





## Trend in pharmaceutical effluent discharge and management using microorganisms

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### ABSTRACT

Recent rising population has been matched by a corresponding increase in pharmaceutical companies and products worldwide. Pharmaceutical effluents are causing unprecedented environmental pollution, risking ecosystem health and public safety. The discharge of treated or untreated wastewater is drawing attention from scientific and political communities due to its implications for climate change. Hence, a global effort is needed to enhance understanding of the impacts of pharmaceutical wastewater on soil, animals, human health, food security, biodiversity, and ecosystems. This has inspired studies on eco-friendly biotechnological and bioremediation strategies using microorganisms to address pollution challenges. Therefore, this review aims to explore the trend, consequences, and microbial roles in pharmaceutical wastewater management, discharge characteristics, and utilization.

### 1. Introduction

In recent decades, the rising human population and their activities (intentional and unintentional) are intensifying a corresponding increase in the depreciation of the earth's capacity to safely sustain the existence of living things. Industrialization, urbanization, and food production intensification, even though they undermine ecivilization, are some of the historic anthropogenic underscoring civilization and humanity's quests for an improved existence (Ninkuu et al., 2011; Ren et al., 2022). Demand for healthy living, a shift in apothecary practice, rising personal care consciousness, and humanity's growing susceptibility to varying infections resulted in the explosion of pharmaceutical industries' effluents' discharge and the need to mitigate their effects on both the environment and biotic agencies. These industrial discharges (wastewater effluents) usually contain a variety of harmful substances, including heavy metals (HMs), which infiltrate the food chain through underground waters and contaminate fresh food crops and bush meats (Schweitzer and Noblet, 2018; Yerima and Atoshi, 2023).

Many developed countries like Japan, France, Germany, Japan, the United Kingdom, and the United States are lead producers of drugs and contributors to pharmaceutical pollution. These five countries accounted for more than two-thirds of the world's drug production and emission of over 60 megatonnes of carbon (iv) oxide equivalent (CO<sub>2</sub>e). At the same time, India and China dominate the international market for affordable natural or organic-based pharmaceuticals (World Health Organization, 2017). Pharmaceutical-based pollutants are generated from different stages of drug manufacturing operations (Gadipelly et al., 2014). Pharmaceutical substances exhibits varying characteristics and toxicity levels in the environment, threatening human and aquatic health (Verlicchi et al., 2012; Yousefi et al., 2024). Pharmaceutical production waste disposal management, drugs (unused, expired, residual) handling, and environmental compliance processes are the major sources of pollutant effluxes into municipal drinking, underground, farm irrigation, and rural utility waters without consideration of pre-processing (Adetunde et al., 2019; Kumari and Tripathi, 2019). Nevertheless, secondary treatment technologies are suggested to degrade only 18–32% of pharmaceutical residues, while tertiary

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treatments improve removal efficiency to 30–65%. Additionally, membrane bioreactors (MBRs) achieve 28–100% removal, depending on the pharmaceutical product (Khan et al., 2020). That notwithstanding, more sophisticated and environmentally friendly techniques are required to remediate this pollution.

Several recent studies have explored the impact of effluent disposal, its environmental hazards, and associated management techniques (Alsubih et al., 2022; Carraro et al., 2016; Chauhan et al., 2023; Hossen et al., 2024; Wang et al., 2023). While these topics have been reviewed in recent literature (Khan et al., 2022; Li et al., 2024; Vijay Pradhap Singh and Ravi Shankar, 2024; Wen et al., 2024), the existing reviews are often limited in scope, focusing on specific fields or management techniques. This highlights the need for a more comprehensive and up-to-date literature review. This review examines the characteristics and emerging trends of pharmaceutical wastewater effluents, focusing on their treatment and management strategies. It highlights the presence of heavy metals and other pollutants in pharmaceutical wastewater and explores various biological management approaches, including microbial treatments. The article also discusses the potential of wetlands for treating pharmaceutical wastes, the survival dynamics of microbiomes in pharmaceutical effluents, and the biological degradation of pharmaceutical compounds. Additionally, we reviewed the factors influencing biodegradation processes and the application of microbial fuel cells in remediating pharmaceutical waste, illustrated (Fig. 1).

