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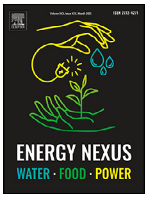

Pharmaceutical wastewater as Emerging Contaminants (EC): Treatment technologies, impact on environment and human health

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ABSTRACT

A wide range of unregulated chemicals of synthetic origin or derived from natural sources, which may be a contender for future regulations are called Emerging Contaminants (ECs). The concentration of ECs ranges from ng/L to μg/L, which is comparatively smaller as compared to other pollutants present in water and wastewater. Even though the environmental concentration is low, ECs still possess a great threat to the humans and ecosystem. These compounds are being widely studied due to their potential health effects, pervasive nature, and difficult degradation through conventional techniques. Pharmaceutical active compounds (PhACs) or pharmaceutical contaminants (PCs) are one of the major groups of ECs which can cause inimical effect on living organisms even at very lower concentration. These contaminants don't degrade easily and persistent for longer periods in the environment due to their stable structure. With the increase in demand of Pharmaceuticals and Personal Care Products (PPCPs), there has been a sharp increase of these pollutants in water bodies. This is mainly due to the inefficiency of conventional wastewater treatment plants in treatment and removal of these PhACs. The proper identification of pharmaceutical groups and development of removal techniques is crucial in the recent times. This review represents a comprehensive summary on PCs, various groups of PCs and an overview of approaches and treatment systems available for their removal. Efficient and effective treatment methods can be useful for completely eradicating these compounds and making the water bodies safe for use. So, the investment of capital and time on research on PCs and their removal techniques can be beneficial for the future.

1. Introduction

Water is indispensable to both humans and wildlife and the functioning of the world depends upon the availability of clean water. Quality monitoring of ground and surface water is necessary as these are the major contributors of water for domestic and industrial uses. In the recent time water bodies are being affected by Emerging Contaminants (ECs), which have the potential to sneak into the ecosystem and cause adverse impact on human health and ecology [1–3]. Pharmaceutical contaminant (PC) is one of the major worrying classes of ECs which arise from pharmaceutical industries that are biologically active compounds used to prevent, cure, or treat diseases [102,147,167]. Personal care products (PCPs) are mainly used to improve the quality of daily life which include lotions, detergents, hair dyes, lipsticks, cosmetics, creams, bath soaps, dental care products, shampoos, toothpaste, sunscreens, fragrances, and other household items, etc. [48,144]. Pharmaceuticals and Personal Care Products are together considered as the source for pharmaceutical contaminants in the environment (Fig. 1). There has been a massive hike in the manufacturing and use of PPCPs over the last few decades. Though there has been a massive surge in production and use of PPCPs, the treatment of the PCs released from the PPCPs has not been able to keep pace with the production. When the effluent from PPCPs is discharged into the water stream, it leads to genotoxic, mutagenic and ecotoxicological effects to plants, animals, and human. Constant release of PCs to water bodies and its exposure may result in long-term (chronic) effects in aquatic plants and animals. Jukosky et al. [83] found that vitellogenesis is induced in male *Oryzias latipes* (Japanese Medaka) by estrogen. The mortality rate of fish is also increased by high estrogenic-

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Abbreviations: ECs, Emerging Contaminants; PhACs, Pharmaceutical active compounds; PCs, Pharmaceutical contaminants; PPCPs, Pharmaceuticals and Personal Care Products; WWTP, Wastewater Treatment Plant; NSAIDs, Non-steroidal anti-inflammatory drug; ARGs, Antibiotic resistance genes; SSRIs, Selective serotonin reuptake inhibitors; SNRIs, Serotonin-norepinephrine reuptake inhibitors; SARIs, Serotonin amtagonist amd reuptake inhibitors; NRIs, Norepinephrine reuptake inhibitors; NDRIs, Norepinephrine-dopamine reuptake inhibitors; EAOP, Electrochemical Advanced Oxidation Process; SBRs, Sequencing batch reactors; UAFB, Up-flow Anaerobic Fluidized Bed; SBB, Sequencing Batch Bio-filter; ABR, Anaerobic Baffled Reactor; CPC, Compound Parabolic Collector; BDD, Boron Doped Diamond; MLSS, Mixed liquid suspended solids.

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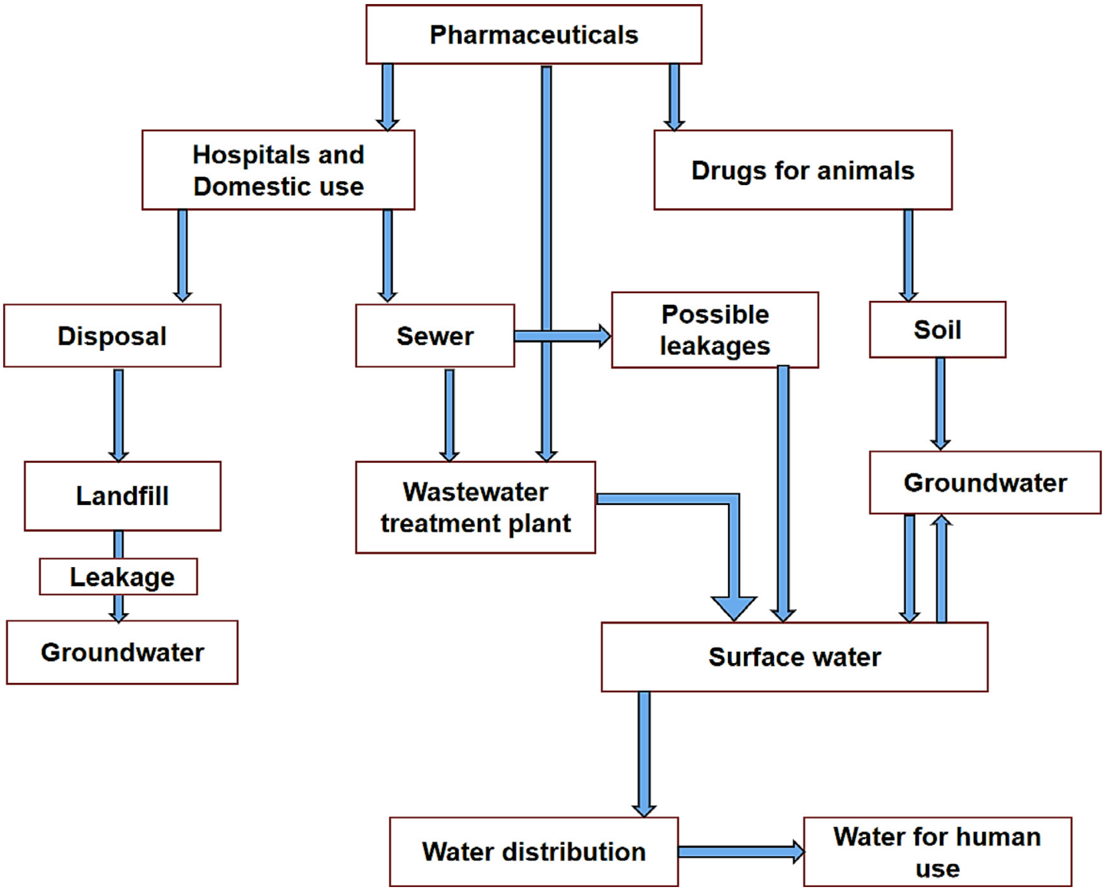

Fig. 1. Routes of pharmaceutical contaminants (PCs).

ity. Exposures to PCs may also lead to change in inherited trait and the behavior of living beings [167]. Conversion of male fish into female ones by the development of female traits due to presence of estrogen in water bodies is one such example of shift in inherited trait. Moreover, PCs in drinking water can cause harmful effects in new-borns babies, the elderly and people who are suffering from kidney or liver failure. The occurrence of estrogens in drinking water can slacken men fertility too. It can further increase the incidence of breast and testicular cancer [103,154,180]. The anti-cancer drugs present in drinking water can penetrate the blood-placenta barrier causing teratogenic and embryotoxic effect, being particularly dangerous to pregnant women due to their cytotoxic activity [10,164,196]. Many such adverse effects can be found both in humans and animals due to the presence of PCs in water bodies. Therefore, it is very much essential to create effective and efficient treatment methods for the removal of PCs from wastewater. Several mechanisms and techniques are studied for the removal of PCs and the treatment of pharmaceutical wastewater, but the most effective removal mechanism in the recent time is treatment by Wastewater Treatment Plant (WWTP) using biological approaches [9,23,26,28]. Some of the biological treatment schemes include Waste Stabilization Pond (WSP), membrane bioreactor (MBR), Activated Sludge treatment Plant (ASP), Constructed Wetland (CW), Rotating Biological Contactor (RBC) and algal photobioreactor, etc. [143,167] (Fig. 2).

The purpose of this review paper is to identify and classify the major classes of pharmaceuticals that contribute PCs to wastewater and to analyze the effectiveness of various available treatment technologies. The harmful effects of these PCs on environment, ecosystem and humans are also included within the literature. The fate, regulatory guidelines, and the Environmental Risk Assessment (ERA) regarding the pharmaceutical contaminants have also been discussed.

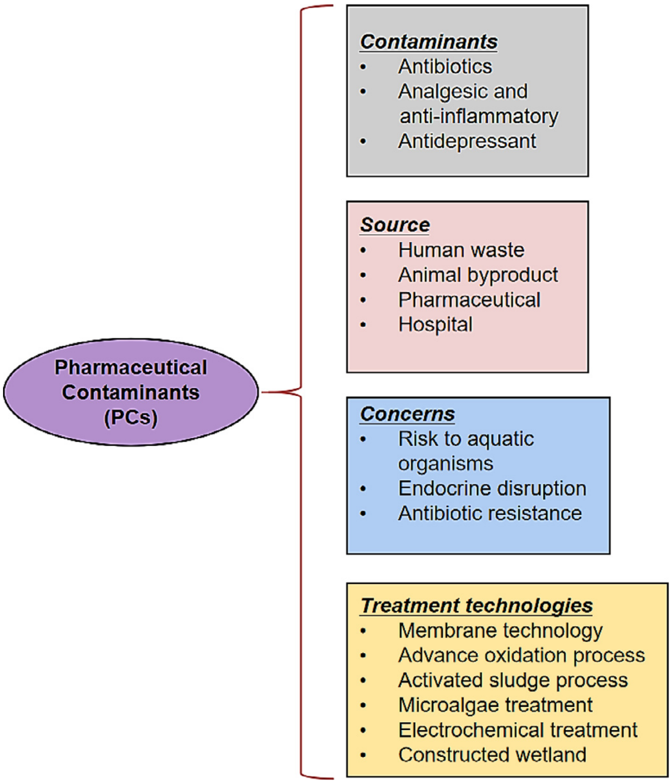

Fig. 2. Overview of pharmaceutical contaminants (PCs).

