor* and leads to >98% clarification. This technique resulted in the complete removal of single cells from the medium and provided the added benefit of subsequent use of biomass and clarified effluent. *S. obliquus* and *Chlorella pyrenoidosa* have been shown to biotransform progesterone present in aqueous systems into 3β-hydroxy-5α-pregnan-20-one, 3, 20-allopregnanedione and 1, 4-pregnadiene-3, 20-dione via processes like hydroxylation, oxidation, and reduction (Fig. 2b). Similarly, norgestrel was transformed into 4,5-dihydronorgestrel and 6,7-dehydronorgestrel (Peng et al., 2014). *Desmodesmus subspicatus* has been observed to remove and biotransform 17α-ethinylestradiol to products with lower estrogenic potency compared to parent molecules (Maes et al., 2014). Algal pond dominated by *Coelastrum* sp. has been used to remove 64 pharmaceutical and personal care products including 33 antibiotics. When compared with traditional activated sludge treatment techniques, this technique had 5-50% better removal. A cyanobacteria *Spirulina platensis*, has been used to remove the pharmaceutical product carbamazepine (Wang et al., 2020). This alga is simple to grow, has a faster growth rate, and the addition of simple organic molecules like glucose can promote its growth and increase activity.

The development of an efficient analytical procedure is also important. Encarnação et al., (2020a) developed a reverse-phase high-performance liquid chromatography (RP-HPLC) method for simultaneous quantification of various pharmaceuticals during microalgae bioremediation and the method was able to detect paracetamol between 0.03-0.10 μg/mL, ibuprofen (0.03-0.09 μg/mL), olanazapine (0.04-0.13 μg/mL), simavastantin (0.27-0.83 μg/mL), and simavastantin acid (0.05-0.14 μg/mL).

4.0 Mechanisms involved in organic pollutant removal

Water is an essential part of life, playing a crucial role in daily metabolic activities, regulating osmotic pressure in cells, and acting as a solvent for several industrial processes. As a result of industrial and commercial processes, water contaminated with organic pollutants is discharged into aquatic systems, worldwide. However, the organic pollutants from pulp-paper, textiles, and pharmaceutical industries are more lethal than those discharged from household sewage, as commercial pollutants are xenobiotics and highly toxic. Before reusing water for human consumption and recreational purposes, it is necessary to remove and/or degrade organic pollutants. The most common methods employed are physical (filtration and adsorption) or chemical processes (precipitation, flocculation, coagulation, oxido-reduction, and ozonolysis) (Guo et al., 2017; Karpińska and Kotowska, 2019; Titchou et al., 2021). Mahmoodi et al. (2021) explored graphene oxide–chitosan (GO–CTS) and amine graphene oxide–chitosan (AGO–CTS) hydrogel as adsorbents for the removal of diclofenac and reported 90.42% and 97.06% removal, respectively. Kim et al. (2020), investigated maple leaf-derived biochar for the removal of tetracycline and reported the main mechanism involved included metal complexation, H-bonding, and hydrophobic interactions. Another researcher used microalgae (*Spirulina* sp.) derived biochar and reported tetracycline removal of up to 132.8 mg TC/g biochar in a batch experiment (Choi et al., 2020). Fu et al. (2019), performed a pilot-scale study for removal of PPCPs from drinking water, employing two parallel trains of two-stage biofiltration (sand/anthracite biofilter coupled with a biologically active granular carbon post filter) and were able to remove PPCPs up to 53.4%. The major drawbacks of the conventional approach are cost, membrane fouling, and the generation of toxic byproducts. For this reason, biological methods are preferred over conventional methods. Microorganisms utilize organic pollutants as substrate or co-substrate and degrade the pollutants during carbon metabolism. In comparison to fungi and bacteria, algae offer additional advantages due to their autotrophic nature. Microalgae-mediated pollutant removal processes involve various mechanisms like adsorption, accumulation, and degradation (Fig. 3). Algal-mediated degradation does not require any additional supplement or energy source. It utilizes organic contaminants as carbon sources for photosynthesis in the presence of sunlight/artificial light. The mechanisms have been clustered into direct- and indirect-, based on the involvement of algae.

4.1 Direct methods: The mechanisms involved in direct treatment involve either metabolism-associated degradation, binding at the surface or accumulation of the pollutants within the cells. The processes are summarized below:

Adsorption: Removal of pollutants by adsorption is a common and generalized approach for which various adsorbents can be used. Adsorbents have been adopted and modified to suit the chemical nature of pollutants. Adsorbents are derived from microbial biomass and naturally degradable substrates which not only reduces the chemical waste generation but also lowers the cost of treatment (Vahabisani and An, 2021). In comparison to other biomasses, algal biomass offers the advantage that it can be used as an adsorbent without pyrolysis/carbon extraction, and can facilitate the biotransformation of organic pollutants. In addition, algae are cost-effective and efficient as their cell surface contains amino, carboxyl, phosphate, imidazole, and sulfate groups along with bounded protein and exo-polysaccharides such as alginic acid, which also offer good adsorption capacity (Vahabisani and An, 2021).

To date, several mechanisms have been proposed to define the adsorption potential of algal biomass and are classified into two categories: metabolism dependent (bioaccumulation) and metabolism independent (biosorption). Biosorption is a passive and rapid process, facilitated by the formation of complexes, ion exchange, electrostatic interaction, and surface precipitation. The process has special consideration to the physical and chemical nature of biomass, available functional groups at the surface, composition, and nature of the surface. Overall the algal cell wall is negatively charged, thus attracting and conjugating with cations (Bilal et al., 2018). All the factors that affect the inter- and intra- molecular interaction determine the type and strength of attachment of pollutants on the cell surface and also the adsorption rate. The majority of the literature has reported the dominance of electrostatic interactions and contribution of the net charge of surface functional groups and proteins in the adsorption of organic pollutants. Therefore, pH is a crucial factor that determines the net charge on biomolecules such as proteins. The effective distance between organic pollutants and algal cells is another important factor that determines the type and strength of physical or chemical bonding (Torres, 2020). Algal cells utilize all possible types of interactions and bonding to associate with organic pollutants. Saldarriaga-Hernandez et al. (2020) have described four types of interactions between pollutants and algal cell surface: chemisorption, physisorption, ion exchange, and microprecipitation. Some other researchers have included surface complexation and covalent bonding (Singh et al., 2021). Based on the nature of bonds, interactions can be classified into two categories: physisorption that is facilitated by hydrogen bonds, Van der Waal forces, hydrophobic, Coulombic, dipole, and л interaction, and chemisorption in which molecules interact with each other through covalent bonding. These interactions are further diversified in surface precipitation and complexation.

Angulo et al. (2018) evaluated the algal biomass of *Chlorella* sp. for the removal of cephalexin. Algal biomass was grown and recovered for lipid extraction. Obtained biomass was categorized into two groups: nonliving *Chlorella* sp. which was used as control as well and treated biomass left after lipid extraction. In comparison to treated, crude biomass has a higher antibiotic removal rate of 82.77% with maximum adsorption of 129.87 mg/g biomass. Adsorption experiments showed that biosorption followed the Langmuir model. Balarak and Chandrika (2019) reported that the adsorption of ciprofloxacin from aqueous solution onto *Lemna minor* (LM) was governed cumulatively by both boundary layer and pore diffusion and followed a pseudo-second-order kinetic model. Removal of tetracycline by *Cladophora* and *Spirulina* involved electrostatic interaction between antibiotic and surface functional groups. Fourier-transform infrared spectroscopy (FTIR) spectrum analysis suggested that available –OH and –NH stretch in amides in algal biomass participate in the adsorption process. Adsorption was affected by various factors including the concentration of pollutant/antibiotic, pH, temperature, and mixing rate. Maximum removal efficiencies of 1.25 g/100 mL *Cladophora* (95%) and 0.5 g/100 mL *Spirulina* (94%) were reported under optimal conditions of 25 °C, pH 6.5, mixing rate 200 rpm, and pollutant concentration of 50 mg/L. The adsorption process followed the Langmuir model and pseudo-second-order kinetic model for *Cladophora* (0.97) and *Spirulina* (0.99), respectively (Abd and Mohammed-Ridha, 2021). Pollutants attached to the surface of living algal cells are imported into the cell by transporters, which leads to their accumulation within the cell (bioaccumulation). The imported molecules may then participate in cellular metabolic processes or be consumed by enzymes as substrates, resulting in their degradation.

***Accumulation**:* Bioaccumulation plays a major role in the removal of xenobiotic compounds using biological systems in contaminated waters (Mackay and Fraser, 2000) and is an active metabolism-dependent process that is facilitated by the attachment of organic molecules (biosorption) at the cell surface followed by transport to the cell interior (Bilal et al., 2018). In the case of those pollutants that are highly toxic or non-degradable for algae itself, cells start accumulating it and become reservoir and either undergoes slow degradation or die. Fu et al. (2019) studied the removal of testosterone from water by *C. vulgaris* where testosterone also exhibited concentration-dependent growth inhibition of algae. It was found that a concentration of 58 mg/L had an inhibitory effect on algae after 96 h. Considering the environmental concentration of testosterone two experimental groups were created: low concentration experiment group (LCEG) which operated at an initial concentration of 0.02 mg/L; and a high concentration experiment group (HCEG) which operated at 0.2 mg/L. There were two control groups (no testosterone, no algae). Testosterone had no effect on algae growth, but both groups had different concentrations of testosterone accumulated within cells. LCEG had a high accumulation (40.10%) followed by HCEG (11.49%) while no accumulation was reported from either of the control groups. The high concentration group had a higher rate of degradation with pollutants reduced by 69.64% while in LCEG it was 42.48%. Algae exhibited a sigmoidal accumulation pattern however biodegradation was the major mechanism of elimination. The difference in accumulation and degradation patterns was possibly due to differences in mechanism as at higher initial concentration of testosterone, the degradation followed second-order kinetics instead of conventional zero-order kinetics (as at lower initial concentration) (Fu et al., 2019).

Navicula sp. removes pharmaceuticals from wastewaters using bioaccumulation and biotransformation, as reported by Ding et al. (2020), who proposed that the transformation of bezafibrate (BZF) in *Naviculis* sp. is via hydroxylation, glucuronidation, and demethylation. During 21 days of the experiment, both adsorption and desorption, observed as BZF removal, lowered from 72.61% to 23.04% from 15 days to 21 days due to desorption from algal cells. Along with it, naproxen removal was also noted to have increased from 46.24% to 82.16% after 21 days. Wang et al. (2020) reported the use of polystyrene neoplastic (PNP) to overcome the inhibitory effect of ibuprofen on *Chlorella pyrenoidosa*. In the presence of PNP, the IC50 value for pollutant was increased from 45.7 mg/L to 63.9 mg/L and showed improved growth. In the control group, the concentration of the pollutant was 3.3 mg/Kg on the third day which lowered to 1.1 mg/Kg on the 42nd day while in the treated culture the concentration was 2.8 mg/Kg on the third day which was reduced to 0.8 mg/Kg in the same time frame, but the half-life reduced from 28.9 days to 24.8 days. It was observed that the bioaccumulation was followed by biodegradation but the rate was quite slow.

Biodegradation: Although organic pollutants may act as sole carbon source, their complex structure and toxicity can affect algal growth and metabolism as seen in the case of *C. pyrenoidosa*, *Anabaena cylindrical* (Zhong et al., 2021), *Desmodesmus subspicatus*, *Pseudokirchneriella subcapitata*, *Anabaena flos-aquae*, and *Navicula pelliculosa* (Guo et al., 2016). The presence of antibiotics affects algal growth, cell density, chlorophyll, and carotenoid content. Growth may be stimulated by the presence of additional carbon sources which support the algal metabolism during the adaptation phase and pollutants can be used as a cosubstrate. Previous studies also emphasized that the presence of additional carbon sources might be beneficial for pollutant elimination and improve overall degradation. Algae can also fix carbon dioxide via photosynthesis. Hence the integration of algal-based treatment of wastewater for the removal of pharmaceutical pollutants will increase its application in environmental conservation. The addition of CO_2 improved the efficiency of antibiotic removal by *Microcystis aeruginosa* by 30.16% with an associated increase in CO_2 absorption rate of 10.94% (Du et al., 2018).