### 1.1. Wastewater effluent

Whether primary or secondary, wastewater from multi-pharmaceutical sources contains a high level of heterogeneous pollutants (solid, gaseous, ionic), including non-biodegradable organic and inorganic genotoxic substances. Pharmaceuticals (antibiotics, a range of prescription and non-prescription drugs as well as personal care products, hormones, analgesics, cytostatic agents, steroids, anti-inflammatories, anti-depressants), surfactants, metals (lead, chromium, nickel, mercury, etc.), metabolites, and other pollutants were reported in the scientific literature as pharmaceutical pollutants (Kumari and Tripathi, 2019; Vaudin et al., 2022). Influxiation of pharmaceutical pollutants into the environment is from a myriad of scattered points, popular amongst which are pharmaceutical production plants (PPP), wastewater treatment plants (WWTPs), hospitals, and landfills. Nickel (Ni), iron (Fe), phenols, detergents, organic compounds, and other toxic elements are found in pharmaceutical effluents (Cosgrove et al., 2016). These have exacerbated the toxic and hazardous effect of pharmaceutical wastewater on plants, animals, and humans' well-being, as well as becoming a growing global environmental, food safety, and public health concern mainly because of their genotoxicity, mutagenic, and soil community disruptive potentials (Kanakaraju et al., 2018). Indiscriminate discharge of untreated or poorly treated pharmaceutical wastewater in the surrounding ecosystems (aquatic bodies, soil, and air) and some biological systems is rampant in many developing nations with limited capacity for effluent pre-treatment processes and