Table 1

Pharmaceutical contaminants (PCs).

Sl. No.	Class/Group of Pharmaceutical	Pharmaceutical Contaminants	Formula	Mass (g mol^{-1})	pK_a	$logK_{ow}$	Ref.
1	Analgesics and Anti-inflammatories	Aspirin	$C_9H_8O_4$	180	3.5	1.2	[57]
2		Diclofenac	$C_{14}H_{11}C_{l2}NO_2$	296.2	4.91	4.51	
3		Ibuprofen	$C_{13}H_{18}O_2$	206.3	4.15	4.51	
4		Paracetamol	$C_8H_9NO_2$	151.2	9.38	0.46	
5		Naproxen	$C_{14}H_{14}O_3$	230.3	4.15	3.18	
Sl. No.	Class/Group of Pharmaceutical	Pharmaceutical Contaminants	Formula	Mass (g mol^{-1})	pK_a	$logK_{ow}$	Ref.
1	Antibiotics	Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	253.279	5.6–5.7	0.89	[167]
2		Erythromycin	$C_{37}H_{67}NO_{13}$	733.93	8.88	2.48	
3		Trimethoprim	$C_{14}H_{18}N_4O_3$	290.32	7.12	0.73	

2. Pharmaceutical contaminants (PCs)

Pharmaceuticals are the wide varieties of biological compounds that are used for the treatment of infections and diseases. The presence of painkillers, birth control hormones, estrogen and other medicines in water bodies is too much concerning [17]. Pharmacological active contaminants generated from PPCPs are persistent in aqueous media and show resistance against degradation. PCs have variable structures and are the target specific compounds which are developed to absorb and distribute within the human body. PPCPs usage is dependent upon various factors like socio-economic conditions of a country, location and region, healthcare facilities and seasonal variation, etc [32,35,49,55]. The increase of usage of any specific drug during a pandemic will result in an increased load of PCs in waste streams. The manufacturing and consumption of PPCPs have substantially increased over the past few decades and due to this increased production and consumption, concentration of PCs in wastewater has escalated rapidly. PCs have the property of interacting and getting absorbed within living organisms which makes it a potential hazard for the whole ecosystem. The PCs in the form of hospital effluents (from hospital), industrial discharges (from pharmaceutical industries), agricultural runoffs (pesticides and fertilizers) and human as well as animal excreta (from households and sewers) enter the environment and damage the ecosystem [56,65,73]. Hospital effluents such as hazardous chemicals, solvents, actives drugs, metabolites, disinfectants, and heavy metals can endure in the surroundings for ages and can cause serious threats to the nature and, they have high mobility in liquid phase [17,142,145]. Effective treatment of these effluents is important before discharging it to water bodies. There are many classes or groups of pharmaceuticals present based on their curative applications. Various physio-chemical and biological treatment mechanisms are adopted for the treatment and removal of the PCs from wastewater [17,27,44,189]. Identification of these classes or groups of pharmaceuticals present in the wastewater will be helpful in devising the best treatment method for its removal.

Pharmaceuticals are classified into different classes or groups based on their mechanism of action (binding and acting against their biological target), mode of action, chemical structures, and the treatment of diseases. When the pharmaceuticals are classified based on their curative or remedial use (the pathology they intend to treat) are categorized as *therapeutic classes/groups of pharmaceuticals.* Some of the classification include analgesics and anti-inflammatories, antidepressants, antibiotics, antiviral, anticoagulant, sedative, cardiovascular, etc. Table 1 shows some of the important pharmaceutical contaminants along with their chemical properties.

2.1. Analgesics and anti-inflammatories

Analgesics and anti-inflammatories are the major contributors of PCs in wastewater, which are heterogeneous in nature and used to achieve anodyne (i.e., relief from pain or to reduce fever). Based on mechanism of action, analgesics are classified into paracetamol (acetaminophen), NSAIDs (Non-steroidal anti-inflammatory drug), opioids (morphine), cannabis (medical marijuana), alcohol, COX-2 (cyclooxygenase) inhibitors, etc. [20]. The most common, commercially available, and extensively used anti-inflammatory and analgesic drugs are diclofenac, ibuprofen, paracetamol, etc [76,82,91]. Paracetamol is being used mostly for curing fever. Non-steroidal anti-inflammatory drugs (NSAIDs) are a major group of pharmaceuticals used widely to relieve pain, reduce inflammation, and bring down high temperature. These drugs are mostly used to relieve symptoms of headaches, painful periods, sprains and strains, colds and flu, arthritis, and other causes of long-term pain. NSAIDs are found in negligible quantities (mostly nano and micro grams) in soil, wastewater, surface water, groundwater, sediments, snow, antarctic ice and drinking water [170]. Despite negligible detectable amounts in the environment, NSAIDs have prolonged ecotoxic effects on the biotic components of ecosystems [170]. According to Feng et al. [57], ingestion of NSAIDs is greater than 30 million doses per day and is vastly increasing day by day. Removal of these class of PCs becomes more important because of its large usage in the current times. Contaminants in the form of NSAIDs can cause major organ disorders in living organisms through usage of untreated water. Invertebrates and vertebrates when exposed to NSAIDs can form induced oxidative stress in their bodies which includes changes in the activity of antioxidant enzymes (catalase, superoxide dismutase, glutathione-S-transferase, etc.), the total number of proteins as well as lipid peroxidation [126]. According to the research conducted by Selderslaghs et al. [157], the presence of diclofenac and ketoprofen resulted in cardiovascular defects and cardiac anomalies in freshwater fish *Clarias gariepinus* and *Danio rerio*. NSAIDs also induce metabolic perturbations in invertebrates and vertebrates ranging from changes in the activity of detoxification enzymes to mitochondrial dysfunction and decreased functional stability of membranes [109]. According to Liu et al. [97] and Mezzelani et al. [109], NSAIDs tend to contribute to changes in gene expression and DNA damage. In addition to these toxic effects, NSAIDs cause endocrine disorders too. Nas et al. [122] investigated the fate of different NSAIDs in advanced biological treatment process and Waste Stabilization Pond (WSP) and found that diclofenac concentration reduced by 62% and 94%, respectively. Similarly, Tormo-Budowski et al. [168] reported a removal efficiency of 90% acetaminophen and 18% ibuprofen in a stirred tank bioreactor with *Trametes versicolor*. Some of the major health risks involved with the usage of analgesics and anti-inflammatories are hypertension and depression, drowsiness, myocardial infarction, insomnia, acute ecotoxicological effect, etc. [17].

2.2. Antibiotics

Anti-microbial compounds that kill microorganisms and act effectively against the growth of bacteria in the body are known as antibiotics and this is entrenched for the treatment of contagious diseases, safeguarding human health and the assistance of animal growth. Antibiotics help in synthesizing protein and stop the inhibition of bacterial growth in the body [17]. Antibiotics are highly demanded prescribed

Table 2
Classification of antibiotics.

Nature of antibiotics	Name
Bactericidal Activities	Penicillin and Cephalosporins (Antibiotics targeting cell walls of bacteria) Polymyxins (Antibiotics targeting cell membrane of bacteria) Rifamycins, Lipiarmycins, quinolones and sulfanomides (Antibiotics interfering with the bacterial enzymes)
Bacteriostatic Activities	Macrolides,Lincosamides and Tetracyclines (*protein synthesizing inhibitors*)
Target Specificity	Narrow-spectrum antibiotics (*gram -ve or +ve bacteria*) Broad-spectrum antibiotics
Clinical Use	Lipopeptides (*daptomycin*) Glycylcyclines (*tigecycline*) Oxazolidinones (*linezolid*) Lipiarmycins (*fidaxomicin*)

pharmaceutical, whose usage and demand has increased by 30% over the last decades [167]. The presence of antibiotics in the surrounding nature can encourage the evolution and spreading of antibiotic resistance genes (ARGs), have been classified as a global public health crisis [181]. Its presence within the environment is increasing due to continuous addition into the environment and it is termed as pseudo-persistent compounds [167]. Antibiotics kill and stop the growth of microorganisms in wastewater which eventually hampers the treatment mechanism of WWTPs that depend on microbial activities for its treatment process [167]. Based on mechanism/ spectrum of action and chemical structure, antibiotics are classified as follows ([22,60]; Cunha, [38]) (Table 2). Among all the above-mentioned classes of antibiotics penicillins, lincomycins, macrolides, tetracyclines, cephalosporins, sulfonamides and quinolones are some of the most used antibiotics. Tiwari et al. [167] has reported that approximately 90% of the antibiotics consumed by humans are removed via urine or feces. These antibiotic contaminants get mixed up with the sewer and if not treated properly will cause damage to the ecosystem. The ground and surface water are also vastly affected by antibiotic usage. Dolliver and Gupta [47] stated that antibiotics pollute the ground and surface water by leaching process and mixing in agricultural runoff. Some of the major health risk involved with usage of antibiotics are cardiac arrhythmia, disruption of immune system, dysfunction of hepatic, suppression of bone marrow, affecting food chain, etc. [17]. A removal efficiency of 55% was reported by Tormo-Budowski et al. [168] for the antibiotic class cephalexin in a stirred tank bioreactor with *Trametes versicolor*. Della-Flora et al. [43] conducted research and concluded 63% chloramphenicol removal in solar fenton process and 97% removal in adsorption process. Overall antibiotics are a major contributor of PCs in wastewater and proper treatment mechanisms should be developed for its removal before discharging into freshwater bodies.