Xiong et al. (2020), compared five algal species including *Pseudokirchneri ellasubcapitata*, *Scenedesmus quadricauda*, *S. obliquus*, *Scenedesmus acuminatus*, and *C. pyrenoidosa* for biodegradation of sulfamethoxazole (SMX). Among algal species, *C. pyrenoidosa* has a higher degradation rate for SMX with a removal efficiency of 14.9% after 11 days when used without any other carbon source. The addition of sodium acetate improved the removal efficiency to 99.3% after 5 days. Metabolic profiling identified oxidation, hydroxylation, formylation, and general breakdown as the main mechanism for biodegradation. In the same line, the metabolism efficiency of doxylamine by *S. obliquus* increased from 56-63% when bicarbonate was added as a cosubstrate during algal treatment (Xiong et al., 2020). The major challenge for research is to identify the mechanism behind the biodegradation process. The majority of organic pharmaceutical pollutants are prone to autodegradation in the presence of sunlight and water by photolysis and hydrolysis respectively, but algal growth hinders the path of UV rays and limits their action.

Metabolite tracing methods are used to detect the fate of compounds as the end product of the cellular biochemical process. The use of isotope-labeled tracers allows the visualization of the dynamics of the metabolic process. Compounds are labeled by replacing specific atoms with a radioactive isotope. The compound is then allowed to metabolize and undergo reactions. The position of the isotope in the products is monitored to determine the reaction sequence that the radioisotope followed in the cell's metabolic pathway. Nuclear magnetic resonance detects atoms with different gyromagnetic ratios. Pan et al. (2021) used this application of metabolite tracing by HPLC-ToF-MS to reveal the metabolic pathway for the degradation of tetracycline. Biodegradation exhibited a close association with biosorption and bioaccumulation. The removal of tetracycline was facilitated by adsorption to the cell surface, followed by ingestion of molecules into the cells (bioaccumulation) which finally led to the molecule’s participation in metabolic pathways. As shown in Fig. 2c, three pathways have been identified for tetracycline degradation in algae, of which pathway 1 is considered generalized while pathways 2 and 3 are species-specific. Overall, the degradation of tetracycline within cells relies on dealkylation, deamidation, dehydrogenation, hydrolysis, ring fragmentation, etc. (Pan et al., 2021). Yu et al. (2017) studied the degradation of ceftazidime antibiotic and performed metabolites analysis of supernatant. In this process, Δ-3 ceftazidime isomer was produced by the translocation of a double bond from the 2-position to the 3-position. Ceftazidime and its derivatives further followed different fragmentation pathways and 7-aminocephalospranic acid (7-ACA) was detected. A similar pattern was found also in Zhou et al.’s (2021) work on chlorotetracycline by

S. platensis, in which chlorotetracycline was attached to the cell surface by electrostatic interaction and was then taken in by the cells. Enzymatic degradation of chlorotetracycline was facilitated by both intracellular and extracellular enzymes. The main role of extracellular enzymes is to increase the hydrophilicity of molecules that make it prone to hydrolysis, reduction, and oxidation. Intracellular enzymes act primarily on ring structures and further degrade molecules.

Zhou et al. (2021) also identified hydroxylation and side-chain breakdown as a major mechanism for the degradation of chlortetracycline by *S. platensis* and reported more than 98% of antibiotic removal after treatment. The concentration range of above 1 mg/L of chlortetracycline (CTC) and oxytetracycline (OTC) above 1 mg/L suppressed the growth of *S. platensis* as well as antibiotics removal while at lower concentration neither of the antibiotics had any toxic effect on algae. Wastewater containing CTC and OTC has a risk quotient of 15.85. Growth inhibition was also distinct from inhibition of phycocyanin production, increased saturated and polyunsaturated fatty acids contents, and lowered superoxide dismutase activity (Zhou et al., 2021). In another study, a combination of multiple algae-culture improved decomposition and absorption rate. A microalgae-mediated antibiotic treatment system with *C. pyrenoidosa* exhibited 41.47 ± 0.62% elimination of cefradine after 24 h which was higher than the control group (no algae) which had a removal rate of 12.37%. The use of multiple microalgae species (*C. pyrenoidosa* with extract of *Microcystis aeruginosa*) further improved the removal rates to 75.48 ± 0.29 (Xiao et al., 2021).

4.2 Indirect methods: Indirect treatment is the approach in which algae is first grown, harvested, and then further utilized for pollutant removal (Gurav et al., 2021). Microalgae-derived biochar applications have been reported in different areas of study such as CO_2 adsorption and pollutant removal. Shi et al. (2021) prepared N-doped porous biochar from *Chlorella* and *Spirulina*, further used for CO_2 adsorption, and reported 3.44 and 3.09 mmol/g adsorption capacity at 25 °C. Microalgae-derived biochar also has applications in bioelectrochemical systems where it can be used for electrode preparation (Lee et al., 2018). The advantages of biochar use in bioremediation are summarized below.

Bioadsorption by algae-derived adsorbents (Biochar): As discussed earlier, algal cells have the potential to bind with pollutants at their cell surface and can be used as living biomass during cultivation as well as dead biomass generated from different processes. However, the surface area and pore profile of biomass itself are quite insufficient and incomparable to commercial-grade adsorbents generated from various natural or artificial resources like activated carbon. Such adsorbents usually have a surface area above 1000 m^2/g in comparison to algal biomass with a surface area of 10-300 m^2/g. In addition, activated carbon can be subjected to surface modification and high adaptability as required (Kumar and Jena, 2016; Lu and Xue, 2019; Kumar et al., 2020). On comparing the adsorption potential/capacity of living and dead biomass with biochar, the trend is as follows: Living cells < Dead cells < Biochar. Algal biomass which is discarded after the extraction of lipid or metabolites in other processes can be used for biochar generation, as most of the impurities and bound material degrade thermally during char preparation. Based on carbonization conditions, biochar preparation methods can be classified into pyrolysis, hydrothermal carbonization, and torrefaction (Bhatia et al., 2021b). Pyrolysis can be classified further as slow or fast pyrolysis based on the heating rate. The slow process involves heating at a temperature between 300-700 °C for a longer time (eg. hours or days) at a lower heating rate (0.1 to 1 $°Cs^{-1}$). In fast pyrolysis, biomass is heated at a higher temperature between 600-1000 °C for a short time (seconds) at a higher heating rate (10-10000 $°Cs^{-1}$) (Tan et al., 2021).

Due to the difference in operating conditions, the byproducts are also different. Slow pyrolysis results in biochar as the major product with bio-oil as a side product while in the case of fast pyrolysis the major product is bio-oil. In hydrothermal carbonization, algal biomass carbonizes in the presence of solvent (mostly aqueous) at high pressure to produce hydrochar that is rich in hydroxyl or related functional groups. In contrast to pyrolysis, torrefaction is carried at a lower temperature range of 200-300 ^{o}C at atmospheric pressure in the absence of air. The generated product from torrefaction is biochar without any significant byproducts (Michalak et al., 2019; Sekar et al., 2021; Singh et al., 2021). To overcome the heating rate and mode of heat transfer, an advanced approach such as microwave use has been integrated. Among different carbonization processes, hydrothermal carbonization is one of the most versatile methods that is subjected to change as required. As a result of high-temperature exposure, the majority of volatile material and minerals degrade or evaporate, leaving a carbon backbone with some functional groups. Surface functionality can be modified further as needed by having extra functional groups added or the carbon backbone can be used as it is. The backbone can interact with other molecules via physical interactions that can be modified by adding impurities and functional groups to promote ionic/electrostatic interaction.

A large amount of algal biomass of *Ulva prolifera* is produced in green tides especially in the coastal zone. In one study (Lu et al., 2017), *U. prolifera* biomass was dried and underwent liquefaction at 200 ^{o}C. The biochar prepared from the biomass contained 2.66% N along with carbon as a major constituent. The biochar exhibited surface area and pore volume of 25.43 m^2/g and 0.121 cm^3/g. Biochar surface featured the functional groups –OH, –N-H, –C=O, and – C=C.

N-doped biochar removed the majority of bisphenol-A from water samples with a maximum adsorption capacity of 9.38 mg/g 4 h. pH had a negligible effect on adsorption capacity while adsorption capacity increased with ionic strength (0-500 mM). The Langmuir model of adsorption capacity (Qm) also exhibited an increase from 33.30 to 84.19 mg/g when the temperature was increased from 25 to 45 °C (Lu et al., 2017). Chabi et al. (2020) prepared biochar from the biomass remaining after biofuel extraction from *Chlorella* by hydrothermal carbonization. Biomass underwent liquefaction at 250 ^{o}C and 10 mPa followed by phase separation. The resulting biochar was washed, dried, and used for the removal of the tetracycline. Algal-based biomass, being mesoporous, has a surface area of 126.4 m^2/g and an average pore diameter of 11.62 nm. The biochar was modified with aluminum boride carbide and boehmite and as a result exhibited a maximum adsorption capacity of 25.94 mg/g which was mainly contributed to physisorption (Chabi et al., 2020). Table 4 summarizes some of the major findings for pharmaceutical pollutant removal using algal biochar.

5. Methods to improve the contaminant removal efficiency

To improve the efficiency of pollutant removal, research has focused on different strategies such as enhanced reactor design, the use of algal-microbial consortia, and integration of wastewater treatment processes with resource recovery and byproducts acquisition technology.

5.1 Improved reactor design: An open system is a conventional approach for onsite wastewater treatment on a large scale. In an open system, naturally available or artificially constructed ponds, lakes or lagoons are used for wastewater storage and onsite treatment with microorganisms under aerobic conditions. The Raceway pond system at Calipatria USA is the largest open pond system designed for *Spirulina* biomass production. The major advantage of an open pond system is that algae utilize the majority of nutrients from the environment. Sosa Texcoco, Earthrise Farm, Japan Spirulina, Taiwan Chlorella, Far East Microalga, Microbio Resource, Betatene, Cyanotech, Western Biotechnology, and Parryn Nutraceuticals are major companies that have exploited open pond systems for algae cultivation. LiveFuels, Kent BioEnergy, and Algaeventure systems are commercial companies using algal-based open pond systems for wastewater treatment and removal of pharmaceutical pollutants (Molazadeh et al., 2019; Xiaogang et al., 2020).

Open pond systems have lower construction costs and can be operated onsite and so reduce the transportation cost of wastewater to treatment plants. However, such systems have limitations and are prone to contamination. Lack of uniform distribution of nutrients and oxygen is one of the biggest constraints due to the absence of mixing. It also brings abnormal variation in pH and temperature as well. In the case of higher microbial density and system vertical depth, the system may become anaerobic or semi-aerobic. To support algal growth and photosynthesis, a CO_2 supply is needed at regular intervals. Both of these conditions also affect the penetration of sunlight and hinder agal growth as well as the photolysis of pollutants. The CO_2 generated during microbial metabolism may escape to the environment along with water and volatile matter by evaporation and further pollute the air (Al-Jabri et al., 2021). To reduce such emissions, artificial closed or semi-closed system photobioreactors have been designed where conditions are maintained artificially and allow the recycling of CO_2 during photosynthesis. The bioreactor system was further modified into a tubular, flat panel and Tic bag photobioreactor. Such systems are inexpensive and provide good biomass production, despite there being diverse features for each. For example, the tubular system undergoes adverse variation in pH and CO_2 concentration. In the flat panel photobioreactor, temperature regulation is difficult to maintain while the Tic bag system generates plastic bags which can prove harmful to the environment.