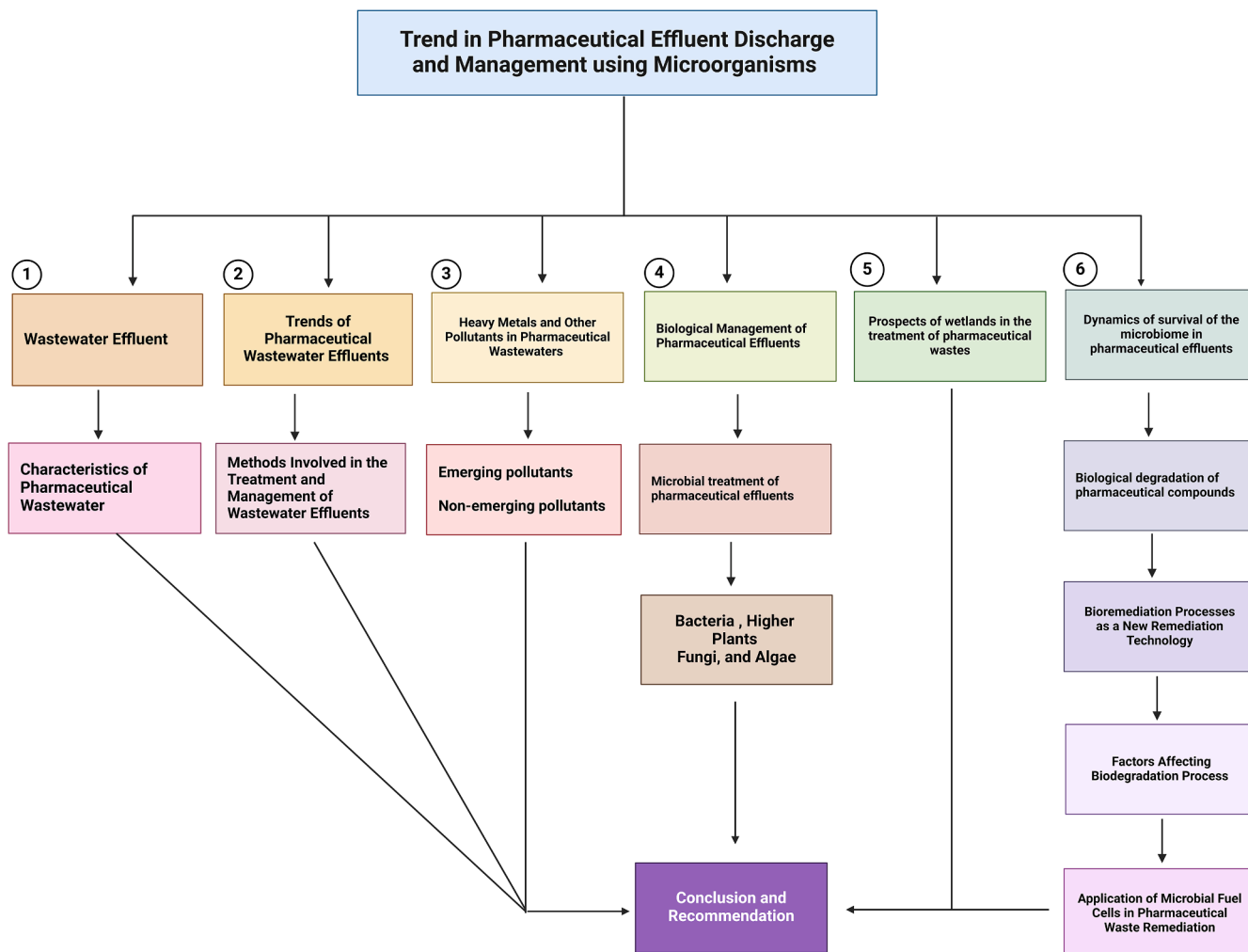


Fig. 1. Schematic overview and flow chat of topics covered in this review".

technologies. While the world is witnessing a rise in the effects (loss of arable lands, outbreaks of chronic diseases, food safety and security issues, ecosystem dysfunction, potable water scarcity, the emergence of resistant microorganisms) of pharmaceutical pollutants accumulations beyond the natural environment threshold, mitigating their effect or removing them from the environment is also receiving proportionate.

### 1.2. Characteristics of pharmaceutical wastewater

The composition of pharmaceutical wastewater is generally complex, with a high concentration of organic matter, microbial toxicity, salt, recalcitrant, and emergent compounds (Andersson and Hughes, 2012).

In addition, most pharmaceutical factories are process-categorized, with stages having their attendant raw materials and collectively influxing varieties of pollutants into different wastewater. While the characteristics of pharmaceutical effluents may vary with product and source types, level of urbanization and industrialization, degree of commitment to environmental protection laws, and waste management culture, their physicochemical (biological oxygen demand, dissolved oxygen, chemical oxygen demand, pH, salinity, total suspended solids) and biological characteristics, remain inconsistent throughout the world (Deo, 2014). Hence, different kinds of pharmaceutical wastewater have different characteristics. Pharmaceutical wastewater is also characterized by strong fluctuations in the diversity of pollutants. The spent water may have high-risk levels of hydrocarbons, nitrogen, sulfate concentration, dissolved organic compounds (DOCs) (proteins, carbohydrates, fats, oils, trace elements, and metals), biological toxicity, and chroma. However, Shon et al. (2006) noticed that a variable composition and genre of organic compounds having different refractory properties, structures, and origins constitute over 50% of the pollutants in pharmaceutical wastewater. It is therefore expected that chemo-pharmaceutical and biopharmaceutical effluents would be characteristically different in pollutants' heterogeneity and concentration, with the former having more biological pollutants, highly soluble metabolites/transformation products or toxins, and fewer non-biodegradable compounds. The confluence of bio- and chemo-pharmaceutical effluents may cause an increase in their siltation, eutrophication, nuisance, and toxic capacities. Sugar, glycosides, organic pigment, anthraquinone, tannins, alkali matter, cellulose, lignin, and inorganic matter are reported in pharmaceutical wastewater (Ortúzar et al., 2022). A good understanding of the pollutants' composition in pharmaceutical effluents is critical for the choice of treatment and reuse.