2.3. Antidepressants

Neuroactive pharmaceutical compounds employed to treat disorders related to anxiety and depression, manage addictions, and treat chronic pain conditions are called as antidepressants. These compounds are mostly basic in nature and are used to ameliorate the chemical imbalances of neurotransmitters and are absorbable in nature with a bioavailability of 60 to 100% [17]. Existence of these kinds of contaminants in wastewater can cause corporeal and all other deleterious health effects [17]. Pharmacological and structural classification of antidepressants which are clinically approved are as follows: SSRIs (Selective serotonin reuptake inhibitors), SNRIs (Serotonin-norepinephrine reuptake inhibitors), SMSs (Serotonin modulator and stimulators), SARIs (Serotonin amtagonist amd reuptake inhibitors), NRIs (Norepinephrine reuptake inhibitors), NDRIs (Norepinephrine-dopamine reuptake inhibitors), TCAs (Tricyclic antidepressants), TeCAs (Tetracyclic antidepressants), MAOIs (Monoamine oxidase inhibitors). Lajeunesse [92] and Metcalfe et al. [108] through their studies found out that antidepressants and metabolites are found in surface water, sewage and even in the effluent of wastewater treatment plants. Some of the major side effects of antidepressants are hypoglycemia, acute and chronic toxicity, growth inhibition of aquatic organisms and sexual dysfunction [17]. There is an inflated threat of suicidal thinking and behavior in children and juvenile when they consume these antidepressants. Sometimes people also undergo discontinuation syndrome which resembles their past depression when they stop taking these antidepressants [62,185]. Therefore, certain effective and efficient removal techniques should be adopted for removal of these antidepressants. Gornik et al. [66] through batch experiment (biodegradation by activated sludge) reported a 90% removal efficiency of antidepressant class sertraline in just 0.25 hrs. Hollman et al. (2020) informed more than 99% removal for antidepressant class venlafaxine in an electrochemical advanced oxidation process (EAOP). Cao et al. [24] observed 40% and 98% removal efficiencies for citalopram and fluoxetine, respectively by sludge adsorption method. Proper treatment and removal of these antidepressants before discharging into freshwater is important in saving the ecosystem form the harmful effects of these kind of PCs.

3. Environmental risk assessment and regulatory guidelines regarding PCs

3.1. Environmental risk assessment of PCs

The older generation of the modern world is heavily dependent on pharmaceutical drugs, so with the increasing prevalence of chronic diseases, more therapeutic products are expected to be used [94]. Water habitats are heavily polluted by various pharmaceutical residues and due to potential effects of drug residues on the ecosystem, several countries have implemented environmental risk assessment (ERA) systems for global pharmaceutical control. ERA systems are being developed to protect and save the environment from potential harmful effects of pharmaceutical residues. ERA programs for pharmaceutical drugs plays an important role in disseminating environmental awareness in the pharmaceutical industry and protecting environmental health. European Union (EU), the USA, and Canada use the ERA in medicine which are briefly described below:

I In the EU, all pharmaceutical products intended for market placement in member states are subject to ERA [Directive 2001/83/EC Article 2 (1)]. The European Medicine Agency (EMA) is responsible for the drug ERA (Directive 2001/83/EC) in the EU. Prior to marketing pharmaceutical products to member countries, authorization must be obtained from the EMA [Directive 2001/83/EC Article 6 (1)]. The ERA in the EU is done in two phases: phase I is the preliminary test phase for measuring the value of pharmaceutical drugs/substances released to the environment. In phase II, the environmental conclusion and effect analysis was performed in tier A and tier B. In Tier A, the environmental effects and side effects of the drugs are analyzed and in Tier B, a more complex and extended risk assessment is performed.

II The United States Food and Drug Administration (U.S. FDA) is the official ERA pharmaceutical authority in the USA. In the USA, all pharmaceutical drugs covered by the U.S. FDA, e.g., NDAs, ANDAs, INDs, and BLAs are subject to ERA [171]. In the USA, EA is required, if active pharmaceutical ingredient concentration in the effluent increases upto 1 ppb or more [171]. The EA process is focused on reflecting the fate and results of the extruded pharmaceutical objects.

III Health Canada, and Environment and Climate Change Canada has a joint responsibility to assess the environmental risks of pharmaceutical drugs in Canada. According to CEPA, a company or individual wishing to manufacture or import new products in Canada must submit a report containing information on the toxic content of the substances to the environment, to Environment and Climate Change Canada. In conjunction with Health Canada, Environment and Climate Change Canada may review submitted information and assess whether there are any adverse environmental impacts or expected adverse effects of the substances. For this purpose, NSNRs should include information on ecotoxicity and genotoxicity as well as substance identity. To assess the negative effects of substances on humans or the environment; risks, genetic mutations, reproductive effects, and organ toxicity should be considered. To analyze the human exposure and environmental factors, considerations should be given not only in physico-chemical factors such as the movement and flow of an object, but also in quantity, frequency, and chemical composition of the substance released [67]. If an item is determined not to endanger the environment or human health, that is added to DSL [51].

3.2. *Regulatory guidelines regarding PCs*

Different organizations around the world have developed different regulatory guidelines to modulate the potential toxic effects of various emerging pollutants on the environment. These control levels include the combination of compounds in a liquid body, which, if overused, can be harmful environment with prolonged exposure [90]. Earlier ECs like PCs were mostly ignored by different environmental protection organizations. Slowly with the rising contamination in the environment and the rising interest among researchers, these organizations have started to take actions. Like a suggestion was made in 2007 by the European Parliamentary Committee Environment, Public Health and Food Security to include ECs such as carbamazepine, bisphenol-A, diclofenac, etc., under the list of priorities [52]. In the US, EPA updates the list of priority substances every five years concerning the harmful impacts on humans. Few pollutants, namely diuron, 17 β-estradiol, etc., as listed as unsafe substances or high-status pollutants in drinking water candidate list 4 by USEPA [173]. EU under the 2008/105/EC directive provided guidelines for permissible and acceptable concentration of 33 ECs, including ibuprofen, ciprofloxacin, caffeine, bisphenol A, mecoprop, etc., in the aquatic environment [53]. For many reported conditions the concentrations of ibuprofen, ciprofloxacin, carbamazepine, diazinon, malathion, and diuron in fluids were present in exceeding values as the guidelines set by the EU. In 2011, WHO made an amendment to the Guidelines for Drinking Water Quality and included other chemicals which had not been considered before [182].

4. Diagnostic techniques for detection of PCs in wastewater

Acquisition methods for ECs such as PCs can be performed using chromatography and spectroscopic techniques as well as metal analysis. Chromatography methods are the most common analytical methods for the identification and detection of various compounds in any type of sample. Some of these techniques are discussed briefly:

a *Liquid chromatography:* High-performance liquid chromatography (HPLC) or LC is a gold analysis method used to analyze a wide number of relatively polar and unstable ECs in different samples. In most cases, the ultra-high-performance liquid chromatography (UHPLC) has been chosen instead of the standard HPLC as these LC techniques provide an effective standing phase by reducing particle size, resulting in better fixation and shorter duration [71]. The UHPLC uses particles with a size of <1.7 μm and is almost always carried out in a reversible phase mode [132]. Generally, for the reversed phase separation of ECs acidified water (with small amounts of formic or acetic acid), methanol, or acetonitrile as organic solvents (in some cases also acidified with formic acid or acetic acid) are used as mobile phases. Díaz-Cruz et al. [45] reported that among all the LC methods, a retractable phase (RP) with octadecyl C18-bonded or octyl C8-bonded silica packaging is the most used stationary phase method for pharmaceutical analysis.

b *Gas chromatography:* Gas Chromatography (GC) is one of the analytical methods that can be used to classify, analyze, and identify chemical compounds of any sample. GC combined with MS is the most common method and can produce an accurate result. However, GC is used more than LC in determining the most polar impurities, such as drugs and personal care products [104]. Due to the high polarity and low flexibility of analytes, such as hydroxyl, phenolic EDCs, amines, and amides, the GC pathway requires the incorporation of alternative output to improve chromatographic behavior of analysts [133]. In fact, the release of ECs from other variable outputs is mandatory to improve the sensitivity of acquisition and selection and to enhance divergence. Different extraction techniques often involve the use of acylation, alkylation, or silylation reagent. Silylation is the main extraction method in which active hydrogen in the active groups of ECs is replaced by trimethylsilyl (TMS) which increases the flexibility and stability of compounds [81]. The most common silication agents are N-methyl-N- (trimethylsilyl) trifluoroacetamide (MSTFA), N, O-bis (trimethylsilyl) -trifluoroacetamide (BSTFA) and N- (t-butyldimethylsilyl) -N-methyltriflu MTBSTFA) [81].

c *Fourier transform near-infrared:* Recently, techniques like the Fourier transform near-infrared (FT-NIR) spectroscopy are developed to overcome traditional barriers. Quintelas et al. [135] in his research developed a combination between FT-NIR and chemometrics to determine pharmaceutical compounds, such as ibuprofen, carbamazepine, β-estradiol, ethinylestradiol, and sulfamethoxazole in contaminated water. The chemometric method was used using the Kolmogorov-Smirnov test to assess data validity, boxplot vendor identification and key component analysis (PCA) aimed at identifying interaction samples and defining data sets. Next, a small-scale reversal analysis (PLS) was performed to determine the best guessing model for pharmaceutical drug measurement purposes.

5. Treatment of pharmaceutical contaminants and fate

5.1. *Treatment of pharmaceutical contaminants*

Active pharmaceutical contaminants (APC) are released into surface water via wastewater treatment plants (WWTPs), aquaculture facilities, run-off from the agricultural fields and releases to the soils through the application of bio-solid and manure. The major contributor for pharmaceutical related contaminants are the treated/untreated effluents of WWTPs, as those are not designed to eradicate every environmental pollutant hence the contaminants get incorporated into the aquatic systems. The other exposure pathways include the emissions from the manufacturing sites, disposal of unused/expired medicines into sewage, hospital discharges, disposal of carcasses of treated animals and irrigation with wastewater. Sources of pharmaceuticals can be categorized into two forms i.e., point based which include sewage sources, domestic solid waste, pharmaceutical-related industrial sector waste effluents, bio medical wastes, and diffuse based contaminants include agricultural runoff, urban runoff, and unrecognized leakage of WWTP [129]. The sources of point-based contaminants can be easily identified and can be treated at the source itself but in the other cases it's difficult to identify the exact source of contaminants as it passes through various other forms which also brings in the change in concentration in an uncontrolled manner. There should be strict government rules for the proper and safe disposal of unused/expired medicines and all the other products containing pharmaceutical contaminants. Advanced wastewater treatment plants should be installed, or conventional treatment systems should be used with advanced combined compartments to treat the contaminants. Usage of fertilizers and pesticides in agricultural fields need to be eliminated and traditional organic farming should be chosen over it. In longer term alternative sustainable pharmaceutical compounds shall be manufactured to ensure a safer environment to live in. Different technologies have been adopted to completely eradicate the PCs present in

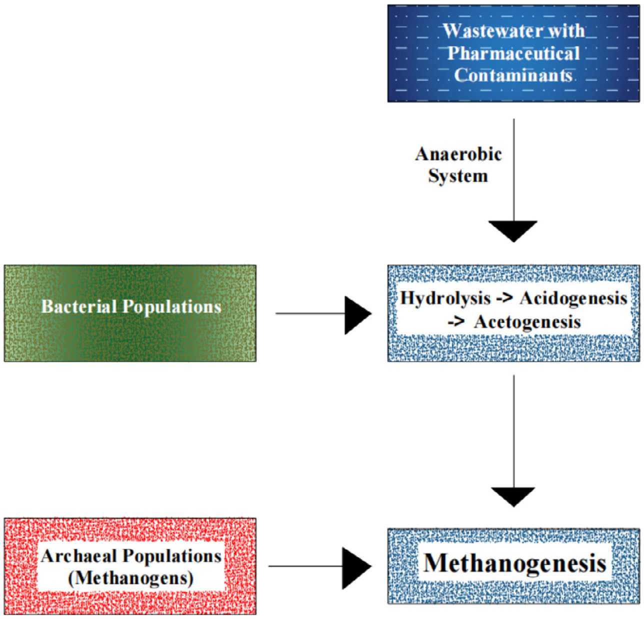

Fig. 3. Anaerobic biotechnology treatment.

water bodies and streams. Some of the treatment methods are described below and listed in Table 3 .