Xiong et al. (2018) constructed a photo-bioreactor system using microalgae-bacteria consortia containing mixed bacterial and algal cultures. Consortium-filled photo-bioreactors were added in line with an anaerobic membrane bioreactor which discharged biogas and effluent. The major aim of this study was to remove carbon dioxide (CO_2) from biogas while utilizing the nutrient from effluent. The effluent was divided into two different tanks containing high dose tetracycline and low dose tetracycline. Tetracycline dose was found to have no impact on CO_2 removal and it was found that approximately 29% v/v of CO_2 was required to be completely removed to liberate > 20% v/v of oxygen from both the reactors. In contrast, nutrient consumption and biomass generation were reduced when tetracycline concentration increased from 150 µg/L to 20 mg/L. Tetracycline concentration also influenced the microbial community by reducing populations of denitrifying microorganisms such as *Hydrogenophaga* and nitrogen-fixing genera including *Flavobacterium*, unclassified *Burkholderiales,* and *Rhizobiaceae,* and phosphate-accumulating microorganisms such as *Acinetobacter* spp. and *Pseudomonas* spp. (Xiong et al., 2018). Open photobioreactors have also been used for the removal of Contaminants of Emerging Concerns (CECs) (Lapez-Serna et al., 2019). Algae bacterium tubular photobioreactors have better results for the removal of volatile organic compounds like toluene, compared to traditional bacterial bio-trickling filters. This is mainly attributed to the synergistic action of bacteria and algae which increases the level of dissolved oxygen and helps in CO_2 fixation, giving overall better efficiency (Oliva et al., 2019). A membrane bioreactor was designed with bioaugmentation of *Haematococcus pluvialis* for the removal of antibiotics from wastewater under aerobic conditions. Augmentation of algae improved the antibiotic removal rate by 20% and attained maximum removal of 89.73%. In addition, it delayed membrane biofouling by 33% (Aydin et al., 2022).

The separation of algal and bacteria cells is a common issue associated with the open and closed treatment systems, requiring high energy and labor input. Immobilization of cells or a diffusible system with microorganisms might be required to reduce separation cost. Gao et al. (2011) compared the free culture of *C. vulgaris* and alginate-immobilized cells for the biodegradation of nonylphenol. Immobilization reduced the algal growth and overall biodegradation efficiency of *C. vulgaris*. Under short-term exposure, the removal efficiency was higher in the case of immobilized cells but in the long term, free cells proved equally competent. In 12 h exposure, the removal efficiency of free and immobilized cells was 59% and 73% respectively. The removal rate of free cells was 93% after 96 h and after 168 h the removal rate was 94% for both forms. The mechanism of nonylphenol removal in both free and immobilized cells followed the same pattern i.e. adsorption onto algal cells and alginate matrix followed by cellular biodegradation. 50-100×10^4 algal cells/bead and 2-4 beads/mL resulted in optimal removal of nonylphenol from wastewater (Gao et al., 2011). Mixed algal culture predominantly containing *Chlorella* sp. and *Scenedesmus* sp. was immobilized on luffa sponge and polyurethane foam for the removal of nitrates and organic microcontaminants including sulfa-antibiotics and commonly used pesticides atrazine, bentazone, bromacil, diuron, and mecoprop from groundwater. In the batch experiment, the removal efficiency was around 87% with an immobilized system. In continuous mode, the efficiency was higher in the case of the luffa system which was 95%, 93%, and 82% for sulfacetamide, sulfamethazine, and sulfamethoxazole respectively (Ferrando and Matamoros, 2020). The benefit of immobilization with microalga-bacteria consortia for the removal of sulfamethoxazole (SMX) from anaerobically digested centrate (ADC) was exploited by Xie et al. (2020). For comparative evaluation, microalgal-bacterial consortium was categorized into three groups *viz* suspended *C. vulgaris* (SCV), immobilized *C. vulgaris* (ICV), and immobilized *C. vulgaris*-with-powdered activated carbon (ICV+PAC). The impact of SMX on the ADC treatment performance, *C. vulgaris* growth, and microbial community shifts was investigated. The presence of SMX suppressed the algal growth as well as SMX degradation while beads defended the consortium from the harmful impact of SMX. Viable *C. vulgaris* in ICV and ICV+PAC were 85.1% and 86.2% which were higher than 74.6% in SCV. The presence of AC neutralized the toxicity of SMX and stabilized the microalgal-bacterial consortium to achieve a maximum SMX removal of 99%. The other counterpart of the consortia was dominated by *Pseudomonas, Brevundimonas,* and *Hydrogenophaga* which also promote SMX degradation (Xie et al., 2020).

The scale-up of technology is also important to implement processes at a commercial level. Matamoros et al. (2015) evaluated the effect of hydraulic retention time (HRT) and ambient temperature/sunlight irradiation on removal efficiency of various emerging contaminants mixture (fire retardants, surfactants, pesticides, pharmaceuticals, personal care products, etc.) from high rate algal ponds (HRAP) fed urban wastewater (Universitat Politècnica de Catalunya–BarcelonaTech, Spain) (Matamoros et al., 2015). The removal efficiency ranged from negligible to 90%, depending on the compounds, with biodegradation and photodegradation the most common pathway. The pollutant removal efficiency was higher during the warm season and HRT effect only noticeable in the cold season. de Godos et al. (2012) studied tetracycline removal mechanism during wastewater treatment in14 L pilot HRAPs. Tetracyclin was removed by up to 69% and the main mechanisms involved were photodegradation and biosorption. It was concluded that the shallow geometry of HRAPs is advantageous to support the photodegradation of antibiotics. In another study, ciprofloxacin removal from real wastewater was studied using 1000 L high rate HRAP and it was reported the main mechanism in antibiotic removal involved photodegradation in the daytime and adsorption to biomass at night (Hom-Diaz et al., 2017).

5.2 Algal-bacterial consortia: Algal metabolism relies mainly on photosynthesis, which is most active during the photoperiod, and latent or suppressed in the dark phase. The addition of nutrients and vitamins to the medium must be considered to support the algal growth in the wastewater, as well as necessary oxygen purging. Microorganisms that are metabolically active in darkness can improve nutrient removal. The addition of different bacterial strains in the construction of consortia has been proven effective for wastewater treatment. Bacteria cells are metabolically active beyond the duration of the photoperiod and promote dark fermentation. Bacteria generate CO_2 during metabolism along with various metabolites like vitamins, phytohormones, etc. that can act as growth promoters for algae. During the photoperiod, algae consume available CO_2 for photosynthesis. Cumulatively, algae and bacteria together removed nitrogenous material by autotrophic and heterotrophic denitrification. For aerobic degradation of pollutants and bacterial growth, the necessary regular supply of oxygen is supplied by algae during photosynthesis. In consortia, both organisms complement each other and reduce the need for oxygen purging by more than 70% as generated oxygen can be consumed by bacteria, and CO_2 liberated mainly from bacterial metabolism can be sequestered by algae. Various techniques including physical (microscopy and flow cytometry) and molecular approaches (genomics, proteomics, transcriptomics, and metabolomics) can be used to study algal-bacteria consortia structure and interactions, as reviewed by Perera et al. (2019). Organic pollutants participate in metabolic pathways of bacteria and algae as electron/proton acceptors or donors. Microbial enzymes may also act on pollutants based on their bonds or functional groups as action sites (Fallahi et al., 2021). In some cases, consortia may also be constructed with different species of algae due to different metabolic pathways as suggested by Bano and colleagues who constructed algal consortia with *Chlorella* sp., *Merismopedia* sp., *Closteriopsis* sp., and *Scenedesmus* sp. and evaluated for the removal of estradiol, diclofenac, and triclosan from wastewater (Bano et al., 2021). The microbial consortia successfully grew in the presence of organic pollutants and resulted in the removal of around 74.68% diclofenac, 91.73% estradiol, and 78.47% triclosan during microalgal growth. Neither diclofenac nor estradiol has any detrimental effect on chlorophyll content or algal biomass except triclosan. Ji et al. (2019) also used algal-bacterial consortia of *C. vulgaris-Bacillus licheniformis* for the treatment of municipal wastewater. The treatment efficiency was calculated in terms of total nitrogen, phosphorus, and COD. Treatment resulted in the removal of total nitrogen (88.82%), ammonium (84.98%), orthophosphate phosphorus (84.87%), and chemical oxygen demand (82.25%).

Microalgal-bacterial consortia were isolated from a tilapia fish breeding tank located at the botanical garden at the Federal University of Ouro Preto (UFOP) predominantly containing *Chlorella sorokiniana* as its algal species. The consortia were used for treating wastewater containing sulfamethoxazole (SMZ) and functioned symbiotically as the oxygen provided by algae was consumed by the bacteria and so promoted the degradation. The consortia removed 54.34 ± 2.35% SMZ from WWTP effluents (da Silva Rodrigues et al., 2020). Algal-bacterial consortia containing *S. almeriensis* removed veterinary medicinal products (VMP) including ciprofloxacin, tetracycline, sulfadiazine, and sulfamethoxazole from wastewater by adsorption. Adsorption of organic pollutants on consortia followed pseudo-first-order and pseudo-second-order kinetics. At lower concentration, the maximum removal efficiency was reported with ciprofloxacin (43-100%) and tetracycline (75–82%), producing maximum adsorption rates of 0.11–26.66 and 1.78–27.09 mg/μg/h, respectively. In contrast, sulfadiazine and sulfamethoxazole had lower removal rates which did not exceed 32% (Zambrano et al., 2021). Wang et al. (2022) also reported the efficient removal of antibiotics including oxytetracycline (OTC) and enrofloxacin (EFX) from polluted water by an algal-bacterial consortia system. In the low antibiotic dose group (EFX <1 mg/L and OTC <5 mg/L), algal growth was enhanced by 21.83% and 22.11% respectively. Consortia removed approximately 42% of EFX, 99% of OTC, and >70% of total organic carbon and phosphorus. In comparison, the high dose group with 5 mg/L EFX and 10 mg/L OTC inhibited algal growth and lowered nutrient removal. Metabolite analysis revealed increased activity of superoxide dismutase and catalase, and malondialdehyde content with lowered chlorophyll-a. These results demonstrate the direct influence of pollutants on physiological performance of algae (Wang et al., 2022).

5.3 Algal-fungal consortia: To overcome tedious biomass harvesting and insufficient CO_2 supply, co-culturing of algae with filamentous fungi has been proposed. Fungal mycelium aided in the harvesting of microalgae by co-pelletizing and auto-flocculation, a method considered more economical and environmentally friendly than physical and chemical methods. Microalgal pellets developed due to interactions between algae and fungi during pelletization, a process supported by physical and chemical interactions as well as the presence of exopolysaccharides, and surface proteins (Leng et al., 2021; Rosero-Chasoy et al., 2021; Wang et al., 2019). Microalgae-filamentous fungi consortia offer promising results for wastewater treatment in comparison to algae and fungi alone. Different physical and chemical properties of fungi and algae support consortia formation and the survival of individual members. Fungal members of consortia metabolize organic molecules and release inorganic material while algal members metabolize inorganic nutrients (nitrogen and phosphorous) for photosynthesis and release oxygen and organic molecules. Fungal members also degrade large organic molecules and pollutants with the help of a wide range of intracellular and extracellular enzymes that remove heavy metals and pollutants via biosorption (Chen et al., 2020; Leng et al., 2021).

Algal-fungal consortia can withstand high COD load and have a higher removal rate due to mixotrophic behavior. Inorganic carbon, available either as carbon dioxide or carbonate ion, is accepted by microalgae cells and converted to organic molecules via photosynthesis and released into surroundings along with oxygen, while fungi utilize these organic nutrients and oxygen to discharge carbon dioxide and inorganic nutrients (Chen et al., 2020; Gonçalves et al., 2017; Wang et al., 2016). The phenol removal capacities of algal and fungal strains including *Desmodesmus* sp., *Chlamydomonas* sp. *Rhizopus* sp. and *Mucor* sp. were compared and these strains exhibited excellent phenol removal capacities in the range of 70%, 56% (from algae; 25 days; 25 mg/L), 84%, and 82%, respectively (from fungi; 25 days; 100 mg/L). The consortia were constructed with *Desmodesmus* sp. and *Rhizopus* sp. exhibiting a phenol removal capacity of 95% (initial concentration 25 mg/L) after 25 days (Al-fawwaz et al., 2016). Jiang et al. (2019) evaluated algal-fungi consortia comprised of *Chlorella variabilis* NC64A and *Ganoderma lucidum* for nutrient removal from synthetic wastewater containing inorganic nutrients and glucose. Microbial consortia of 1:3 mass ratio exhibited maximum removal of nutrients and pollutants *viz* 75.5% COD, 76.7% total nitrogen, 74.7% total phosphorus, and 90% ammonium nitrogen. Microalga-fungal consortia were constructed with *C. vulgaris* and *Aspergillus niger* to determine the effect of wastewater quality in a special context to the presence of diclofenac on lipid accumulation in biomass. After five and eight days of growth, there was no effect of diclofenac on algal biomass was observed. The removal of nutrients and pharmaceutical pollutants was significantly increased after the addition of the fungal component on day 5. At the end of the experiment (day 8) the reduction in total nitrogen and phosphorus was 47.4% ± 18.4%

and 94.4% ± 3.2% respectively, along with 46.4% reduction in micropollutant concentration. The total lipid content decreased after the addition of the fungal component but this was offset by the increase in biomass production (Hultberg et al., 2019).