## 2. Trends of pharmaceutical wastewater effluents

The global pharmaceutical industry is a rapidly expanding and critical indicator of industrialization. Its operations are beset with multiple waste generation sources (production, distribution, utility, and disposal) as well as varied environment-impact compliance and disposal options. Studies have affirmed that the wastewater streaming from pharmaceutical industries is complex and may be released to the environment as liquid, gas, or solid wastes. In the context of the current study, it comprises wastes from primary health care centers (hospitals, clinics, and maternity homes), pharmacies (places where medications are dispensed and sold or even prescribed and administered), and households (domestic sources) including those (urine and feces) disposed of in the sewage system. Suffices to say pharmaceutical waste, particularly its spent water, has a heterogeneously disproportionate concentration of used, unused, and expired prescription or non-prescription drugs from orthodox or traditional origins, personal care by-products, controlled substances as promulgated by nations, and other potentially hazardous compounds capable of inducing toxicological reactions in environmental matrices (Arshad and Zafar, 2020). The widespread use of pharmaceutical products is as expansive as its waste sources coupled

with their transmission through the environment (Figs. 2 and 3). While much research focused on estimating the effect and quantification of pharmaceutical emissions, more efficient pre-treatment technologies and the level of compliance of the industry to environmental protection laws, global perceptions of the associated risks posed by the diversity of pharmaceutical wastewater effluents, and intermediate products in the environment are now generating interest (Götz et al., 2019a). Some of the contents of pharmaceutical effluents may escape treatment technologies into drinking water and other water bodies in trace amounts in the range of nanogram (< 100ng/l) or microgram (< 0.1µg/l) per litre (Houthuijs et al., 2023). Studies on pharmaceutical (biopharmaceutical and chemical pharmaceutical) wastewater contents showed a heavy presence of organic matter (OM), microbial toxins (MT), salt, suspended solids (SS), heavy metals, and other synthetic or natural chemicals of prescription, veterinary and therapeutic drugs. Even though the effects of exposure of aquatic biota to mixtures of these pharmaceutical pollutants are poorly understood, their toxicity or bioaccumulation effects have been linked to altered behavior, reproductive defect, morbidity, a growth defect, and neural challenges by Zaugg et al. (2014).

The diversity of dissolved substances' compositional characteristics (both organic and inorganic) in pharmaceutical wastewater effluents, as well as their compositional demography (compositional patterns), holography, and scientometrics or measured environmental concentrations or estimate the collective risks to humanity, are still poorly understood, despite being crucial to choosing the appropriate treatment technology (Aus der Beek et al., 2016; Götz et al., 2019b). However, pharmaceutical waste discharge is now attracting recognition in many countries as a public health hazard whose major pathway is household waste (Götz et al., 2019a). This contradicts the report that regarded urban wastewater as the dominant global emission pathway for pharmaceuticals. However, the pathway may have a potentially logical implication on the composition of pharmaceutical wastewater pollutants, heterogeneity, and toxicity in different parts of the world. Although portable water is used as an influent for manufacturing bulk pharmaceutical chemicals, it becomes contaminated effluent with varying degrees of bioactive substances at the end of the manufacturing cycle. More than often, pharmaceutical wastewater is perceived from a negative standpoint, intoxicating the ecosystem and escalating acute and chronic public health-related risk factors rather than from a value-adding position (Liu et al., 2019; Semerjian et al., 2018). Global potable or drinkable water scarcity has forced the emergence of water treatment plants and recycling technologies to facilitate wastewater reuse for mostly non-potable applications, including agricultural irrigations and product recovery (Ahmad et al., 2022; Grabicová et al., 2020).

Aside from this, the use of pharmaceutical effluents for product recovery, non-potable applications, and their remote role in ecosystem evolutionary dynamics are seldom reported in scientific literature. Therefore, pharmaceutical wastewater effluents may be hypothetically explored for potential industrial, agricultural, and domestic applications after being subjected to a selective treatment protocol that produces preferential agronomic, aquacultural, and other non-potable application benefits. Exponentially increasing population and untamed climate change situations have changed the focus on water management systems worldwide to decontaminating wastewater for reuse. Therefore, the menacing impact of pharmaceutical wastewater effluents in many communities via treatment and discharge regulations must be systematically decelerated. Effluents from various pharmaceutical industries may be hypothetically collected in a central non-potable wastewater recycling system (NWRS) for end-use-based treatments. Since it has been reported that contaminants (biological and chemical) in pharmaceutical effluents may escape any one treatment technology, proper identification of their constituent mixture of synthetic, natural, and emerging bioactive chemicals has been crucial to the choice of decontamination technique(s) required for the treatment (Samal et al., 2022). In addition, the physicochemical characteristics of the effluents also, to a significant