5.1.1. *Anaerobic biotechnology treatment*

Anaerobic wastewater treatment is deemed to be the most cost-efficient technology for the treatment of organically polluted effluents released from the industries. Energy generation takes place during the process of anaerobic digestion (which is in the form of methane) and in addition to it anaerobic digestion has the capability to bear a high rate of loading [30,120]. In this system the larger portion of the biodegradable material is converted into biogas and only a few of the organic materials result in sludge formation (Fig. 3). Seghezzo et al. [156] in his study mentioned on comparing with aerobic method that the slow growth rate of anaerobic bacteria results in a lower sludge production. Fox and Venkatasubbiah [61] evinced the use of anaerobic bio reactor (ABR a baffled system) for the treatment of pharmaceutical wastewater containing high sulfate, showed a COD removal efficiency of 50%. Similarly, Massé et al. [105] reported a COD removal efficiency of 80% while treating pharmaceutical wastewater in sequencing batch reactors (SBRs). While treating pharmaceutical wastewater containing aromatic and aliphatic organic chemicals, Mohan et al. [111] demonstrated the use of Anaerobic Suspended Film Contact Reactor (ASFCR) and found the COD removal efficiency in the range 60–80% with the methane content being in the range 60–70%. Nandy and Kaul [120] informed a COD removal efficiency of 76–98% using a fixed-film reactor (FFR) while treating herbal based pharmaceutical wastewater. Further under hydraulic and organic shock loadings the reactor didn't get destabilized. Saravanane et al. [151] found 88.5% COD removal while treating anti-osmotic drug based pharmaceutical effluent (acetic acid and ammonia) in a fluidized bed reactor (FBR) under anaerobic conditions. Saravanane et al. [152] also researched upon the Up-flow Anaerobic Fluidized Bed (UAFB) system for treatment of cephalexin drug based pharmaceutical effluent. The treatment performance of an Up-flow Anaerobic Filter (UAF) for a chemical synthesis-based pharmaceutical wastewater (Bacampicilline and Sultamicilline tosylate) was studied by Ince et al. [78] and a COD reduction of 65% was obtained. Buitrón et al. [21] examined the capability of a Sequencing Batch Bio-filter (SBB) integrating anaerobic-aerobic conditions in one tank to treat a pharmaceutical wastewater (Phenols and O–Nitroaniline) and found the COD removal efficiency of 95–97%. A combined system of Anaerobic Baffled Reactor (ABR) followed by a Biofilm Airlift Suspension Reactor (BASR) was analyzed and used by Zhou et al. [195].

5.1.2. *Solar/ferrioxalate photo catalysis*

Advanced Oxidation Processes (AOPs) for the removal of PCs have already been extensively researched. Dantas et al. [39] have researched on the applicability of ozone for the removal antibiotics present in the wastewater. Similarly, Andreozzi et al. [8] and Rosenfeldt and Linden [140] have mentioned various UV/H_2O_2 or H_2O_2 processes for the degradation of acetaminophen and treatment of some hormones. Several studies have also been made on the use of fenton and photo-fenton reactions for the degradation of PCs. Penicillin along with diclofenac can be reduced by this method. Ferrioxalate-induced photo-fenton process is one such AOP which is used for the degradation and removal of PCs. In this process, production of photo-chemically induced reactive intermediate species (such as hydroxly radical, HO, singlet oxygen, $^1O_2$, hydroperoxyl radials HO_2 or the superoxide radical anion) takes place which results in a higher degradation rate [113]. Monteagudo et al. [114] experimented on ferrioxalate-induced photo-fenton process for pharmaceutical wastewater from a pharmaceutical production plant and concluded that ferrioxalate-induced photo-fenton process shows a higher removal efficiency. Monteagudo et al. [116] used a pilot plant containing Compound Parabolic Collector (CPC) solar reactor for the degradation of PCs using a photocatalytic reaction (Fig. 4). The CPC pilot plant contains a solar reactor that consists of a continuously mixed tank, a centrifugal recirculation pump and a solar collector unit. In another experiment conducted on solar photo-fenton by Della-Flora et al. [43], the removal efficiency of PCs chloramphenicol, fluconazole, flutamide and gemfibrozil were found to be 63%, 40%, 54% and 79%, respectively. Chloramphenicol belongs to the group of antibiotics, fluconazole to the group of triazoles, flutamide to the group of anti-testosterone/anti-androgens and gemfibrozil belongs to the group of fibrates class of pharmaceuticals. From this it can be concluded that photo-fenton method is an effective and efficient treatment technique for the removal of various kinds of PCs from various classes of pharmaceuticals.

5.1.3. *Electrochemical removal*

Electrochemical method can be used both for the detection and removal of PCs from wastewater (Fig. 5). This method is preferred for the removal of pharmaceuticals from wastewater due to the low cost of operation and acquiescence with extensive compounds comprehending of organic, inorganic, and ionic species. The sole requirement for this treatment method is the prior removal of large particles from the wastewater which can be done through traditional methods. Electrochemical sensors can be a reliable method for on-site detection of pharmaceutical particles, and it can be easily miniaturized and automated. Merola et al. [107] established an electrochemical immune-sensor utilizing two competitive assays for a sensitive detection of penicilin G and other β-lactam antibiotics. There are two perspectives allowed by the electrochemical techniques: electrochemical conversion in which the recalcitrant organic pollutants are particularly modified into biodegradable compounds and electrochemical combustion within which organic chemicals are mineralized. The Electrochemical Advances Oxidation Process (EAOP) includes the oxidation of pollutants in an electrolytic cell by direct electron transfer between the molecule and the anode or by indirect or conciliated oxidation with heterogeneous radicals formed from water discharge at the anode. Several experiments were conducted for the removal of pharmaceutical substance from the wastewater. A degradation efficiency of greater than 90% was observed by Serna-Galvis et al. [158] for the PCs cephalexin, cephadroxyl, cloxacillin, oxacillin, ciprofloxacin, norfloxacin by using electro-generated active chlorine (Ti/IrO_2 at anode & Zr at cathode in the presence of NaCl). Zaghdoudi et al. [191] evaluated two electrochemical reduction process for the reduction of dimetridazole (a nitroimidazole-based antibiotic) treatment by direct electrochemical reduction (taking graphite as the electrode)

Table 3
Various technologies for treatment of PCs.

Sl No.	Class/Group of Pharmaceutical	Pharmaceutical Contaminants	Treatment Technology/Mechanism	Removal (%)	Refs.
1	Psychoanaleptic metabolite	Hydroxybupropion	U-MBR (ultrafifiltration membrane bioreactor)	82	[117]
	Antirheumatic	Ibuprofen		98	
		Metformin		95	
	Opiate analgesic	Valsartan		92	
2	Macrolides	Azithromycin	Anaerobic Treatment by WWTP	88	[192]
	Tetracyclin Antibiotics	Tetracyclin		73	
		Oxytetracycline		80	
		Chlortetracycline		90	
3	Analgesic and antipyretics	Acetaminophen	hydrogen peroxide-induced UFBR reactor	99	[13]
	Tetracycline	Chlortetracycline	–	100	[177]
		Metacycline		46	
	Sulfonamide	Sulfamerazine		92	
	Macrolides	Clarithromycin		59	
5	Analgesic and antipyretics	Acetaminophen	Cyclic biological reactor	98	[87]
6	Analgesic and antipyretics	Acetaminophen and some other drugs	MBR bioreactor in real scale	100	[88]
			MBR bioreactor in laboratory scale	95	[88]
7	Analgesic and antipyretics	Acetaminophen and some other drugs	Conventinal Activated Sludge Process	67	[118]
8	Analgesic and antipyretics	Acetaminophen and some other drugs	Submerged membrane bioreactor (SMBR)	92.2	[54]
9	Nonsteroidal anti-inflammatory drugs	Diclofenac	Advanced Biological Treatment (WWTP)	61.3	[122]
	Anticonvulsant	Carbamazepine	Advanced Biological Treatment (WWTP)	15.6	
	Nonsteroidal and anti-inflammatory drugs	Diclofenac	Wastewater Stabilization Pond	93.6	
	Anticonvulsant	Carbamazepine	Wastewater Stabilization Pond	24.4	
10	Macrolides	Erythromycin	Gamma irradiation	70	[33]
			Gamma irradiation with peroxymonosulfate(10 mM)	80	
			Gamma irradiation with peroxymonosulfate(50 mM)	100	
11	Analgesics/antiinflammatories	Acetaminophen	Stirred tank bioreactor with Trametes versicolor	90.5	[168]
		Ibuprofen		17.5	
	Antibiotics	Cephalexin		54.8	
	Fibrates	Gemfibrozil		93	
	Methylxanthines	Caffeine		87.9	
12	Antibiotics	Chloramphenicol	Solar Photo-Fenton	63	[43]
			Adsorption process using avocado seed activated carbon	97	
	Triazoles	Fluconazole	Solar Photo-Fenton	40	
			Adsorption process using avocado seed activated carbon	97	
	Anti-Testosterone/Anti-Androgens	Flutamide	Solar Photo-Fenton	54	
			Adsorption process using avocado seed activated carbon	99	
	Fibrates	Gemfibrozil	Solar Photo-Fenton	79	
			Adsorption process using avocado seed activated carbon	100	
13	Anticonvulsant	Carbamazepine	Biochar 25 mg/L	84	[18]
			Biochar 125 mg/L	99	
			Biochar 250 mg/L	99	
14	Opiate analgesic	Codeine (+)	Clay mineral along with Nonionic organoclay & Cationic Organoclay	62.65	[41]
	Antibiotics	Trimethoprim (0)		2.6	
	Nonsteroidal anti-inflammatory drugs	Ibuprofen (-)		88.57	
15	Nonsteroidal anti-inflammatory drugs	Ibuprofen	Biological nutrient removal (BNR) with an anaerobic configuration	81	[79]
		Naproxen		71	
16	Beta Blockers	Atenolol	Two Sequencing batch reactor with powdered composite adsorbent	52	[112]
	Fluoroquinolones	Ciprofloxacin		54	
	Benzodiazepines	Diazepam		59	
17	Nonsteroidal anti-inflammatory drugs	Naproxen	Conventional activated sludge treatment after aerobic and anaerobic digestion. Finally, a tertiary treatment based on UV oxidation	90	[138]
18	Diuretics(water pills)	Furosemide	Photolysis	100	N´avar et al., 2020
			Photocatalysis	97	
	Sulfonamide	Sulfadiazine	Photolysis	68	
			Photocatalysis	87	
19	Fluoroquinolone	Enrofloxacin	Synergic catalytic ozonation and electroflocculation process	99	[77]
	Penicillin	Amoxicillin		89	
20	Analgesic	Acetaminophen	Primary treatment based on the partial removal of suspended solids and organic matter through coagulation, flocculation and sedimentation	23	[19]