5.3. Integrated process design: Algal treatment offers a multifaceted opportunity to use the process for multiple benefits (Fig. 4). Integration can be classified into the following categories:

Coupling with other treatment & oxidation processes: In the case of recalcitrant and highly toxic pollutants, microbial growth and removal potential may be hindered. Therefore, other chemical treatment methods employed that transform the pollutants to degradable form will be utilized by algae during their growth. For disinfection of wastewater, UV-assisted photodegradation is one of the most effective and commonly used methods which can rapidly eliminate pollutants. However, in highly viscous and opaque media, UV can only penetrate close to the surface. For effective removal of pollutants like cefradine, UV treatment has been integrated with algal degradation. Integration of UV exposure with algal cells (*C. pyrenoidosa*) induced indirect degradation and resulted in >78% removal of antibiotics in comparison to algae alone (approximately 20%) along with a reduction in toxicity of >50% (Du et al., 2015). Apart from radiation, advanced chemical reagents can also be employed to increase the degradation via free radical, oxidation, methylation, hydrolysis, and decarboxylation. The Fenton reaction with H_2O_2/Fe(II) and free radical assisted degradation with Fe(III) was exploited for the degradation of norfloxacin, enrofloxacin, and ciprofloxacin (Leng et al., 2020; Li et al., 2015; Zhang et al., 2012). Yang et al. (2017), also reported complete elimination of amoxicillin and cefradine by *S. obliquus* when used with UV treatment. The presence of algenitic organic matter in the growth medium might have inhibited algal growth, therefore wastewater was treated first with direct UV exposure, UV/peroxydisulfate (POD), UV/H_2O_2, and UV/NH_2Cl. As a result, specific UV absorbance (SUVA) was lowered by around 30%, 35%, 40%, and 23% from UV, UV/PDS, UV/H_2O_2, and UV/NH_2Cl respectively. Detailed characterization revealed that UV/PDS and UV/H_2O_2 acted mainly on flulvic and humic-like fractions in AOMs, degraded between 47.26% and 56.31%, and promoted algae growth (Wang et al., 2018).

***Product-based integration*:** Algae biomass and metabolites are the most potent sources of numerous bioactive molecules and biofuels (Kumar et al., 2021). Therefore, algal cultivation has become a source for the industrial production of biomolecules and the associated generation of revenue. The integration of wastewater processes with algal cultivation might become an ideal approach for producing cost-effective production of commercially important compounds such as biodiesel, bioalcohol, and carotenoids (Fig. 4).

Lipids production: Utilization of algae for pharmaceutical wastewater treatment. Algal cultivation for 72 h resulted in the removal of 72% and 62% of carbon and nitrate, respectively, with biomass productivity of 2.8 g/L. The total lipid and neutral lipid production from recovered biomass under light and dark conditions was 17.2%, 6.2%, and 15.8% and 6.5%, respectively (Hemalatha and Venkata Mohan, 2016). Xie et al. (2019), reported the complete removal of bisphenol A and tetracycline and approximately 20% removal of sulfamethoxazole by *Chlamydomonas* sp. Tai-03 via algal-assisted biodegradation along with photolysis and hydrolysis. The presence of antibiotics increased the lipid content in the algal cell from 5% to 49.5%. The composition of lipid may vary with the antibiotic but C18 lipid content increased by 15.2% in the case of 10 mg/L (Xie et al., 2019). Raw pharmaceutical wastewater was treated anaerobically, followed by aerobic microalgal treatment with *Tetraselmis indica* in a photobioreactor. A combination of MFC and algal treatment removed more than 90% of COD, TOC, and phosphate and 81% of nitrate. In the absence of algal degradation, the removal of

COD, TOC, nitrate, and phosphate was approximately 66.30%, 78.14%, 67.17%, and 70.03% respectively. In addition, *T. indica* lipid productivity from algae attained 16.40 mg/L/d and 15.69 mg/L/d with 0.085 and 0.089 g CO_2 L/d in microbial fuel cell effluent and raw wastewater respectively (Amit et al., 2020). Industrial effluents may contain traces of pollutants left after treatment that are added to water bodies. Drainage and household waste also contaminate water reservoirs. Singh et al. (2020) evaluated the potential of *Chlorella* sp. SL7A, *Chlorococcum* sp. SL7B and *Neochloris* sp. SK57 for the removal of pharmaceutical pollutants from river water. The process aimed to generate lipid for biodiesel from algal biomass along with water treatment. Maximum biomass productivity was 520 mg/L from *Neochloris* sp. SK57, followed by 498 mg/L from *Chlorella* sp. SL7A and 450 mg/L from *Chlorococcum* sp. SL7B. In comparison, maximum lipid productivity of 129 mg/L was recorded for *Chlorococcum* sp. SL7B comprising approximately 28% of dry weight (Singh et al., 2020).

Other products: Pharmaceutical wastewater treated by *S. abundans* in photo-bioreactor (PBR). The effluent discharged from the bioreactor was further used in a photosynthetic microbial fuel cell (PMFC) for the production of biofuel and electricity. Algal-assisted degradation in microbial fuel cells led to the removal of 88% COD, 97% nitrate, 93% phosphate and yielded a maximum voltage of 745.96 mV with the maximum power density of 838.68 mW/m^2 (Nayak and Ghosh, 2019). Algal biomass recovered from an urban wastewater treatment plant was explored for bio-oil production using hydrothermal liquefaction (HTL) and produced a bio-oil yield of 28.1% with a heating value of 38-29 MJ/kg (Cheng et al., 2019). The recovered algal biomass after wastewater treatment can also be used as a substrate for microbial fermentation to produce other valuable compounds such as bioalcohol, biogas, and other biochemicals (Arora et al., 2021; Dange et al., 2021).

6. Pharmaceutical control policy

Surplus pharmaceuticals negatively affect water quality, human health, and ecosystems. Current wastewater treatment technologies require behavioral changes (upgrading facilities and improved management of unused and expired medicines) and routine monitoring for risk assessment. The Organization for Economic Co-operation and Development (OECD) has started a program for risk diagnosis and analysis of problematic pharmaceuticals (OECD, 2019). In source-directed policies, measures are taken to prevent the release of toxic compounds in the environment by regulating pharmaceutical companies and healthcare organizations to manage their release. The imposition of bans is another source-directed approach, as was applied to diclofenac which has been banned for veterinary use in India, Pakistan, and Nepal due to adverse effects on vultures. Environmental Quality Norms (EQN) aim to control residual compounds, but the main challenge is a long time lag between the identification of a toxic compound and the introduction of EQN in legislation. In the Netherlands, drinking water supply agencies perform screening of non-targeted compounds to identify new potential hazardous substances. In 2015, authority was able to identify an unknown compound (Pyrazole) at 100 ug/L due to the malfunctioning of a wastewater treatment plant. This incident triggered a Dutch Drinking Water Directive to develop a water quality standard for Pyrazole. The World Health Organization (WHO) has a guideline for drinking water quality under the Water Safety Plan (WSP) which considers the risk assessment and management from water source to tap and adopting preventive measures (World Health Organization, 2012). The objectives include the prevention of contamination of water resources, removal of contamination through treatment, and prevention of contamination during storage and supply (Bartram et al., 2009).

Good Manufacturing Practices (GMP) and Best Available Techniques (BAT) are two of the policy tools used to regulate industries to help control the emission of pollutants (OECD, 2019). BAT contains guidance documents that control industrial design, operation, maintenance, and discharge permit conditions. The United States and EU both have BAT for pollution prevention and control during pharmaceutical production (DIRECTIVE 2010/75/EU, 2010; EPA 821-F-05-006, 2006). GMP ensures the quality of medicinal products and their intended use. Due to OCED regulation, most pharmaceuticals are produced in developing countries. For example, Sweden imports almost one-third of its antibiotics from the countries where the environment requirement and regulation enforcements are weak (India, China, and Puerto Rico) (Bengtsson-Palme et al., 2018). Use-oriented policies impose and encourage reduced consumption of pharmaceuticals by changing the behavior of physicians, pharmacists, and patients. Excretion and wastewater treatment plant effluent are major sources of pollutants in the environment and a user-oriented approach will be the most effective and economic approach to control pollution in comparison to end-of-pipe solutions (Daughton, 2014). In Sweden, almost 75% of unused drugs are returned and some pharmacies provide rewards and discounts to customers (Apoteket, 2018). In the US the Management Standard for Hazardous Waste Pharmaceuticals implemented a new rule in healthcare sectors and restricted the disposal of pharmaceuticals in the sewer system (EPA-HQ-RCRA-2007-0932, 2019, p. 2007-0932). The Indian government has started a medicine take-back program to dispose of unused medicine and their disposal by incineration at temperature >12000 °C. There is a need for guidance documents on managing and minimizing hazardous pharmaceutical waste around the globe to prevent toxic effects on humans and the environment.

6. Challenges and future direction: Although microalgae-based systems appear as promising and clean alternatives for the removal of organic pollutants in wastewater systems, it is clear that some challenges need addressing for the development of commercial wastewater treatment strategies. The major challenges are summarized below:

- *Efficacy of algal culture with real wastewater:* Most research has focused on either a single or a combination of a few pharmaceutical/organic pollutants at a relatively small scale (Encarnação et al., 2020b; Ouasfi et al., 2019) but the composition of real wastewater from industries and municipal sewage systems is more critical and diverse. More than 200 pollutants have been identified from sewage systems and the exact composition of pharmaceutical pollutants is mostly unknown. Some pollutants are recalcitrant, xenobiotic, and highly toxic, and may be present in very high concentrations. Several investigations have reported the inhibition/suppression of algal growth in the presence of antibiotics, therefore higher concentrations may be toxic and lethal for the biotreatment process (Bi et al., 2018; Gallagher and Reisinger, 2020). Zhang et al. (2019), reported that lower concentrations of carbamazepine, clofibric acid, ciprofloxacin, and diclofenac in wastewater promote the growth of *C. pyrenoidosa* while at higher concentrations these pollutants have an inhibitory effect. Hence, it is hard to predict the efficacy of algal-based treatment as some of the pollutants and metabolites may hinder the growth and/or survival of algae. The composition of activated sludge can even be modulated and changed by pharmaceutical pollutants. Thus, there is a need to develop more efficient analytical methods to detect various pollutants at low concentrations.

- *Diverse nature of pollutants:* The efficiency of biodegradation relies on the availability of pollutants in the aqueous phase so that algae can consume them or interact with them. Some drug molecules are hydrophobic and have very poor solubility in water (Pilli et al., 2020). Celecoxib (osteoarthritis treatment), ritonavir (anti-HIV drug) (Choudhary et al., 2017), paclitaxel, doxorubicin, tamoxifen, herceptin, (anti-cancer), diclofenac (pain killer), nitrendipine (hypertension treatment), isoliquiritigenin (anti-malaria drug) are some of the pharmaceutical pollutants with poor solubility (Larrañeta et al., 2018). These compounds separate themselves from water and become non-accessible to the algae (Choudhary et al., 2017; Pilli et al., 2020). A single operation process is not sufficient to deal with such pollutants, hence a multistage system needs consideration, in which hydrophobic and hydrophilic components can be separated based on their solubility and treated accordingly.