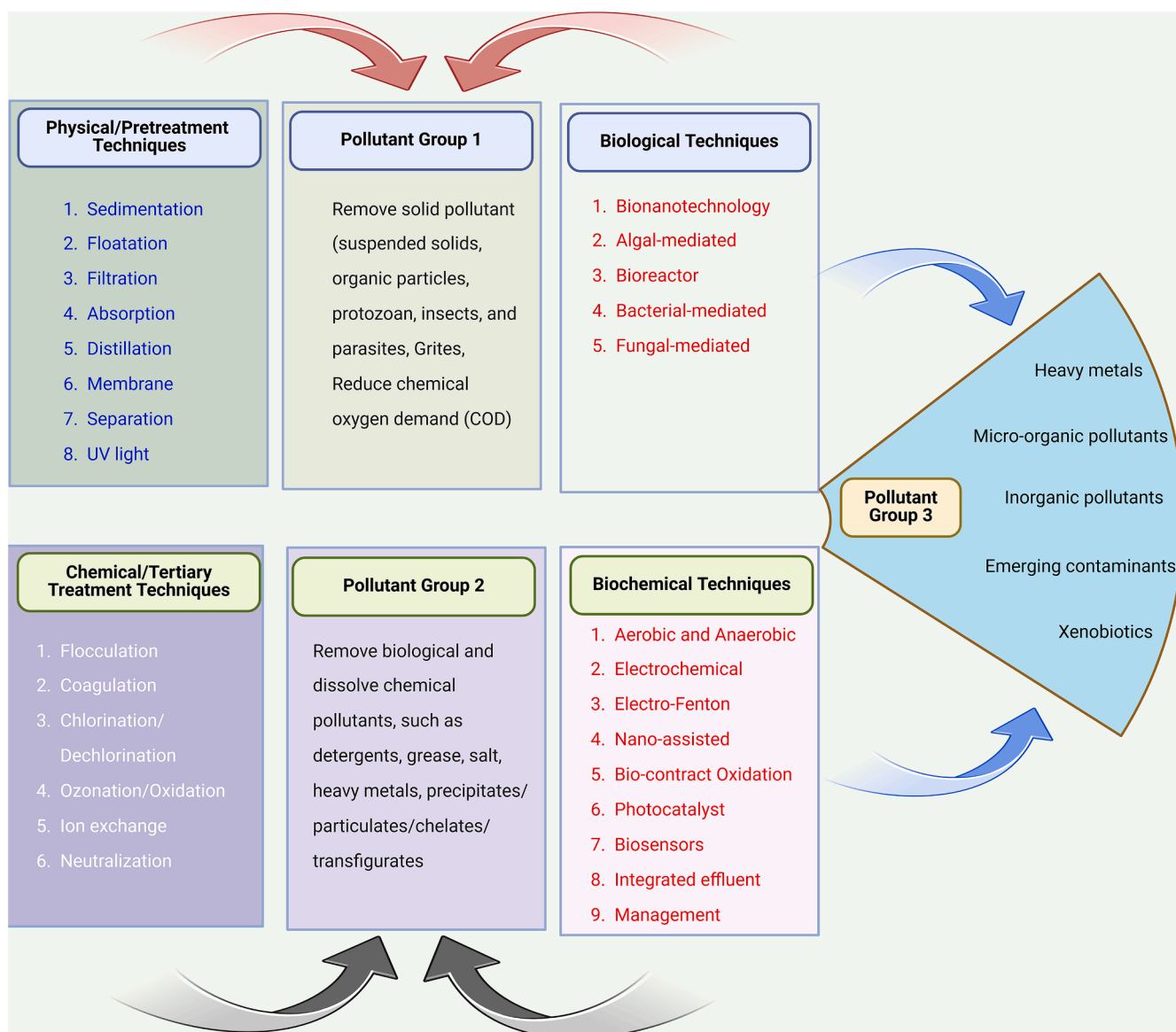


Fig. 2. Illustrative representation of pharmaceutical waste sources, dynamics, and stream in environmental matrices.