(*continued on next page*)

Table 3 (*continued*)

Sl No.	Class/Group of Pharmaceutical	Pharmaceutical Contaminants	Treatment Technology/Mechanism	Removal (%)	Refs.
21	Tetracycline antibiotic	Oxytetracycline hydrochloride	Electrocoagulation process.	88	[121]
22	Nonsteroidal anti-inflammatory drugs	Diclofenac	Electrocoagulation process.	34	[50]
	Anticonvulsant	Carbamazepine		35	
	Penicillin	Amoxicillin		36	
23	Analgesics	Ibuprofen	High Rate Algal Ponds	90–99	[176]
			Upflow anaerobic sludge blanket digestion(UASB)	92	
		Acetaminophen	High Rate Algal Ponds	90–99	
			Upflow anaerobic sludge blanket digestion(UASB)	92	
24	Antiepileptics	Lamotrigine	High Rate Algal Ponds	47–48	Eliana et al., 2020
	Hypolipidemic drugs	Fenofifibric acid		69–84	
	Analgesics and anti-inflflammatory drug	Paracetamol		76–100	
	Tranquilizers	Pentoxifylline		30–55	
25	Antibacterial and Antifungal	Triclosan	Activated Sludge	99.8	[139]

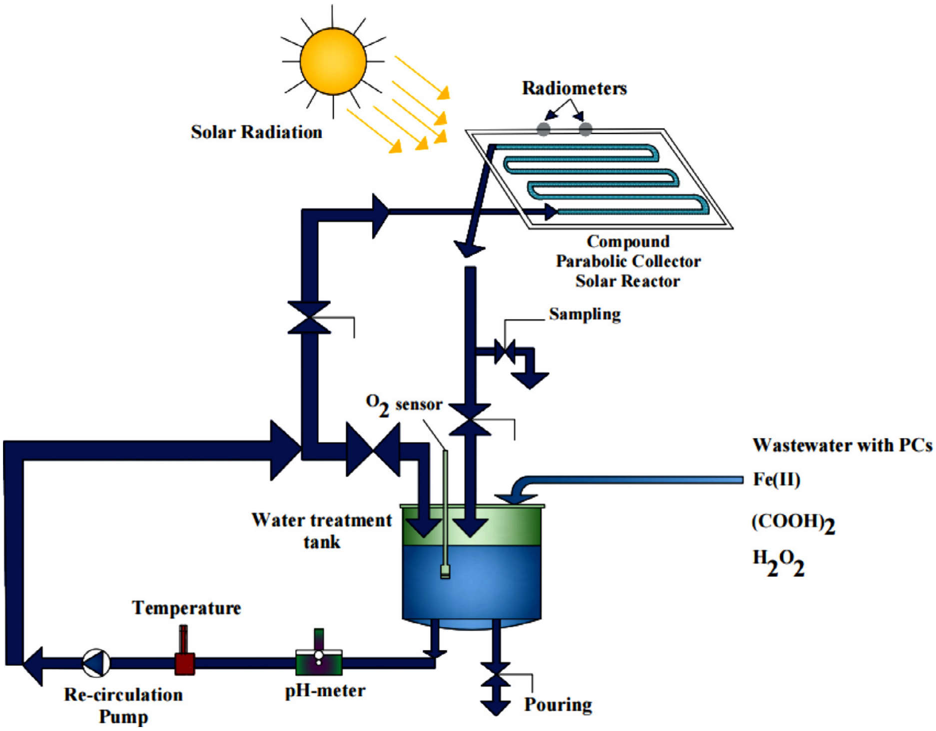

Fig. 4. Solar/ferrioxalate photo catalysis: compound parabolic collector solar reactor.

and indirect electrochemical degradation in the presence of titanocene dichloride. Sopaj et al. [162] reported a degradation upto 100% for the amoxicillin when the sample was attacked by hydroxyl radicals electrogenerated on the surface of anode in the presence of carbon-felt and carbon fiber. The anode material is a strong influencer in the degradation processes. Overall, electrochemical methods can be successfully applied as a productive technology for the treatment of water carrying pharmaceutical waste substances.

5.1.4. *Membrane bioreactor process*

Membrane bioreactor (MBR) is becoming important in the field of treating wastewater as the process has a higher bio-degradation efficiency, occupies less space, and produces minimal amount of sludge (Fig. 6). Chang et al. [29] treated real pharmaceutical wastewater using a MBR of volume 20 m^3 for 140 days and obtained a COD removal of 96% and BOD 99%. The mixed liquid suspended solids (MLSS) concentration in the MBR tank was maintained in the range of 6000 - 17,000 mg L^{-1}. Sterritt et al. [165] found that activated sludge treatment process has a removal efficiency of more than 50% for heavy metal containing wastewater. The satisfactory BOD, COD and heavy metal removal shows the potential of MBR system in treating pharmaceutical wastewater. This in turn shows the effectiveness of MBR system in removal of pharmaceutical waste particles from the wastewater with stable and satisfactory operative system. Mousel et al. [117] conducted an experiment in Ultrafifiltration Membrane Bioreactor (U-MBR) and reported removal efficiency of 82% for hydroxybupropion, 98% for ibuprofen, 95% for metformin and 92% for valsartan, respectively. This shows the effectiveness of MBR technology for the removal of PCs from wastewater.

5.1.5. *Microalgal bioremediation process*

Algal-based treatment technologies recently have been trending for their potential enactment in treating wastewater and elimination of hazardous contaminant. These technologies have an advantage in reducing operation cost while giving rise to worthy products and confiscating greenhouse gases at the same time. Over the last few decades, the application of microalgae for the bioremediation of nutrients, such as nitrogen, phosphorus and carbon, from various sources of contaminated

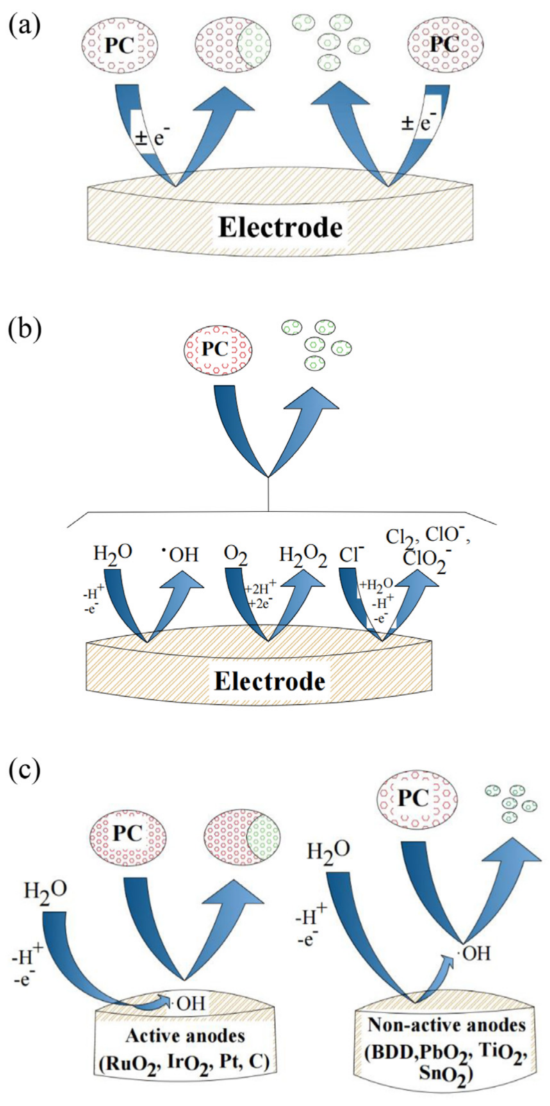

Fig. 5. a. Electrochemical method for the transformation or degradation of PCs by direct electron transfer. b. Electrochemical method for the transformation or degradation of PCs by generation of •OH, H_2O_2 or active chlorine species. c. Electrochemical method for the transformation or degradation of PCs by using active and non-active anodes.

water has been shown to be effective in the large scale [166]. These systems provide natural disinfection which is very effective in eradicating nutrient pollution as compared to traditional wastewater treatment systems [16,37]. Nutrients from wastewater are imbibed into algal biomass, which can be harvested and used as bio-fertilizer. Apart from this valuable product like proteins, carbohydrates, pigments, and vitamins are also produced. Algae based wastewater treatment system is sustainable and beneficial as compared to the other wastewater treatment methods and it has shown great potential in eradicating ECs such as PCs from wastewater. Microalgae based bioremediation of PCs follows an eco-friendly course of action which requires small number of operational inputs and the whole process can also be driven by solar energy. PPCPs from wastewater can be eliminated through the process of sorption, biodegradation, photodegradation and volatilization following algae-based techniques (Fig. 7). Different methods involved in the removal of PCs by microalgae are broadly classified into bio-adsorption, bioaccumulation, intracellular and extracellular biodegradation, further the enhanced methods involved are biomeditation by microbial consortia, acclimation, and co-metabolism. There are other typical algae-based treatment systems available such as high-rate algal ponds, algal turf scrubber, rotating algae biofilm photobioreactor, stirred-tank photobioreactor, flat panel photobioreactor, tubular photobioreactor and membrane photobioreactor, etc. (Table 4). Three major mechanisms through which microalgae remove PCs from wastewater are bio-adsorption, bio-uptake, and biodegradation. A brief explanation regarding the three mechanisms is mentioned below.