- *Stability of algal monoculture and immobilization:* For wastewater bio-treatment systems, algae are used as monoculture or in consortium with bacteria. Evaluation of a potential alga can be assessed in terms of nutrient removal and degradation of target molecules. As discussed in the above sections, a synergistic relationship is a convincing approach for effective results. Monocultures are prone to contamination especially in the case of open systems, which may lead to abnormal changes in pH and production of toxic microbial metabolites. The use of photobioreactors is beneficial for large-scale treatment but each system has its limitations and challenges as already discussed.

  Immobilization of cells in different matrices is another aspect that can aid in working with mono as well as a consortium for wastewater treatment. Cell recycling and separation after completion of the process is recognized as good practice. Entrapment, confinement, and adsorption are the common methods for immobilization, from which confinement/entrapment is the most common practice. It allows the packing of monoculture or consortia together or separately so that they act without harming each other (in case of non-compatible cultures) (Kube et al., 2018). Both natural and artificial matrices can be employed for this purpose but the major drawback is reduced mass transfer as cells are packed in a boundary system and the interactions with the substrate can be restricted (Eroglu et al., 2015). Moreover, matrix selection is another challenge as matrices must not be toxic to microorganisms or liberate any toxic byproduct. In the case of natural polymers, the matrix itself may be degraded by the algae or consortia.

- *Metabolic burden and consortium construction:* Microbial degradation of pharmaceutical and other organic pollutants depends upon the genetic makeup, expression profile, and metabolic pathways of the algae/bacteria. However, most wild organisms are not fit to degrade all organic pollutants mainly due to differential expression. Genetic improvement techniques may introduce external genes which result in a high metabolic burden on cells. A microbial consortium is the safest and most natural approach to reduce this burden. Microbial consortia included microorganisms from the same or different species, genera, or even kingdoms (Jawed et al., 2019; Liu et al., 2018). The use of algae/bacteria consortia has provided better results due to the synergistic and mutualistic relationships involved. However, their individual needs in terms of nutrients and physical conditions are quite different from each other which may become hard to provide to support the growth of both. Algae is an autotrophic microorganism that relies on available nutrients and atmospheric CO_2 to convert solar energy to chemical energy via photosynthesis. In return, it produces many organic and bioactive compounds. In contrast, bacteria and fungi are heterotrophic and survive without any light source, thus the consortium can form a mixotrophic system. Algae require a light source and supply of CO_2 especially during photoperiod, but bacteria require O_2 (except in anaerobic environments). Both conditions are opposite to each other and the organisms' survival together depends upon the extent of tolerance (da Silva and Reis, 2015). Algal species produce many toxic metabolites including alcohols, carbonyl compounds, phlorotannins, alkaloid, tannins, organic acids, polysaccharides, fatty acids, enzymes, peptides, terpenes, polyacetylenes, sterols, hydroquinones, and halogenated furanones that can inhibit bacterial growth (Falaise et al., 2016; Shannon and Abu-Ghannam, 2016). Here, separate compartmentalization of treatment systems, immobilization of microorganisms, and multistage treatment systems are needed. In addition, consortia can be formed with versatile microbes that can flourish without affecting each other. These processes can be further explored as viable alternatives for WWTP.

- *Byproduct generation:* Microorganisms can degrade a diverse range of pollutants via a wide range of mechanisms but sometimes microbial metabolites from the pollutants can be more toxic than pollutants themselves if there is partial degradation eg. acridine produced from carbamazepine and 2-4 dichlorophenol produced from triclosan and methoxy triclosan are both more toxic than their respective original pollutants (Xiong et al., 2018). Examples from the literature have shown that some algal species produce toxic metabolites such as cyanopeptides and cyanotoxins that are lethal to aquatic and terrestrial organisms, including humans (Kust et al., 2020). Therefore, metabolic products must be considered while designing any process to ensure the least possible toxicity of effluent from the treatment plant.

- *Pathogen survival and antibiotic resistance:* The composition and treatment of simulated wastewater are quite different from any real-world industrial wastewater. The wastewater from pharmaceutical industries and healthcare centers also contains a significant fraction of lethal and contagious waste including microbial pathogens. The survival of microbial pathogens is one of the major drawbacks of the algal treatment of wastewater. In successive cycles of treatment, these pathogens can accumulate and their continuous exposure to antibiotics and pharmaceuticals leads to antibiotic resistance which is of greater concern for society (Pilli et al., 2020). To lower the possibility of pathogen survival, biodegradation must be integrated with advanced detoxification such as UV-treatment which can kill microbial pathogens without affecting algae or members of algal consortia.

Algal-based treatment systems have immense potential for wastewater treatment and environment conservation as they can address multiple challenges simultaneously. To develop these systems into commercially sustainable enterprises, challenges to their success must be addressed carefully.

7. Conclusions

Conventional wastewater treatment methods are costly and inefficient for removing emerging pollutants. Microalgae-mediated wastewater treatment processes are gaining attention due to their ability to remove various micropollutants. The use of algae-bacterial and algae-fungal consortia and their coupling with other treatment technologies such as photodegradation and chemical degradation has the potential to make the wastewater treatment process more economical and efficient. Most of the studies available are limited to synthetic wastewater and systems scaled to laboratory size. There is a need to investigate the potential of this technology in realistically sized field trials. In addition to this burgeoning scientific approach, the emerging issue of pharmaceutical pollutants will be aided by greater public awareness with regard to unprescribed use of drugs and incorrect disposal of expired medicine. Formulation of policies to regulate pharmaceutical companies to manage their effluent will also be helpful to deal with the problem.

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Figures legend

Fig. 1 Illustrates the visualization network of countries involved in wastewater mediated wastewater treatment. Distinct clusters can be identified with different colors assigned to countries. The size of the circle corresponds to the frequency of publications while the thickness of the lines represents the co-authorship link and relative strength. Co-occurrence mapping is based on publication numbers (minimum number of occurrences = fifteen).

Fig. 2a Representative pathways for the photodegradation of ciprofloxacin.

Fig. 2b Different reactions involved in the biotransformation of progesterone.

Fig. 2c Pathways involved in tetracycline degradation.

Fig. 3 Mechanism of the removal of pollutants from wastewater, A. adsorption; B. bioaccumulation and, C. biodegradation.

Fig. 4 Integrated process design for micropollutant removal and product synthesis.

Table. 1 Distribution of various pharmaceuticals and antibiotics in wastewater.

Compound	Concentration (μg/L)	Source	Country	Ref.
Chlortetracycline	483.7	Influent of wastewater treatment plants	South Korea	(Kim et al., 2020)
Erythromycin	0.152	Mankyung river water	South Korea	(Kim et al., 2020)
Sulfamethazine	251.2	Influent of wastewater treatment plants	South Korea	(Kim et al., 2020)
Sulfathiazole	230.8	Influent of wastewater treatment plants	South Korea	(Kim et al., 2020)
Oxytetracycline	25.7	Influent of wastewater treatment plants	South Korea	(Kim et al., 2020)
	0.012	Wastewater treatment plant	Oslo, Norway	(Thomas et al., 2007)
Tetracyclines	0.10	Wastewater treatment plant influent	Australia	(Watkinson et al., 2009)
	0.003–0.008	Municipal wastewaters influents	Tianjin China	(Y. Wang et al., 2018)
	0.6–5.7	Surface water	Kwazulu-Natal, South Africa	(Agunbiade and Moodley, 2014)
	0.510	Wastewater treatment plant	Oslo, Norway	(Thomas et al., 2007)
Aspirin	0.664	Cilfynydd wastewater treatment influent	South Wales, UK	(Kasprzyk-Hordern et al., 2008)
	874	Influent sewage treatment plants	Canada	(Metcalfe et al., 2003)
	44.20	Wastewater treatment plant effluent	South Africa	(Agunbiade and Moodley, 2016)
	125-184	Influent of the wastewater plant	Manipal, India	(Praveenkumarreddy et al., 2021)
Ibuprofen	1.68	Cilfynydd wastewater treatment influent	South Wales, UK	(Kasprzyk-Hordern et al., 2008)
	5-8	Wastewater effluent	Canada	(Brun et al., 2006)
	117	Water bodies	Kwa Zulu-Natal, South Africa	(Matongo et al., 2015)

	0.41	Mankyung river water	South Korea	(Kim et al., 2020)
	5-12	Influent of wastewater	Manipal, India	(Praveenkumarreddy et al., 2021)
	0.21-1.85	Hospital wastewater	Hanoi, Vietnam	(Tran et al., 2014)
Naproxen	11-217	Influent of wastewater	Manipal, India	(Praveenkumarreddy et al., 2021)
	0.838	Cilfynydd wastewater treatment influent	South Wales, UK	(Kasprzyk-Hordern et al., 2008)
	52-55	Wastewater treatment plant influent	Gauteng, South Africa	(Amdany et al., 2014)
	0.15-0.49	Hospital wastewater	Hanoi,Vietnam	(Tran et al., 2014)
Diclofenac	12-68	Influent of wastewater	Manipal, India	(Praveenkumarreddy et al., 2021)
	22.3	Wastewater treatment plant influent	Kwazulu-Natal, South Africa	(Agunbiade and Moodley, 2016)
	15.3-19.4	Wastewater treatment plant	Germany	(Ternes et al., 2004)
	0.21-0.49	Wastewater treatment plant effluent	France	(Rabiet et al., 2006)
	0.251	Municipal wastewater treatment plant influent	Sapporo Japan	(Kimura et al., 2007)
	0.14-0.25	Hospital wastewater	Hanoi, Vietnam	(Tran et al., 2014)
	0.882	Wastewater treatment plant	Oslo, Norway	(Thomas et al., 2007)
Sulfamethoxazole	0.33-0.61	River and sewage water	Beijing, China	(Li et al., 2007)
	3.0	Wastewater treatment plant influent	Australia	(Watkinson et al., 2009)
	34.5	Wastewater treatment plant influent	Kwazulu-Natal, South Africa	(Matongo et al., 2015)
	0.049	Wastewater treatment plant influent	Scaynes Hill, UK	(Zhou et al., 2009)

Table 2: Major organic pollutants (antibiotics and pharmaceutical) and their impact on health and the environment

Pollutant	Use	Effect on health and environment	References
Cephalexin	Antibiotics	Nausea, diarrhoea, heartburn, rectal or genital itching, extreme tiredness	(Anh et al., 2021; Shraim et al., 2017)
Erythromycin	Antibiotic	Antibiotic resistance, delayed hatching, the lower survival rate	(Vumazonke et al., 2020)
Clarithromycin	Antibiotics	Nausea, vomiting, dark urine, stomach pain	(Vumazonke et al., 2020)
Sulfamethoxazole	Antibiotics	Anorexia, colic, vomiting, headache, drowsiness, and unconsciousness	(Vumazonke et al., 2020)
Ciprofloxacin	Antibiotics	Antibiotic resistance, digestive system disorder	(Ajibola et al., 2021; Mahmood et al., 2019)
Norfloxacin	Antibiotics	Genotoxicity, metabolic ailments, delayed development and decreased immunity	(Ajibola et al., 2021)
Ofloxacin	Antibiotics	Diarrhoea, headache, dizziness, lightheadedness	(Ajibola et al., 2021)
Levofloxacin	Antibiotics	Nausea, vomiting, diarrhoea	(Mahmood et al., 2019)
Amoxicillin	Synthetic auxin; digestive ailments associated with fat	Cardiac ailments, irregular breathing, respiratory discomfort	(Mahmood et al., 2019)
1-Naphthyl acetic acid	Synthetic auxin; digestive ailments associated with fat	Skin corrosion, rashes, allergy, eye damage	(He et al., 2021)
Naproxen	Osteoarthritis	Suppress metabolizing enzymes, alter mRNA expression, hepato-cellular degeneration	(He et al., 2021; Wojcieszyńska and Guzik, 2020)
Ibuprofen	Non-opioid; analgesics	Decrease fish spawning, endocrine disruption, membrane damage digestive glands and tract	(Chopra and Kumar, 2020; He et al., 2021)

Acetaminophen	Non-opioid; analgesics	Increased oxidative damage, oxidative stress, behavioral alteration, high cholinesterasic activity	(Nunes, 2020; Phong Vo et al., 2019; Shraim et al., 2017)
Atenolol	Antihypertensives	Cardiac ailments, irregular breathing, respiratory discomfort	(Shraim et al., 2017)
Metformin	GI disorders, antidiabetics (type 2)	Behaviour alteration in fishes (aggressive)	(Shraim et al., 2017; R. Zhang et al., 2021)
Norfluoxetine	Antidepressant	Have oxidative and apoptotic potential in *D. magna*	(Över et al., 2020)
Carbamazepine	Anti-convulsant	Congenital malformations, neuro-developmental	(Vumazonke et al., 2020)
Bezafibrate	Hyperlipidaemia	Inhibition of cell proliferation	(Pomati et al., 2006)
Estrone	Steroid	Unwanted estrogenic effect; perturbed development in fishes, feminizing the fish population, cardiovascular disease in human	(Adeel et al., 2017; Chi et al., 2013)
Aspirin	NSAID	led to renal failure, poor eggshell quality, and imbalance in the sex ratios of certain fish	(Shreya and Kannan, 2017)
Metroprolol	Used for heart failure, and moderate hypertension	Can harm bacteria, algae, insects, and plants	(Tolboom et al., 2019)
Tramadol	In the management of moderate to severe pain	Affect fish in the early stage of life	(Sehonova et al., 2017)
Trimethoprim	Used in the treatment of urinary tract infection	Having a toxic effect on *Tigriopus japonicus*	(Han et al., 2016)

Table. 3 Microalgae and processes involved in antibiotics and pharmaceutical removal.