extent, influence the choice of treatment technology. This range of emerging contaminants in wastewater of pharmaceutical origin may cause a change in inherited traits in soil microbial populations, small animals, and plants, resulting in genetic speciation. Notwithstanding this and other stricter regulations on wastewater treatment and disposal, recycling pharmaceutical wastewater effluents for reuse may potentially relieve the demand pressure on cleaner drinking water, reduce the outbreaks of water-borne, facilitate irrigation agriculture and aquaculture, save cost on water bills, protect underground water sources from contamination, and improve the socioeconomic quality of the community. While the fight against climate change dominates many national agendas worldwide, the efforts to curb the effects of effluents discharged from pharmaceutical and industrial sources on the environment are far from matching the demands for safe, clean water. Furthermore, the added and pollutant diversity knowledge of pharmaceutical effluents is crucial in revolutionizing their management.

### 3. Methods involved in the treatment and management of wastewater effluents

Over the recent decades, numerous methods (Fig. 3) such as

biological removal, chemical precipitation, cementing, floatation-flocculation, sorption (adsorption, biosorption), ion exchangers, catalysis (photocatalysis, catalytic ozonation, photo-electro-Fenton process), electrokinetic, nanotechnology, and reverse osmosis have temporally evolved as either pre-treatment or remediation technologies with different environmentally-friendly outcomes (Saravanan et al., 2022; Zewail and Yousef, 2015; Zhu et al., 2014). Notwithstanding all these methods, the scientific community and environmentalists remain skeptical about the capacity of each of these techniques to remove completely all forms of pollutants from wastelands, polluted soils, or wastewater effluents. Suffices to say a few pollutants, particularly some HM, may escape removal by any one of these techniques except a combination of the techniques is used as a remediation model (Chen et al., 2019; Wu et al., 2022). The variation in pollutants' physico-chemical characters, interactive propensity or stoichiometry, concentration, and relevance to *in situ* organisms may be vital in the choice of remediation technique. For example, catalysis techniques in their diverse application forms have been effective in ramping the oxidation process in the remediation of organic pollutants, carbon dioxide, and other small molecules (Jiang et al., 2022). However, it is sensitive to climate change and disrupts *in situ* microbial communities even though