- Bio-adsorption mechanisms by microalgal species occurs when PCs are either adsorbed to the components of the cell wall or on the organic substances that are excreted by the cell into the surrounding environment [85,141]. Chemical structure of PCs, surface area, surface chemistry affects the rate of adsorption on microalgal cell surfaces [125]. Hydrophobic, cationic ECs are actively attracted to the microalgal cell surface due to electrostatic interactions, while hydrophilic ECs are repelled [187]. Hydrophilic PCs tend to show lower bio-adsorption rates and in studies conducted by Peng et al. [130] and de Wilt et al. [42], lower level of adsorption of pharmaceutical residues were reported. de Wilt et al. [42] observed less than 20% adsorption rates for six pharmaceutical drugs onto the cell surface of the green microalga *Chlorella sorokiniana*. Similarly, Peng et al. [130] reported approximately 10% adsorption rate of the hormones progesterone and norgestrel by *Scenedesmus obliquus* and *Chlorella pyrenoidosa*. The drugs or the compounds studied in both above research were soluble in water, or hydrophilic in nature which was the reason for their low bio-adsorption rates. Hydrophilic compounds are anionic (poorly charged) and have low bio-adsorption affinity with the microalgal cells. In contrast, lipophilic pharmaceutical drugs, which are cationic, have high levels of bio-adsorption affinity with microalgal cells. Modification of microalgal biomass either by chemical or physical pre-treatment techniques can enhance the bio-adsorption rates. Ali et al. [7] modified microalgal biomass with 0.1 N NaOH and reported a 70% higher bio-adsorption rate for the pharmaceutical drug, tramadol.
- Bio-uptake mechanism of the algal species involves the active transport of the contaminants into the cell through the cell wall, where it binds to intracellular proteins and other compounds, however the process can take in hours to days. Unlike bio-adsorption, bio-uptake of PCs can only occur in the living microalgal cells. Microalgal cells can capture ECs in three major ways:
  1. *Passive diffusion:* Passive diffusion of PCs into the cell occurs through the cell membrane from a high (external) concentration

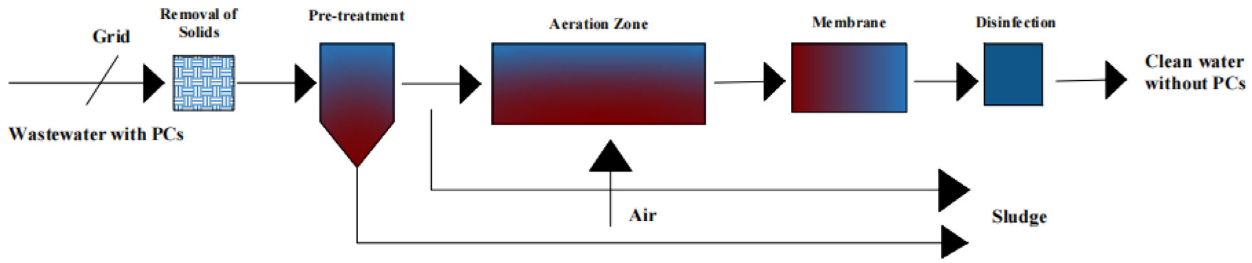

Fig. 6. Membrane bioreactor (MBR) technology.

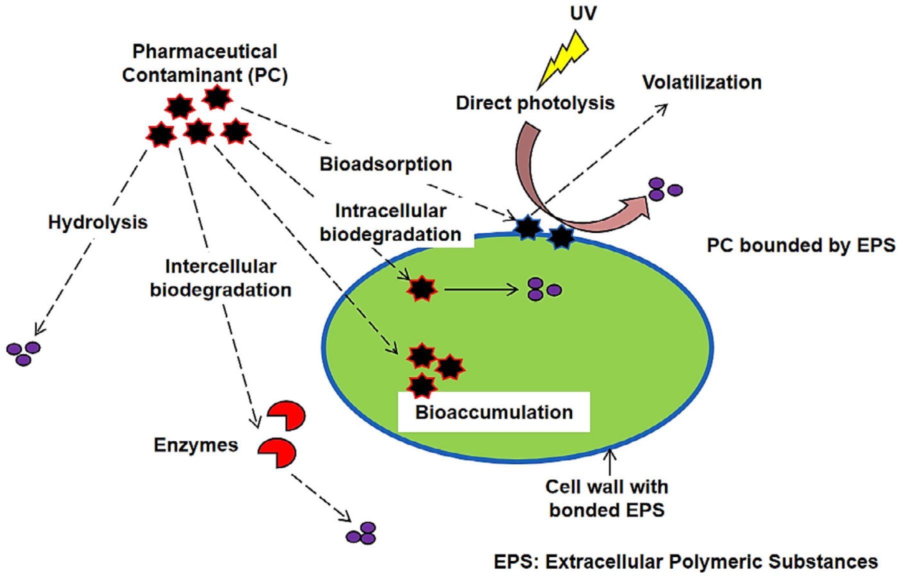

Fig. 7. PCs removal process in microalgae.

to a lower (internal) concentration without any requirement of energy excretion.

2. *Passive-facilitated spread:* Passive-facilitated diffusion is the process where PCs diffuse across the cell membrane with the help of transporter proteins, whose role is to mediate the influx of polar molecules into the cell.
3. *Energy-dependent/active uptake:* Active transport of the EC across the cell membrane requires the use of energy by the cell. Often in active transport, the compound moves against a concentration gradient, although this is not always the case.

Several studies have shown bio up-taking as an effective and efficient method for the removal of lipophilic pharmaceutical drugs by microalgae [63]. In an experiment conducted by Maes et al. [101], the bio-uptake removal of 17$\acute{\alpha}$-Ethinylestadiol by green algae *Desmodesmus subspicatus* was reported to be around 23%. Irrespective of the mechanism, bio-uptake is affected by the physico-chemical environment including temperature and pH, the metabolic state or health of the cell, and the presence of any metabolic inhibitors [183].

- Microalgal biodegradation of ECs includes the conversion of complex compounds into molecules that are easily broken down using catalytic metabolic deterioration. Biodegradation provides one of the most promising technologies for the troublesome management of contaminants as it can convert the contaminants into less toxic compounds instead of acting as an organic filter. In studies conducted by Peng et al. [130], the microalgal biodegradation of the hormone progesterone and norgestrel were reported to be successfully by pure microalgae, *Scenedesmus obliquus* and *Chlorella pyrenoidosa*. Hom-Diaz et al. [75] reported the removal through the biodegradation of the hormones 17β-estradiol and 17$\acute{\alpha}$-ethinylestradiol by microalgae *Selenastrum capricornutum* and *Chlamydomonas reinhardtii*. Peng et al. [130] identified as dehydration (hydrogenation), hydroxylation, oxidation (dehydrogenation) and side-chain breakdown as the primary reaction involved in the microalgal conversion of progesterone and norgestrel. Xiong et al. [187] under laboratory conditions successfully demonstrated the co-metabolic removal of ciprofloxacin by the green alga *Chlamydomonas mexicana*.

Mixotrophic microalgae can switch their metabolism nature between autotrophic and heterotrophic depending on the availability of carbon sources and nutrients in the environment. This property imparts flexibility to the micro-algae which helps it to survive in any extreme environments. Culturing micro-algae reduces the addition of external chemical fertilizers/nutrients for treatment. This concept provides a zero-waste rule where the wastewater is employed as the source of nutrient for the cultivation of mixotrophic micro-algae followed by the subsequent utilization of produced biomass as a feasible feedstock for sustainable biofuel production to stimulate a more sustainable practice for the microalgae biomass-based biofuel industry. The pharmaceuticals and personal care products may affect the growth and function of algae. Algae are normally more sensitive to antibiotics, antimicrobials, and selective serotonin reuptake inhibitors. The other pharmaceutical particles don't hamper the system as much as these, but some of the heavy metals, ammonium, COD, and other organic contaminants when higher in concentrations in wastewater can inhibit algal growth [119,178]. Oller et al. [127] stated that a combination of algae-based technology with further slighter subtle processes such as constructed wetland, treatment pond and advanced oxidation as an advantageous solution to this problem. Algae have the potential to eliminate different PPCPs belonging to estrogenic hormones, antibiotics, antimicrobials etc., and in the process of removal, mainly biodegradation was found to be responsible for it. As per the research conducted by Peng et al. [130] and Zhang et al. [193] the removal efficiencies of hormones progesterone and estrone were found to be $>$ 95% and 85% in biotransformation and biodegradation, respectively. Bai and Acharya [11] noted a 32% degradation of the antibiotic sulfamethoxazole for the process of algae-mediated photolysis. Similarly, Xiong et al. [187] observed a 9.5–91.5% degradation of levofloxacin in a biodegradation process enhanced with NaCl. 7-amino cephalosporanic acid was degraded 100% in a combined process of hydrolysis, photolysis, and adsorption [69]. Antimicrobials like triclosan was degraded to 100% when treated with algal process [11]. The overall study suggests that algae, microalgae, algae bacteria consortia have great capabilities for the removal of pharmaceutical contaminants. The algae-based treatment combined with advanced oxidation processes, microbial fuels cells along with some genetic modifications will be viable for the enhanced removal of PCs.

5.1.6. *Constructed wetland for removal of antibiotics and antibiotic resistance genes*

Constructed wetlands (CWs) is a cost-effective and ecofriendly technology for the removal of PCs in comparison to the other physical, chemical, and biological processes. This is more efficient in the elimination of various micro-pollutants, including antibiotics and antibiotic resistance genes (ARGs) [148]. The mechanism involved in the removal of contaminants in CWs are complicated as it consists of physical, chemical, and biological interaction among plants, substrates, and microorgan-

Table 4
Microalgal process for treatment of PCs.