Compound	Microalgae	Waste	Scale	Comments	Cultivation time & removal (%)	Reference
Antibiotics						
Amoxicillin	*Chlorella* sp.	Simulated wastewater	Flask level	The addition of carbon dots (CDs) increase photosynthetic activity and specific growth rate and improve amoxicillin removal by 18.6%.	13 days, 99.3%	(Zhao et al., 2021)
	Chlorella regularis	Synthetic wastewater	Flask level	Sodium acetate was used as an additional co-substrate and leads to AMO removal % improvement by 36%.	4-5 days, 88%	(C. Zhang et al., 2021)
	Chlorella sp.	Synthetic wastewater	Lab scale photobioreactor	Chlorella sp. treatment followed by activated sludge treatment.	12 days, >99%	(Shi et al., 2018)
Cefradine	*Chlorella pyrenoidosa*	Synthetic media	Flask level	*C. pyrenoidosa* was cultivated in the filtered fluid of *Microcystis aeruginosa* and this multi algae treatment resulted in improved removal.	24 h, 75.4%	(Zhao et al., 2018)
	Chlamydomonas reinhardtii	Synthetic media	Photobioreactor (50 mL)	Light irradiations have an important role and the removal of antibiotics followed pseudo-first-order kinetics.	8 h, 100%	(R. Jiang et al., 2019)

Cephalexin	Microalgae-bacteria	Wastewater	Flask level	The symbiotic interaction between microalgae and bacteria increases removal efficiency.	7 days, 96.54%	(da Silva Rodrigues et al., 2021)
Chlortetracycline	*Spirulina platensis*	Synthetic media	Flask level	Main biodegradation pathways involve hydroxylation and side-chain breakdown.	13 days, 98.6-99.5%	(Zhou et al., 2021)
	Chlamydomonas reinhardtii	Synthetic media	Flask level	*Iso*-chlortetracycline (ICTC), 4-*epi*-*iso*-chlortetracycline (EICTC) were the main degradation product.	24 h, 99%	(Zhao et al., 2020)
Metronidazole	*Chlorella vulgaris*	Synthetic media	Flask level	Metronidazole stimulates EPS production in C. vulgaris which plays role in antibiotic adsorption.	20 days, 59%	(Hena et al., 2020)
Roxithromycin	*Chlorella pyrenoidosa*	Synthetic media	Flask level	Biodegradation is the main mechanism with a minor role of bioadsorption and bioaccumulation.	21 days, 45.9-53.3%	(Li et al., 2020)
Sulfamethoxazole	*Scenedesmus obliquus*	Synthetic media	Flask level	Chlorophyll content decrease while carotenoid increase with the increase of antibiotic concentration.	12 days, Sulfamethazine (31.4-62.2%) and sulfamethoxazole (27.7-46.7%)	(Xiong et al., 2019)
Sulfonamide	*Chlorella* sp. CS-436	Artificial wastewater	Reactor scale 1L	Calcium oxide (CaO_2) pretreatment leads to an increase in EPS	30 days, 24-38%	(Vo et al., 2021)

				production which cause in SMs removal by 5-10%		
Tetracycline	Algal-bacterial biomass	Domestic wastewater	Batch reactor	Indirect photodegradation is the main mechanism with a minor role of sorption	4-7 days, 93-99%	(Norvill et al., 2017)
	Microcystis aeruginosa	Synthetic media	Flask level	Biodegradation was the main pathway and hydrolysis of tetracycline increased with the increase of pH	2 days, 98%	(Pan et al., 2021)
Thiamphenicol	*Chlorella* sp. L38 and UTEX1602	Synthetic media, antibiotic conc. 0-156.8 mg/L	Flask level	A low concentration of TAP stimulates growth. Biodegradation is the main mechanism.	14 days, 95% at 46.2 mg/L antibiotic	(Song et al., 2020)
Pharmaceuticals						
Diclofenac	*Picocystis* sp.	Synthetic media	Batch culture	Biodegradation is the main mechanism involved.	5 days, 73%	(Ben Ouada et al., 2019)
	Graesiella sp.	Synthetic media	Batch culture	Biodegradation is the main mechanism involved.	5 days, 52%	(Ben Ouada et al., 2019)
Naproxen	*Cymbella* sp.	Synthetic media	Flask level	Main degradation steps include hydroxylation, decarboxylation, demethylation, tyrosine conjunction, and glucuronidation.	30 days, 97.1%	(Ding et al., 2017)
	Scenedesmus quadricaud	Synthetic media	Flask level	Hydroxylation, decarboxylation, demethylation, tyrosine	30 days, 58.8%	(Ding et al., 2017)

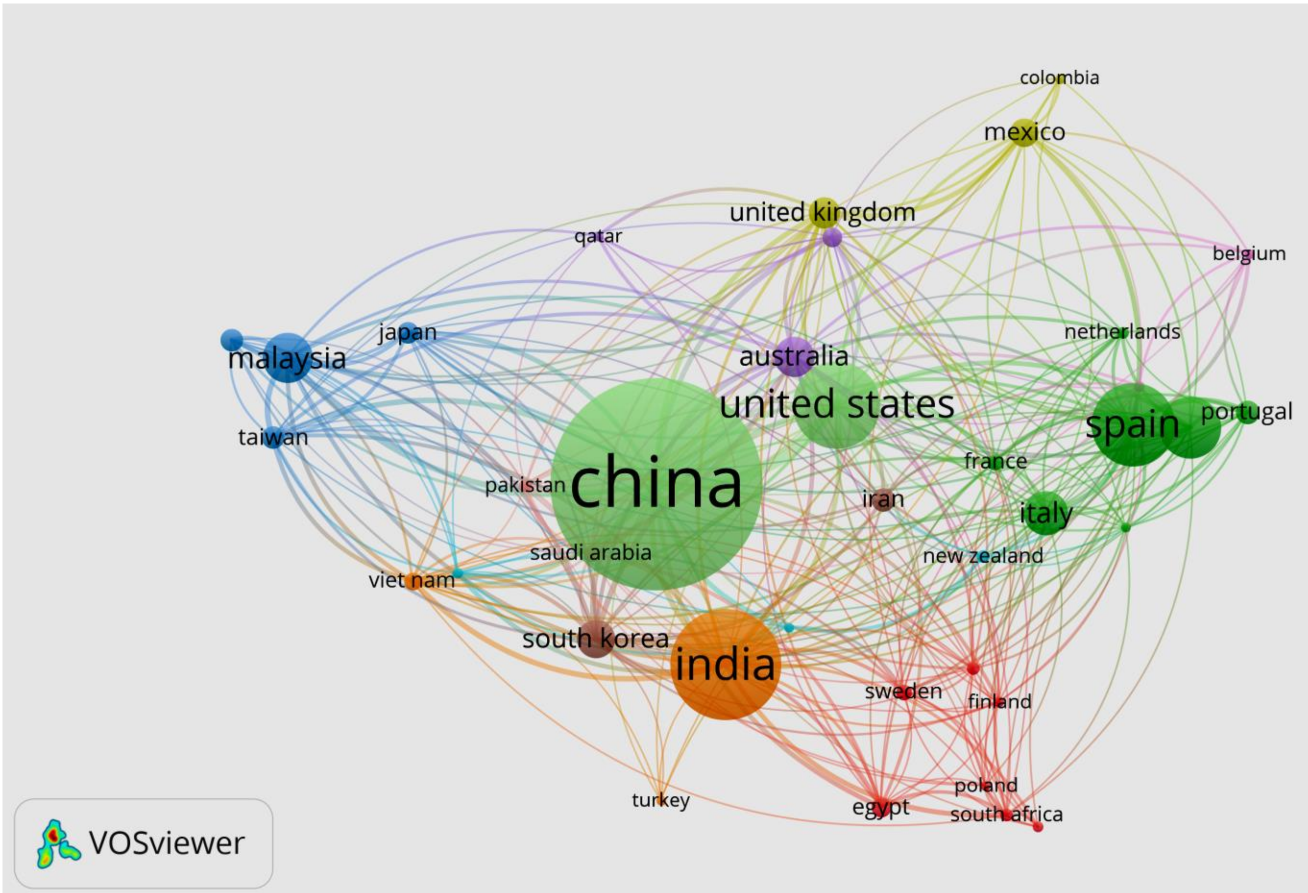
	a			conjunction, and glucuronidation.		
Paracetamol	*Chlorella sorokiniana*	Synthetic media	Bubbling photobioreactor (250 mL)	It induces microalgal growth by 35% at 250 mg/L.	7-8 days, 93%	(Escapa et al., 2017)
17β-estradiol	*Chlorella* sp.	Synthetic media	Flask level	This estrogen affects algal growth and removal efficiency decrease with concentration.	10 days, 92%	(Huang et al., 2019)
Salicyclic acid	*Scenedesmus obliquus*	Synthetic media	Flask level	Microalgae biomass homogenized and used as adsorbent. Follow pseudo second order.	-	(Silva et al., 2020)
Metronidazole	*Chlorella vulgaris*	Synthetic media	Flask level	Metronidazole stimulates EPS production in *C. vulgaris* which plays role in antibiotic adsorption.	20 days, 59%	(Hena et al., 2020)
Ibuprofen	*Scenedesmus obliquus*	Synthetic media	Flask level	Microalgae biomass homogenized and used as adsorbent. Follow Langmuir isotherm model.	-	(Silva et al., 2020)
Testosterone	*Chlorella vulgaris*	Synthetic media	Flask level	Testosterone removal occurs by bioaccumulation and biodegradation.	96 h, 69.6%	(Fu et al., 2019)