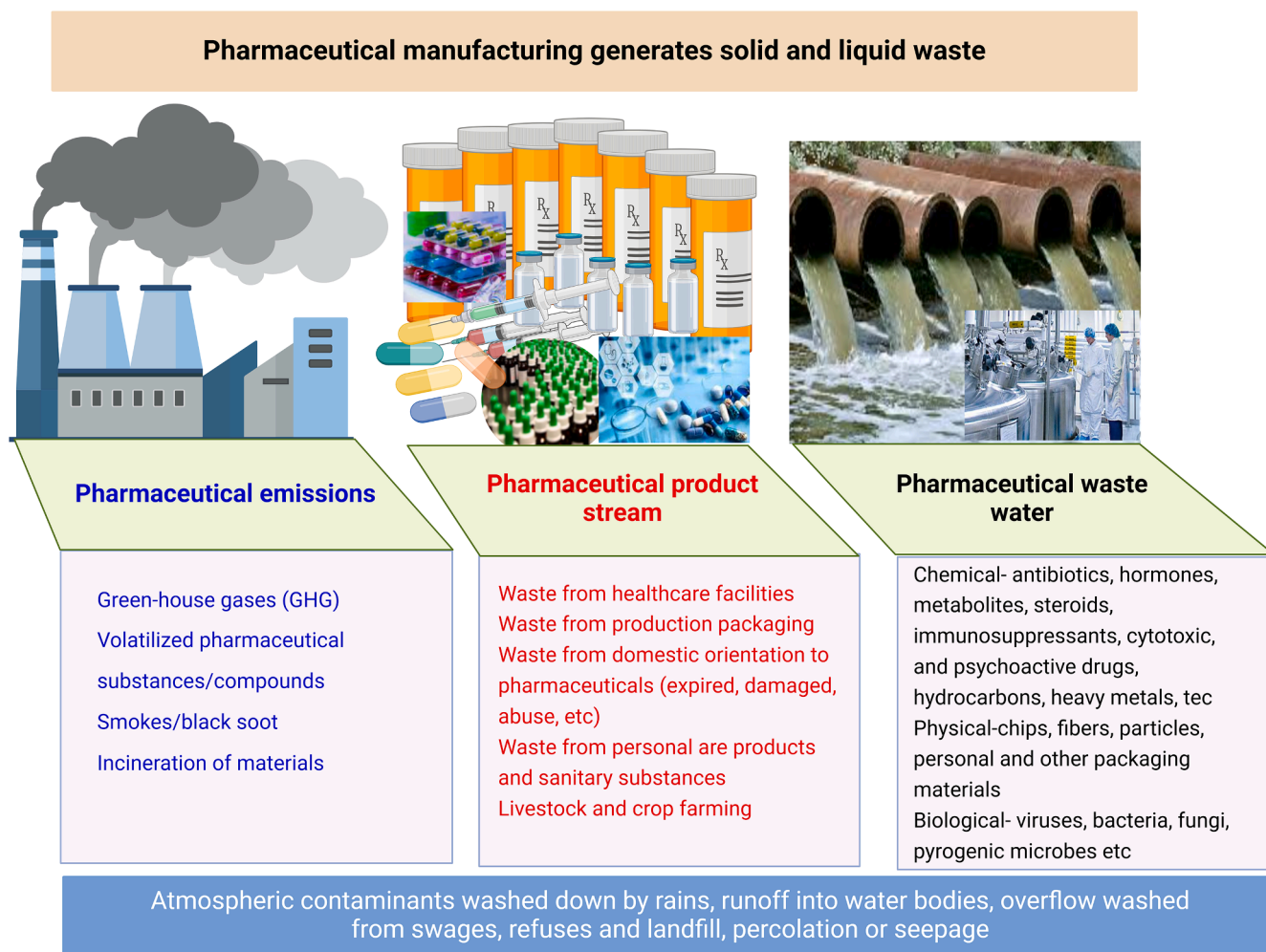


Fig. 3. Effect of pharmaceutical effluent on flora and fauna in the ecosystem.

it generates no hazardous by-products (Ahmad et al., 2016). Also, Doble and Kumar (2005) noted that physicochemical techniques have been used for decades to remove petrochemical, pharmaceutical, agro-allied, and refinery pollutants from soil or water using coagulants or flocculants (alum, lime, ferric chloride, activated charcoal). This method is expensive and laborious, produces sludge by-products, and destroys soil functionality. Consequently, biological remediation, which is also called bioremediation (phytoremediation, phycoremediation, mycoremediation, microbial remediation), became a revered remedial or capped technique used in strategic sequence with other remediation or pre-treatment techniques to remove pollutants, particularly in pharmaceutical wastewater effluents, either prior to or after their discharge into the environment. It is equally a conception of the natural adaptation responses of organisms, particularly microorganisms, to unprovoked changes in their ecological space, which could be facilitated for remediation due to its relative flexibility, efficiency, low cost, versatility, and eco-friendliness (Kumar et al., 2021). This technique has involved using different organisms (plants, algae, microorganisms) or their products to remove a diverse range of toxic and non-toxic pollutants from liquid, water, and air matrices with better prognosis (Rambabu et al., 2020; Singh et al., 2022). The process potentially aids the removal of biologically obnoxious substances from ecosystem components that directly or indirectly intersect with humanity via biostimulation, bioaugmentation, and other intrinsic concepts. Many bioremediants have evolved over time scales strategic tolerant attributes to an environment overdosed with a diversity of biologically destructive substances, including pharmaceutically active compounds (PACs) and HMs. They may be innately

or inducible and able to either transfigure, immobilize (bioaccumulate), volatilize, degrade, filter, metabolize, extract, or stimulate remediation activity in biomes irrespective of whether they exist in a consortium or alone with their spatial or temporal space. Even though this premise inadvertently facilitated the popularization of the bioremediation model, the model seems to advance with the recent use of genetically modified bio-alternatives, especially microorganisms, artificial intelligence (machine learning), computational, and other optimization models (Mohammadi et al., 2022; Mohanty and Paul, 2022). Therefore, this review aims to explore pharmaceutical wastewater effluent discharge trends, composition, and biological management in developing countries.