Sl No.	Pharmaceutical Contaminants	Microalgae	Treatment Technology/Mechanism	Removal%	Ref.
1	Diclofenac	*C. sorokiniana*	Anerobic Digestor along with Algal Bioreactor	50	[42]
	Ibuprofen			100	
	Paracetamol			100	
	Carbamazepine			30	
2	Metronidazole	*C. vulgaris*	Adsorption	100	[70]
3	Bisoprolol	*T. dimorphus*	photobioreactor	97	[64]
	Terbutalin			98	
	Metoprolol			99	
	Hydroxyzine			87	
4	Cephalexin	*B. cepacia, C. luteola, P. fluorescens, B. subtilis, B. megaterium Sterothermophilus, C. freundii*	Biosorption	95	[6]
5	Florfenicol	*Chlorella* sp.	Bioaccumulation, Biodegradation and adsorption	97	[161]
6	Caffeine	*Microalgae consortia in HRAP dominated by Chlorella* sp. *and Scenedesmus* sp.	High Rate Algal Ponds	99	[74]
	Ibuprofen			99	
	Carbamazepine			20	
7	Sulphapyridine	*C. reinhardtii*	Batch Experiments with four Microalgae (Photodegradation, sorption, etc.)	93	Diaz., 2016
		C. sorokiniana		73	
		D. tertiolecta		56	
		P. subcapitata		48	
8	Paracetamol	*C. sorokiniana*	Bubbling column photobioreactors	42	[150]
		C. vulgaris		12	
		S.obliquus		9	
	Diclofenac	*C. sorokiniana*		30	
		C. vulgaris		22	
		S.obliquus		78	
9	Enrofloxacin	*S. obliquus*	Bioaccumulation, bioadsorption and/or biodegradation	23	[186]
		O. multisporus		18	
		Chlamydomonas		25	
		C. vulgaris		26	
		M. consortium		26	
		M. resseri		20	
10	Ibuprofen	*Nannochloris* sp.	Incubation	40	[12]
	Trimethoprim			10	
	Ciproflfloxacin			100	
	Carbamazepine			20	
	Triclosan			100	

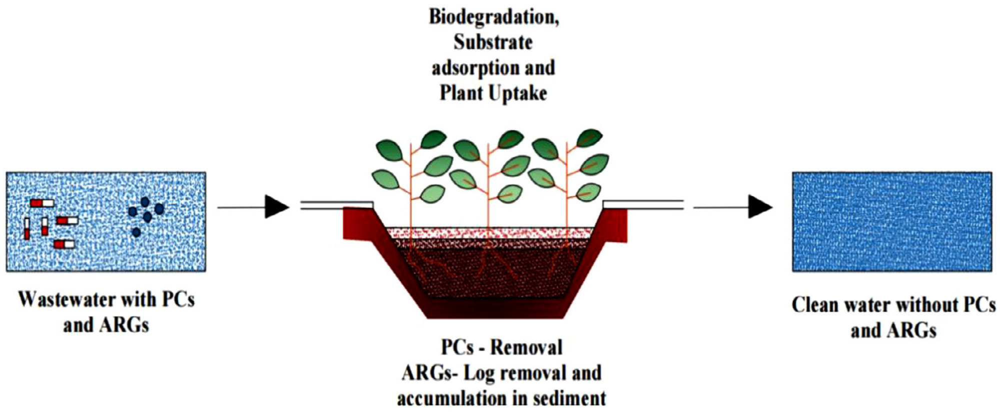

Fig. 8. Constructed wetland for removal of PCs.

isms (Fig. 8). In CWs microorganisms are the main dominating operators for the antibiotic biodegradation and use same antibiotics as carbon sources. The principal microorganisms active in CWs are bacteria, actinomycetes, fungi (basidiomycetes and yeasts) and some protozoa. Fernandes et al. [58] reported that the involvement of the microbial community in the reduction of enrofloxacin and tetracycline was up to 94%. Bacteria was accounted for contributing the highest proportion for the removal of pollutants. Temperature, plants, and concentration of antibiotics are some of the factors affecting the antibiotic removal process via microorganisms. Truu et al. [169] found that at warm temperature nitrifying bacteria and protein-degrading bacteria have favorable bioactivity along with higher reduction ability towards antibiotics. From the study conducted by Liu et al. [96], vertical subsurface flow constructed wetlands (VFCWs) were found to be better for the elimination of antibiotic with an efficiency of over 70%. In Constructed Wetland-Microbial fuel cells (CW-MFC), anode need to be kept in anaerobic environment and cathode need to be placed in aerobic environment to so that redox conditions can be developed naturally in the system. Electricity generation takes places when bacteria oxidize the organic matter leading to improvise the removal efficiency of antibiotics. Moreover, micro-current stimulation can improve microbial activity and accelerate the degradation of pollutants. Chen et al. [31] demonstrated that 99.1% antibiotics and ARGs efficiently eliminated by integrated constructed wetland. Still the removal efficiency of antibiotics like sulfonamide, macrolactone, chloramphenicol, polyether and beta-lactam need to be additionally focused on [96,146].

5.1.7. *Bio-nanotechnology*

Nanotechnology has been the next wave for innovation for decades which sooner will turn into reality. The technologies related to it are being used for the abatement of groundwater, wastewater and drinking water. Nanotechnology has great potential for an effective prevention, treatment, and clean-up of pollution. Nanomaterials play a fundamental role in recent research efforts for the development of efficient water treatment technologies. PPCPs can be treated using nano systems techniques such as adsorption using nanomaterials, photocatalytic degradation, and nanofiltration, etc. [137]. Currently other nanomaterials such as nanosorbents, nanocatalysts, nanostructured catalytic membrane, bioactive nanoparticles (NPs), biomimetic membrane, nanopowder, nanotubes, magnetic nanoparticles, granules, flake, and molecular imprinted polymers (MIPs) have been applied to remove toxic metal ions, microbes, organic and inorganic solutes from wastewater and drinking water [34]. Nanomaterials such as silver and titanium dioxide NPs can be used for point-of-use water disinfection, anti-biofouling surfaces and decontamination of organic compounds. Nanoscale zerovalent iron particles can be used for wastewater treatment and similarly, nanofiltration membrane can be used for reduction of hardness, color, odor, heavy metals [80]. Nano-based technologies have great potentials to make industrial wastewater treatment more efficient and natural nanomaterials/biopolymers with their unique properties, including efficiency, cost-effectiveness and eco-friendliness can be utilized as promising alternatives for water treatment.

5.1.8. *Eco-friendly adsorbent*

Adsorption has attracted particular attention as an efficient method for wastewater treatment. Treating pharmaceutical contaminants in wastewater through this method has been broadly implemented as it's an economical, simple to operate and fast retailing method where no sludge formation take place [86]. An extensive range of materials and devices like gels, films, membranes, particles, etc., are applicable in this method which makes it more relevant. Over the last few years application of bio-based adsorbents formulated by using natural feedstock, polymers, biopolymers have received great attention. Biopolymers and bio-compounds are economical, renewable, and easily available compounds with various functional groups present on the structure which enhance the adsorption capacity [95]. Considering this, chitosan and its derivatives have attracted significant interest as highly active bio-sorbents for the removal of pharmaceutical pollutants from the aquatic environment. Biodegradability, biocompatibility, hydrophilicity, nontoxicity, antimicrobial activity, low immunogenicity, inexpensiveness and accessibility are some of its features [86]. The combination of chitosan and metal organic framework exhibited the highest adsorption capacity toward tetracycline. Studies also indicate that waste coffee grounds composites can be utilized as promising low-cost and eco-friendly adsorbents for the removal of pharmaceuticals from wastewater. More experimental works are still needed on the improvement of adsorbent selectivity toward specific pollutants.

5.1.9. *Carbon filtration through activated carbon*

Activated carbon is a well-known process for removal various organic contaminants and organic carbon. It is commonly applied as a powdered feed or in a granular form in packed bed filters. The granular activated carbon can be used as a replacement for anthracite media in conventional filters, which delivers both adsorption and filtration [160]. In an experiment, the treatment done with granular activated carbon, ozonation and sand filter showed a removal efficiency of 87–95% of the active pharmaceutical ingredients [15]. Activated carbon can be extremely effective for the removal of emerging contaminants. Snyder et al. [160] reported both powdered feed and granular carbon could remove greater than 90% of PCs. Powdered carbon can't recycle through the treatment process. Granular form is highly effective but water-soluble contaminants can break through it much more rapidly than strongly bound hydrophobic contaminants.

5.2. *Fate of pharmaceutical contaminants during treatment process*

Pharmaceutical contaminants through various physio-chemical and biological processes transform into stable compounds which are not harmful in nature. During degradation, the PCs can either undergo mineralisation, degradation, or minor structural changes [84]. Mineralisation of PCs is transformation of these contaminants into carbon dioxide, water, and inorganic ions [84]. Degradation is the process in which PCs deteriorate into smaller/shorter chain products or compounds. The degradation process can occur by co-metabolism or by catabolism. Biotransformation of PCs involve oxidative, reductive, and lytic mechanistic pathways. Alfonso-Muniozguren et al. [5] reported that the biodegradation of the X-ray contrast media iopromide leads to the oxidation of the primary alcohols (forming carboxylates) on the side chains of the pharmaceutical during the treatment by conventional activated sludge, while dehydroxylation at the two side chains occurred in the nitrifying activated sludge, which was associated to a co-metabolism pathway. In similar studies, by analysis of biofilm reactors (BFR) and batch activated sludge it was reported that hydroxyl-ibuprofen was the main biotransformation product under oxic conditions and carboxy-hydratropic acid under anoxic conditions. Carboxy-ibuprofen was found under oxic and anoxic conditions almost only in the batch activated sludge [197]. The biotransformation of naproxen was reported to induce demethylation and decarbonylation of this pharmaceutical. Anaerobic systems advance O-demethylation pathways on pharmaceuticals such as guaifenesin, naproxen, oxybenzone and mestranol [5]. PCs analgesics and anti-inflammatories like Ibuprofen transformed into stable compounds hydroxy-ibuprofen (hydroxylation of alkyl group), carboxy-ibuprofen and carboxy-hydratropic. Similarly, naproxen transformed into its stable form by O-demethylation and Decarboxylation [163,172,174,175]. The reduction pathway is the initial step for the transformation of ketoprofen [5]. The ketone group is reduced during the transformation process to increase the electron density of the aromatic rings, rendering these more reactive. Reduction is preceded by hydroxylation forming a catechol structure. A subsequent oxidative ring-opening of catechol by meta-cleavage, plus hydrolysis leads to the generation of 3-(hydroxy-carboxymethyl) hydratropic acid product. In the final step, alcohol is oxidised to produce the 3-(keto-carboxymethyl) hydratropic acid [134]. For the antibiotic trimethoprim, hydroxylation by microorganisms from activated sludge leads to the generation of α-hydroxy-trimethoprim and hydroxylated-trimethoprim [89]. There are several other studies and research on the transformation of PCs into stable products. PCs' structure changes depending upon various treatment systems and might turn into any of its stable form but at the end of any treatment process suitable for removal of PC, a stable compound is achieved [179,188].