Table 4: Use of algal-based biochar for the removal of organic pollutants

Algae	Biochar preparation	Properties	Comments	Target pollutant (mg/g, % removal)	Reference
Enteromorpha prolifer	Dried algal biomass carbonized at 500 °C for 5 h followed by activation with KOH at 800 °C for 2 h.	SA: 2172.08 m^2/g Oxygen-containing functional groups. Oxidized nitrogen to pyridine, pyrrole, and quaternary nitrogen compounds.	KOH activation added pores. Adsorption is facilitated by chemical interaction, mass transfer, and diffusion.	Sulfamethoxazole (744 mg/g)	(Wu et al., 2021)
Ulva prolifera	Dried biomass was carbonized at 600 °C followed by washing.	SA: 257.41 m^2/g, Pore volume: 0.2830 cm^3/g. Av pore size: 4.40 nm.	Washing eliminated 'O' containing functional groups, improve hydrophobicity.	Ofloxacin	(Yang et al., 2021)
Chlorella sp. PTCC 6010	Algae biomass underwent hydrothermal liquefaction at 250 °C for 10 MPa followed by extraction with dichloromethane.	SA: 126.4 m^2/g Total pore volume: 0.55 cm^3/g. Av pore diameter: 11.62 nm.	Higher amount of -OH and -NH_2 followed by carboxylic functional group. Exhibited endothermic physical adsorption.	Tetracycline (25.94 mg/g)	(Chabi et al., 2020)
Spirulina sp.	Biomass was carbonized at 750 °C for 2 h in an inert environment.	SA: 2.63 m^2/g	Hydrophobic, rich in nitrogen containing functional groups along with carbonyl.	Tetracycline (132.8 mg/g)	(Choi et al., 2020)
Sargassum crassifolium	Biomass pyrolyzed at 500 °C for 2 h. Biochar was impregnated with zeolite for 3 h.	SA 124.359 m^2/g Pore volume: 4.994 cm^3/g. Biochar contain carbonyl, alcohol, and nitrogenous functional groups.	Adsorption was pH-dependent. Electrostatic interaction.	Ciprofloxacin (93.65 mg/g)	(Atugoda et al., 2021)

Laminaria digitata	Biomass impregnated with NaOH + sonicated for 6 h followed by pyrolysis of dried treated biomass at 600 ^oC for 2 h.	SA: 799 m^2/g Av diameter: 1.98 nm. Micropore area: 543 m^2/g.	Carboxylic FG: 2.06 mmol/g. Lactone: 0.86 mmol/g. Phenolics: 3.59 mmol/g. Electrostatic interaction, optimum between pH 3-4.	Ketoprofen (92%) Aspirin (95%)	(Ouasfi et al., 2019)
Cystoseirabarbata, C. agardh	Dried biomass (defatted with chloroform+methanol) + phosphoric acid under microwave treatment for 18 min of 700 w	SA: 1088.806 m^2/g Micropore volume: 0.181cm^3/g. Av pore radius: 2.71 A^o.	Rich in electron donor groups. Monolayer adsorption.	Hydroxychloroquine (98.9%)	(Gümüş and Gümüş, 2021)
Sargassum macroalgae	Macroalgal biomass pyrolyzed at 500 ^oC for 2 h	SA: 3.8 m^2/g. Pore volume: 0.006 ml/g.	Fixed carbon 46.45%. Electrostatic interaction.	Nitrazepam (98%)	(Nazal et al., 2021)
Chlorella, Chlamydomonas, Coelastrum	Microalgal biomass was pyrolyzed at 600 ^oC for 30 min under nitrogen purging	SA: 2.1-15.0 m^2/g. Negative zeta potential. Rich in oxygen-containing and polar functional groups.	Adsorption is facilitated by electrostatic and π-H bonding interaction.	p-nitrophenol (204.8 mg/g)	(Zheng et al., 2017)

Fig. 1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pakistan
china
iran
italy
saudi arabia
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poland
turkey
egypt
south africa
VOSviewer

Fig. 2a

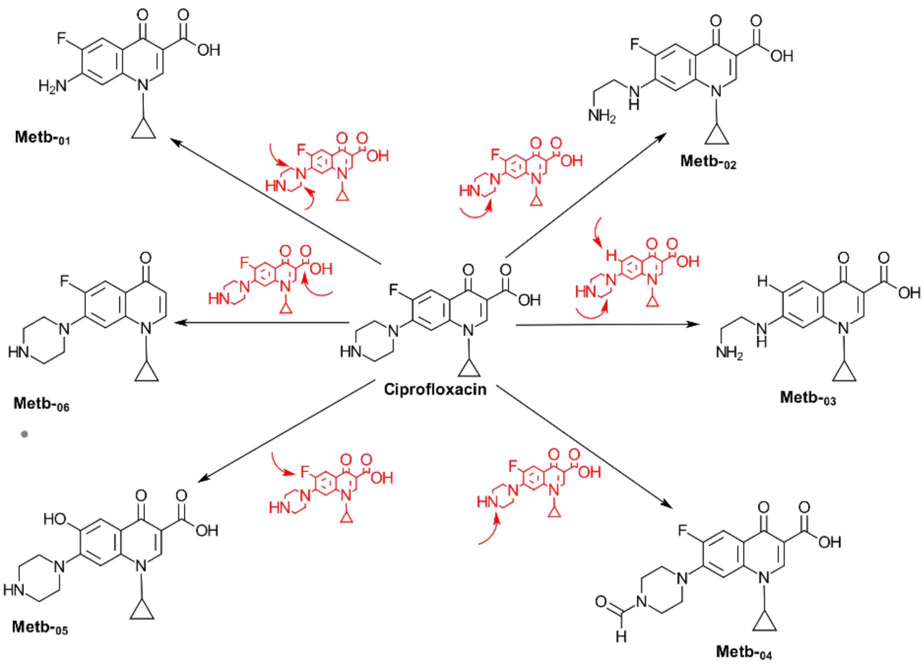
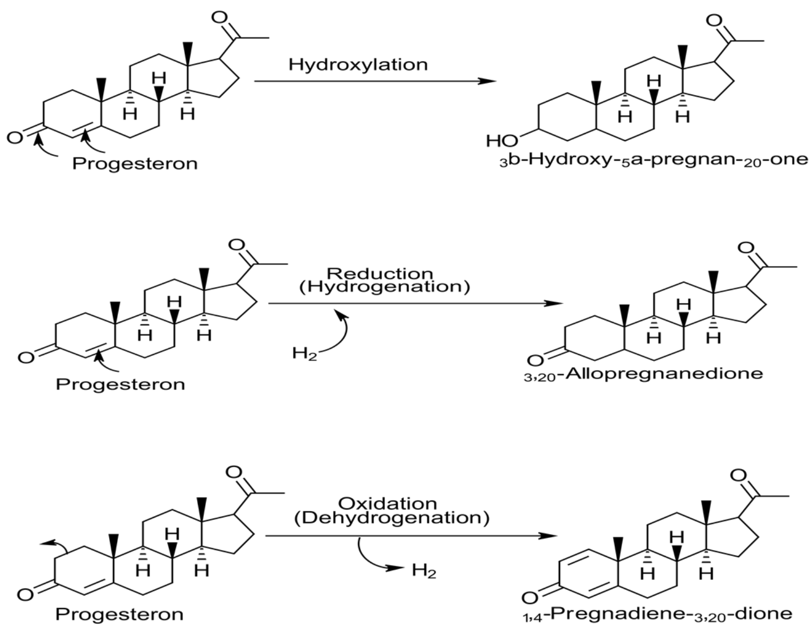


Fig. 2b



...(i)

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Fig. 2c

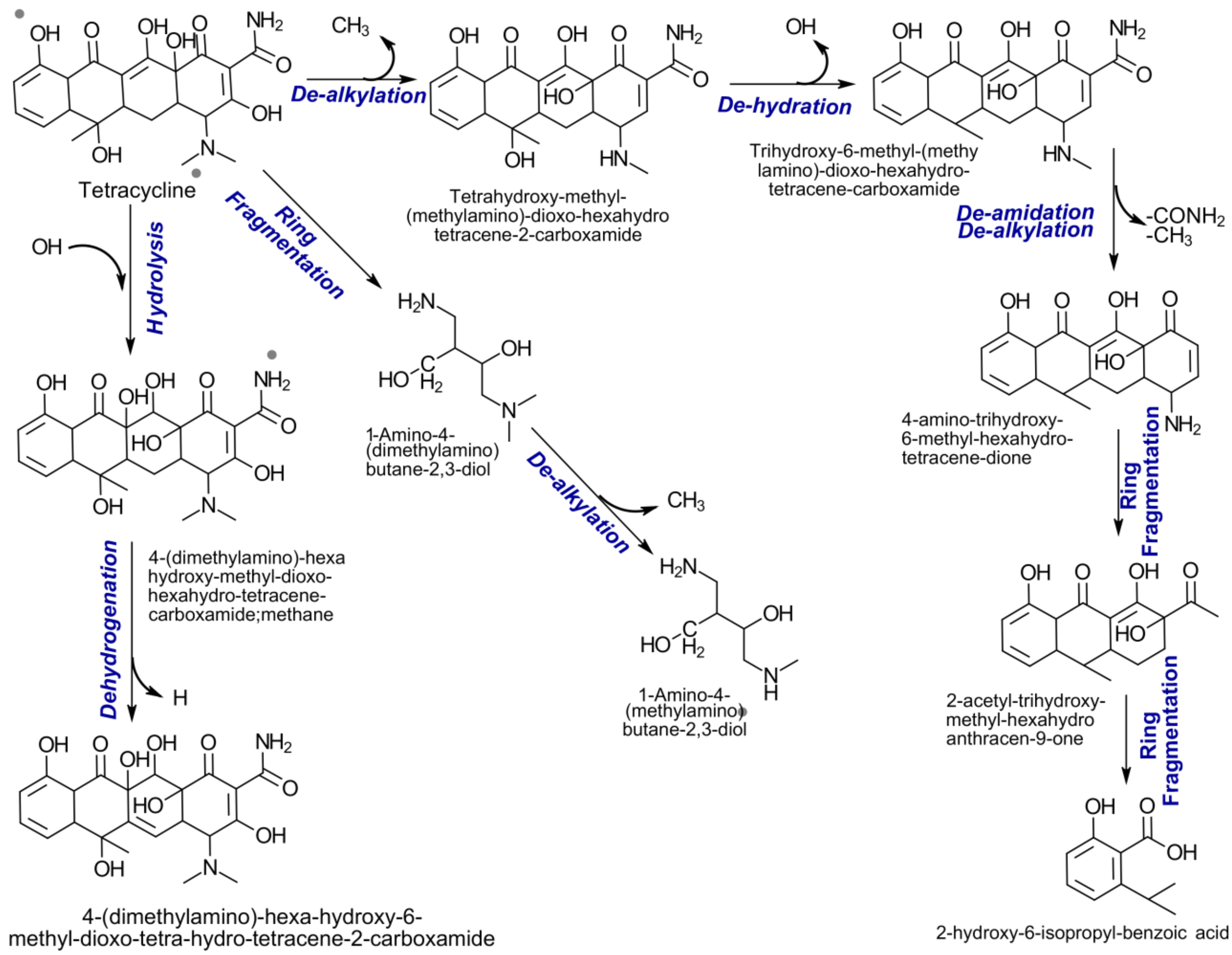

Tetracycline
De-alkylation
CH_3
Tetrahydroxy-methyl-(methylamino)-dioxo-hexahydro tetracene-2-carboxamide
De-hydration
OH
Trihydroxy-6-methyl-(methy lamino)-dioxo-hexahydro-tetracene-carboxamide
De-amidation
De-alkylation
$-CONH_2$
$-CH_3$
4-amino-trihydroxy-6-methyl-hexahydro-tetracene-dione
Ring Fragmentation
2-acetyl-trihydroxy-methyl-hexahydro anthracen-9-one
Ring Fragmentation
2-hydroxy-6-isopropyl-benzoic acid
Hydrolysis
OH
4-(dimethylamino)-hexa hydroxy-methyl-dioxo-hexahydro-tetracene-carboxamide;methane
Dehydrogenation
H
4-(dimethylamino)-hexa-hydroxy-6-methyl-dioxo-tetra-hydro-tetracene-2-carboxamide
Ring Fragmentation
1-Amino-4-(dimethylamino) butane-2,3-diol
De-alkylation
CH_3
1-Amino-4-(methylamino) butane-2,3-diol