6. Effects of pharmaceuticals on environment and ecosystem

Pharmaceutical drugs play an important role in the treatment and prevention of diseases in humans and animals, but the rising concentration of pharmaceutical residues have led to unprecedented changes in the ecosystem [194]. Pharmaceuticals are generally studied and governed by strict regulatory policies which require both pre-clinical and clinical studies to assess their potency and safety before commercialization. The potential impacts on the environment for the production and use of drugs are not well understood and have recently become an area of research and study. Since the 1990′s, pollution of water by pharmaceutical residues has been a major environmental problem [46]. Pharmaceutical residues are deposited into the environment through consumption and excretion by humans, improper disposal, flow of sludge manure and re-irrigation of contaminated water, leaking sewage, and pipes, etc [93,98]. In the studies conducted by USGS, it has been observed that the sources of pharmaceuticals do not limit only till manufacturing plants, but are also obtained from the antibiotics and drugs used in livestock industries, the streams receiving runoff from the animal feeding operations, the excess drugs released by human beings, pharmaceuticals like caffeine, cotinine, diphenhydramine, and carbamazepine, etc [99,100,106]. The consumption and excretion by humans and the improper disposal by industries are the major sources of pharmaceutical drugs in the environmental. The medicines after being ingested and utilized by the body, a part of the active pharmaceutical ingredient is excreted unmodified or only slightly metabolized which enters the sewage system. Pertinent amounts of pharmaceuticals gratuitously turn up to appear in the environment due to their inappropriate disposal via sink or toilet. Pharmaceuticals touch down the water bodies as these can’t be treated by the conventional wastewater treatment plants and these PCs also get into the ground surface and mix with the ground water (though being very low in terms of concentrations). The sewage sludge/manure being used as fertilizers in the crop fields may also contaminate the ground water with pharmaceuticals. The veterinary pharmaceuticals are often being dispersed in the air inside the animal husbandry as drugs are often applied in the form of powder and are dispersed on combining with dust and bio-aerosols [115,123]. This provides a pathway for the pharmaceuticals to get into the air and cause pollution. Studies conducted recently on the impact of pharmaceutical pollution on the world’s rivers reported that pharmaceutical residues threaten the environment and human health in more than a quarter of the tested areas ([184]; BBC News, 2022). The study investigated 1052 sample areas near 258 rivers in 104 countries, representing river pollution of 470 million people. It is reported that the lower- and middle-income countries contained the most polluted areas due to improper wastewater and waste management techniques, and pharmaceutical production. The impact of PPCPs is huge on the environment because these may act in an unexpected way when mixed with other chemicals from the environment or concentrated in a food chain. Some PPCPs are active even at lower concentrations and are often continuously released in large or widespread volumes. Due to the high solubility of PPCPs in water, aquatic organisms are particularly vulnerable to their effects. Researchers have found that a class of antidepressant drugs is significantly delaying the growth rate of frogs. The chemicals in these PPCP products may affect the female reproductive system or the male reproductive system of various aquatic animals, thereby affecting their reproductive levels (Washington State University, 2009). In addition to being found in water only, the ingredients of some PPCP can also be found in the soil. As some of these substances are long-acting or biologically indestructible, those are increasing in the food chain. There are various concerns about the effects of surface water treatment and especially the threats to rainbow trout exposed to contaminated water in the wild. Fick et al. [59] conducted research on rainbow trout, exposed to clear, fresh water in three different parts of Sweden. These rainbow trout were presented for a total of 14 days while 25 drugs were measured in blood plasma at different levels for analysis. The progestin levonorgestrel was found in fish blood plasma at concentrations between 8.5 and 12 ng m/L, exceeding human plasma levels of treatment. Levonorgestrel moderate flow rate in three areas were found to reduce the rainbow trout fertility. Long term effect can lead to the mutation of genes and reduction of fish population. PCs such as sex hormones, veterinary growth hormones, antibiotics and glucocorticoids are known for their endocrine disrupting nature [128,131,155,159]. Further experiments for the identification of more PCs bearing similar properties are still ongoing. Antibiotics present in the effluents and in the aquatic environment intensify the resistance among the microorganisms which leads to their interference with the microbial community structure thus affecting the microbial population and the ecological function of the aquatic ecosystem. There is need to develop a new production technique that uses raw materials that are eco-friendly, produces fewer toxic metabolites and by-products in our environment to prevent the ecosystem destruction.

7. Eco-toxic effects of PCs on microbial communities

Microorganisms play a key role in functioning of our ecosystem. They are the mediators for debris-based food web which help in making a successful use of energy contained in dead organic matter by the detrivores. The existence of handful and varied microbial community is a necessary for a quick and effective response to the various natural and anthropic disturbances that can affect an ecosystem [190]. Microorganisms are involved in ecosystem in self-purification processes as they can degrade contaminants by metabolic and/or co-metabolic pathways. Biodegradation is an essential process for eliminating pharmaceuticals and the recovery from contamination is possible only if toxicity of the molecules does not inhibit microbial activity [25]. Pharmaceuticals typically enter the environment in complex effluents, and thus natural microbial communities are exposed to a mixture of active substances. The insertion of antibiotics into aquatic environments can promote the acquisition of antibiotic resistance genes by microorganisms after a long exposure time, even at trace levels.

Experiments state that naproxen is the pseudo-persistent compound in surface waters and biodegradable in aerobic conditions that have an acute effect on river microbial community. The microbial cell viability and the β-Proteobacteria group decreased significantly and, in its presence, a toxic effect on ammonia oxidizing bacteria was also found in a wastewater treatment plant [68]. Similarly, diclofenac is a polar pharmaceutical compound mostly used as the sodium salt diclofenac-Na in human and veterinary medicine to reduce inflammation and pain. Lotic biofilms composed of bacterial and algal populations, lost about 70% of their overall initial biomass (based on biofilm thickness) when exposed to diclofenac [25].

8. Environmental effects of pharmaceuticals on human health

High concentration of pharmaceutical residue in the environment is always concerning to the human health and the ecosystem. Different factors affecting human health are concentration, type and distribution of drugs, pharmacokinetics of each drug, modification of the structure, metabolism or degradation processes and possible drug overdoses [40]. Studies have shown that PPCPs are present in water worldwide, but no studies have shown a direct effect on human health. However, the absence of empirical data cannot exclude the possibility of adverse effects due to interactions or prolonged exposure to these substances (American Water Works Association, 2009). Sanderson et al. [149] studied the aquatic toxicity of four different PCs groups (antibiotics, antineoplastics, cardiovascular drugs and sex hormones such as estrogens and androgens) and found that daphnia fish and algae were susceptible to these pharmaceutical compounds, while antibiotics and sex hormones were equally threatening for both human as well as aquatic life. As per a study conducted by Mimeault et al. [110], goldfish showed bio-centration factor of 113 when it is exposed to high concentration of PPCPs for 14 days. These chemicals in water can be in the trillions of parts or parts of a billion and it is difficult to determine the actual chemical values. Daughton [40] have focused on determining whether the concentration of these drugs is below or above the acceptable daily intake (ADI). The relationship between risk perception and behavior is often different. Risk management is most effective once the motivation for the disposal of unused pharmaceutical drugs is understood. According to a study conducted by Cook [36], there has been a little correlation between risk perception and information about drug waste. In addition to growing concerns about human health risks from drug overdose, many researchers have speculated about the potential for antibiotic resistance. Hernando et al.

[72] reported that 10 different antibiotics were found in sewage, surface water, and residues which shows the types of different drug overdose. The contamination of drinking water with pharmaceuticals is also a decisive issue, but there is no distinct evidence that prove pharmaceuticals possess threat to human health as the concentration detected in drinking water are usually lower than 0.05 μg.L^{-1}. Still there is a concern due to regular and limitless exposure of pharmaceuticals, hence the drinking water should be observed and examined on frequent intervals [14]. The antibiotic resistance genes, which get into the environment through wastewater treatment plants and manuring exhibit an indirect but outright serious impact on human health. For safeguarding the health of animals and their treatment, veterinary antibiotics are being increasingly used in many regions, which also tend to improve the feed efficiency of livestock, poultry, pets, aquatic animals, silkworms, bees etc. [4,153]. In excreted product of animals, veterinary antibiotics additive can be in active condition hence, a substantial portion of it may spread into the environment in bioactive forms and negatively affect human health [124,136,153]. Studies on long term and low-dose exposure are more accurate and directly reflect the eco-toxicological effects of human and veterinary pharmaceuticals.

9. Recommendations

- Certain groups of pharmaceutical contaminants are very toxic and recalcitrant in nature and abundantly increasing in the environment. So, development of treatment methods for those specific group of contaminants should be focused.
- The efficiency of removal for various pharmaceutical groups for different removal technologies should be evaluated and the best technique should be adopted for their respective industries.
- The correlation between freshwater parameters like BOD, COD, etc., and pharmaceutical concentrations should be developed so that the removal efficiency of these pharmaceutical contaminants can be expressed in terms of these parameters. Experimental models corresponding to it need to be developed.
- Treatment techniques especially biological treatment for removal of various PCs from wastewater should be immensely researched upon as those are environmentally sustainable, cost effective and cause no harm to the environment.
- Combined biological treatment methods with conventional wastewater treatment plant will be beneficial for overall removal of pharmaceuticals and maintaining the required quality parameters for the water streams. Efficiency of these combined systems is also a wide area to be examined.

10. Conclusion

In the past few decades, PCs have emerged as a major emerging contaminant in wastewater. These are extensively detected in aquatic environments due to the incomplete removal by conventional wastewater treatment plants. Studies have indicated the ill impacts of these contaminants on both humans and animals as well as ecosystem. Several studies and research are going on to detect these kinds of compounds in wastewater and to provide an effective treatment method for their removal. The current study includes various pharmaceutical groups, different treatment methods and impact on human and ecosystem. The fate, regulatory guidelines, and the Environmental Risk Assessment (ERA) regarding these pharmaceutical contaminants are also briefly described. The optimization of current techniques which favor environmental sustainability need to be studied more which will not only help in removing these PCs but also help in maintaining the ecosystem. Based on space availability, procurable capital, and effectiveness of contaminant removal, a suitable technique can be selected for removal of PCs from wastewater. So, the knowledge of various groups of pharmaceuticals and their treatment techniques will be very much helpful.

Declaration of Competing Interest

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

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