Fig. 3

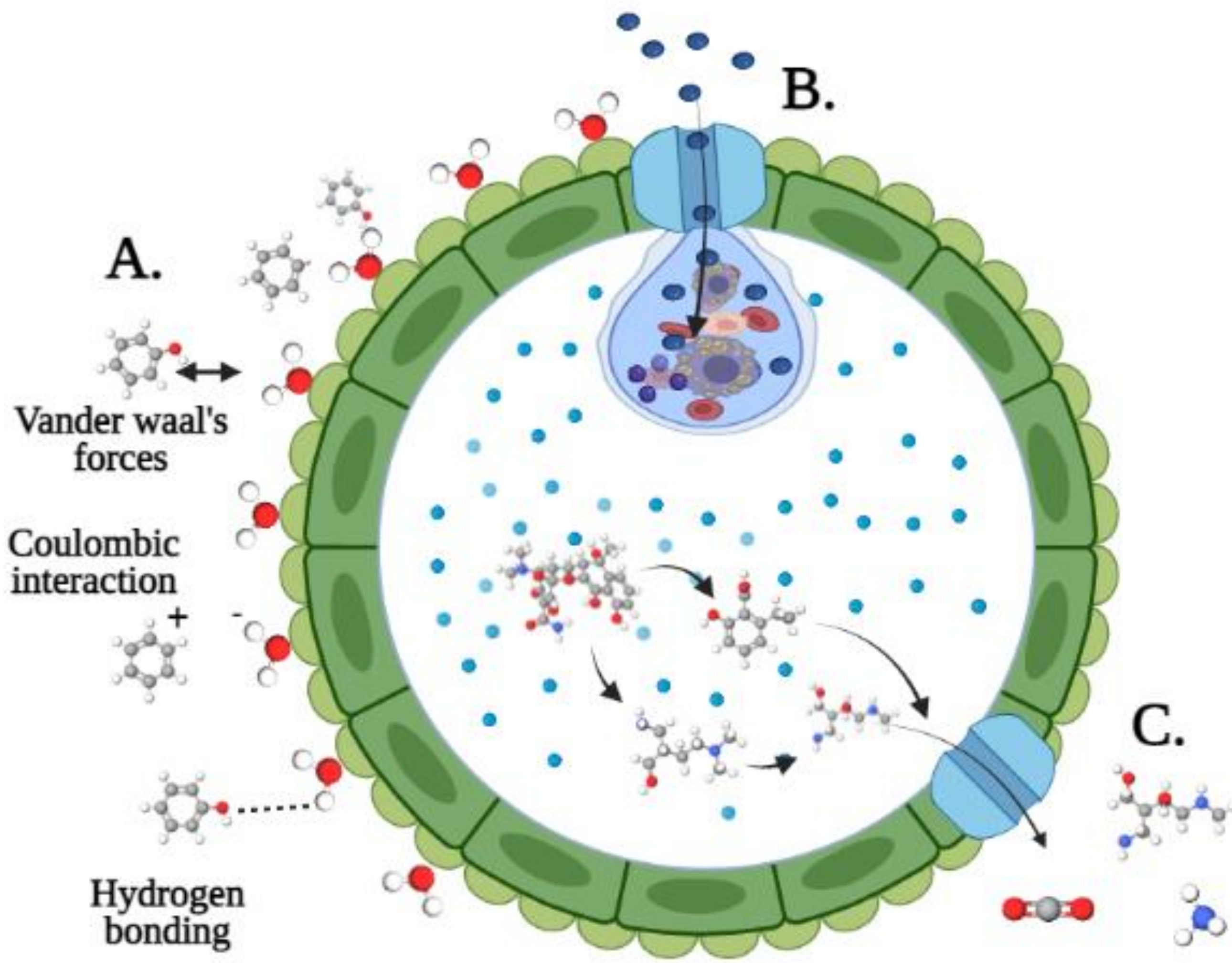
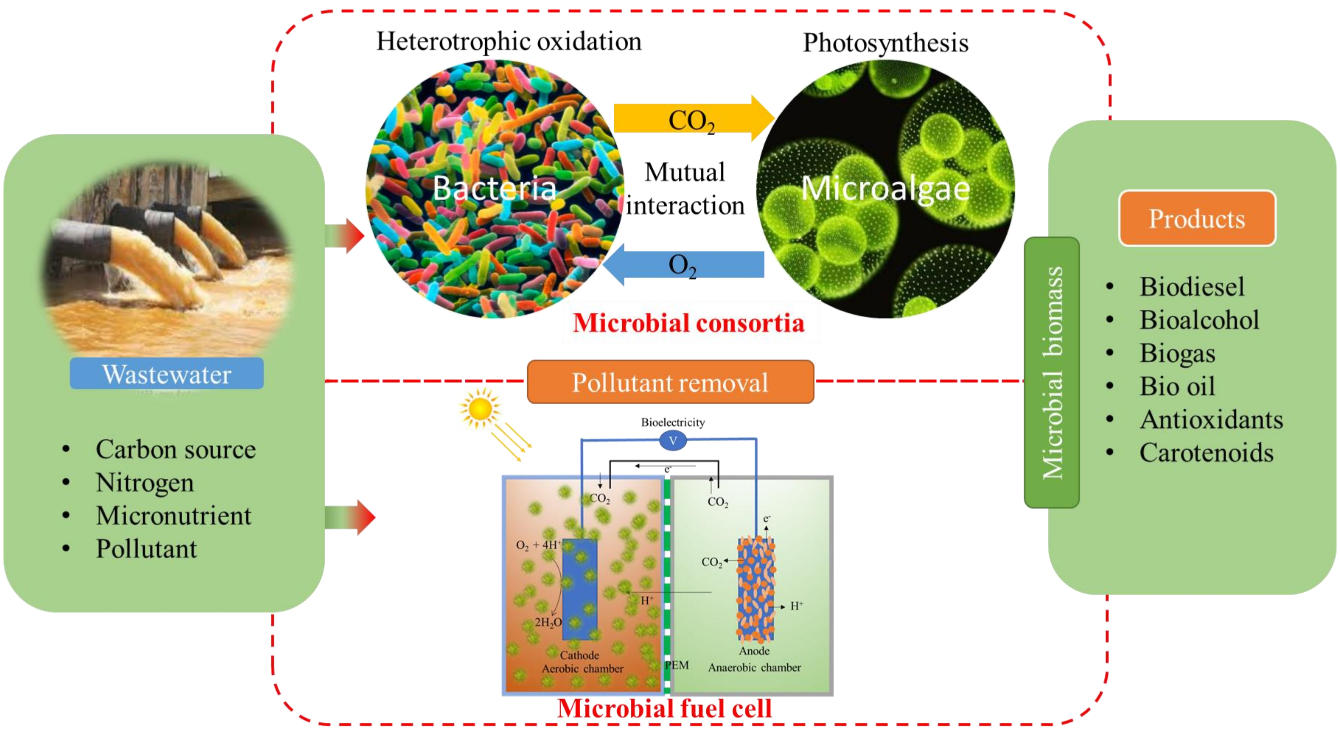

B.
A.
Vander waal's forces
Coulombic interaction
+
-
Hydrogen bonding
C.

Fig. 4


Heterotrophic oxidation
Photosynthesis
Bacteria
CO_2
Mutual interaction
O_2
Microalgae
Microbial consortia
Wastewater
Carbon source
Nitrogen
Micronutrient
Pollutant
Pollutant removal
Bioelectricity
V
Cathode
Aerobic chamber
PEM
Anode
Anaerobic chamber
Microbial fuel cell
Microbial biomass
Products
Biodiesel
Bioalcohol
Biogas
Bio oil
Antioxidants
Carotenoids

Credit author statement

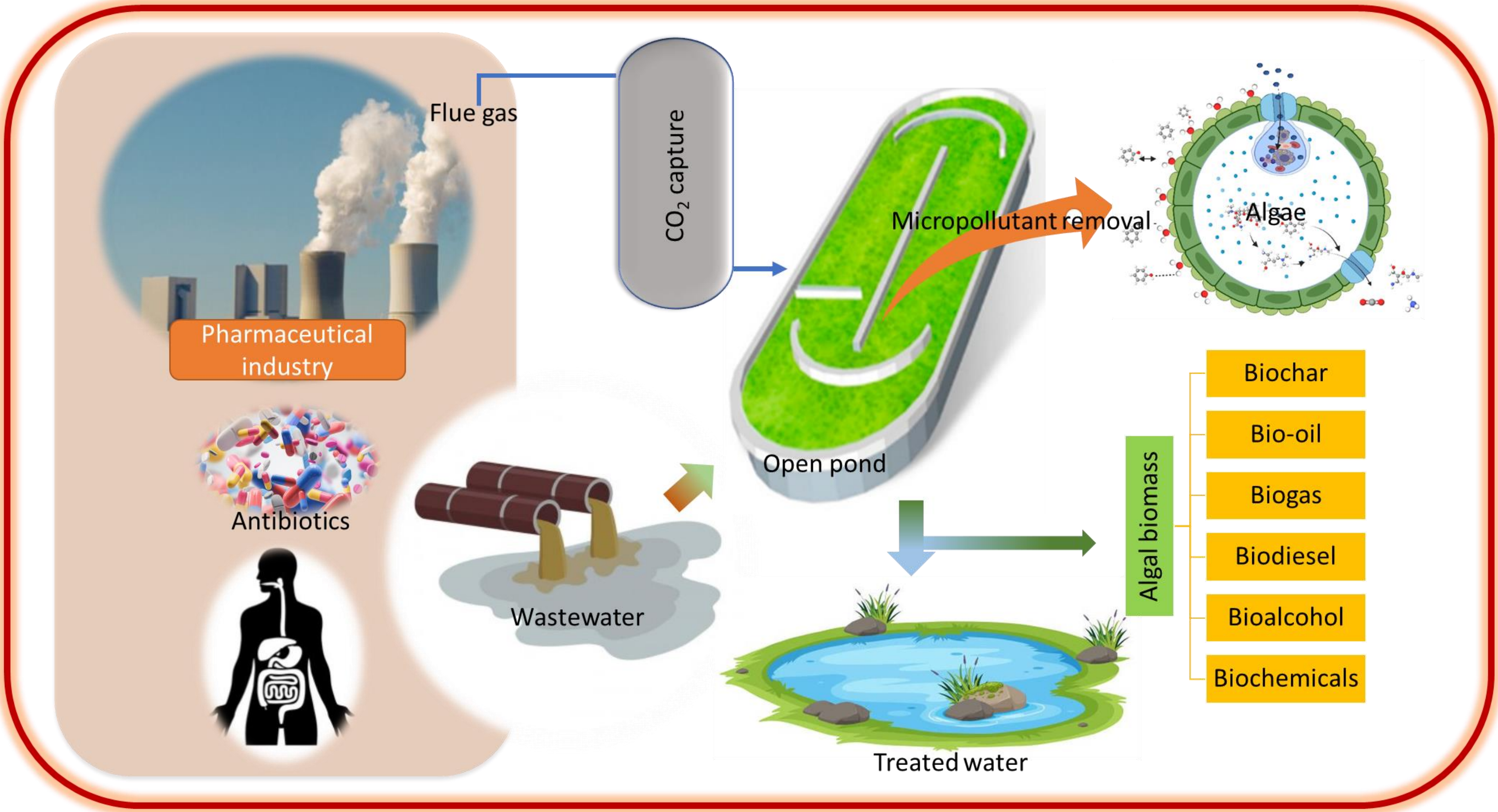
Neha Chandel: Conceptualization, Writing - Review & Editing. **Vishal Ahuja:** Conceptualization, Writing - Review & Editing, **Ranjit Gurav:** Writing - Original Draft. **Vinod Kumar:** Writing - Review & Editing, **Vinay Kumar Tyagi:** Writing - Original Draft, Writing - Original Draft. **Arivalgan Pugazendhi:** Writing - Original Draft. **Gopalakrishnan Kumar:** Conceptualization, Writing - Review & Editing, **Deepak Kumar**: Writing - Original Draft. **Yung-Hun Yang:** Writing - Review & Editing, **Shashi Kant Bhatia:** Conceptualization, Writing - Review & Editing

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical abstract



Highlights

- Uncontrolled use of antibiotics and pharmaceuticals causing health hazards.
- Microalgae-mediated processes facilitate pollutant removal and resource recovery simultaneously.
- Biodegradation, bioaccumulation, and bioadsorption are the main mechanisms.
- Integration of pollutant removal process with product generation is required.