#### 4. Heavy metals and other pollutants in pharmaceutical wastewaters

##### 4.1. Emerging pollutants

The high demand for pharmaceuticals worldwide due to the growing population has increased the number of pharmaceutical compounds to about 3,000 heterogeneous types and the annual production volume to hundreds of tons (Grenni et al., 2018). Bush (1997) classified these substances as anti-inflammatory and analgesics (ibuprofen, paracetamol, diclofenac); antibiotics (sulfonamides, tetracyclines, penicillin,  $\beta$ -lactams, macrolides, fluoroquinolones, imidazoles); antiepileptics (carbamazepine, dilantin, primidone); antidepressants (benzodiazepines); antilipidemic (fibrates); antihistamines (famotidine, ranitidine);

$\beta$ -blockers (metoprolol, atenolol, propranolol); and other substances (barbiturates, narcotics, antiseptics, and contrast media) (Deo, 2014). Moreover, there is relatively little evidence regarding the long-term effects of these medicinal substances on ecosystems, even though they are regarded as emerging pollutants (Dhangar and Kumar, 2020; Valdez-Carrillo et al., 2020). Once pharmaceutical residues reach water and soil, they become incorporated into plants grown in these soils or waters. It has been discovered that cabbage, cucumbers, corn, carrots, lettuce, and green onions can absorb certain pollutants (Boxall et al., 2006; Dolliver et al., 2007; Grote et al., 2007). Furthermore, diverse chemicals, heavy metals, and resilient toxin-producing organisms contaminate the ecosystem (Che et al., 2018; Rana et al., 2017). While anti-inflammatory, antibiotics, and analgesic drugs are reported by Deo (2014) as the most used pharmaceuticals, their impact on the evolution of water-soluble and pharmacologically active organic micropollutants (PhACs) is becoming disconcerting to environmental biologists as well as public health specialists. They have been implicated in microbial resilience, the emergence of antibiotic-resistant microorganisms, and spread with future consequences on human morbidity and mortality (Bondarczuk and Piotrowska-Seget, 2019). The daily range of these drugs used in veterinary and human healthcare services is reflective of their presence in excrement and faeces (Ramírez-Morales et al., 2021). Periodic events such as festivals, ceremonies, public holidays, exams, and athletic events are also associated with an increase in illicit drug usage. Proportionate increases in their migration into wastewater demonstrate this (Dennhardt and Murphy, 2013). These pharmaceuticals in reported wastewater effluents, influents, surface water bodies (freshwater, marine), and groundwater were leachates carried in efflux

from drug production processes (Deo, 2014; Zainab et al., 2020). They are now persistent in the geosphere (Grenni et al., 2018) and biosphere (Bartrons and Peñuelas, 2017) because they easily spread across ecosystems and are slow to metabolize (Mukhtar et al., 2020). Antibiotics, antivirals or antiretrovirals, antihypertensive, and analgesics' presence and concentration in pharmaceutical effluents are influenced by location, literacy, healthcare management orientation, and risk propensity for disease outbreak (Bilal et al., 2020). The concentration of these pharmaceuticals in pharmaceutical effluents was reported to be tolerable between the range of 0.0013 to 0.0125 g/ml in wastewater, 0.0005 to 0.0214 g/ml in drinking water, and 0.0003 to 0.0039 g/ml river water (Hanna et al., 2018). Pharmaceutical presence has been studied in the effluents from hospitals, sewage treatment plants, and pharmaceutical influents, as well as in groundwater, surface water, and drinking water (Balakrishna et al., 2017; Schafhauser et al., 2018). Evaluations have also been done on seasonal, geographical, and temporal variations (Cesen et al., 2018). However, the incidence varies across studies and sources of experimental samples analyzed (Petrie et al., 2015).

#### 4.2. Non-emerging pollutants

Pharmaceutical compounds are human-made chemicals with high biological oxygen demand (BOD), chemical oxygen demand (COD), solids content, dissolved solids, and suspended solids. It also contains heavy metals like aluminium, copper, lead, zinc, nickel, arsenic, manganese, chromium, cadmium, iron, mercury, chlorides, phenols, sulphides, and oil (Che et al., 2018). When released repeatedly into the environment, they harm humans, aquatic life, microbiomes, and global

## Sources and effect of pharmaceutical effluent on the environment

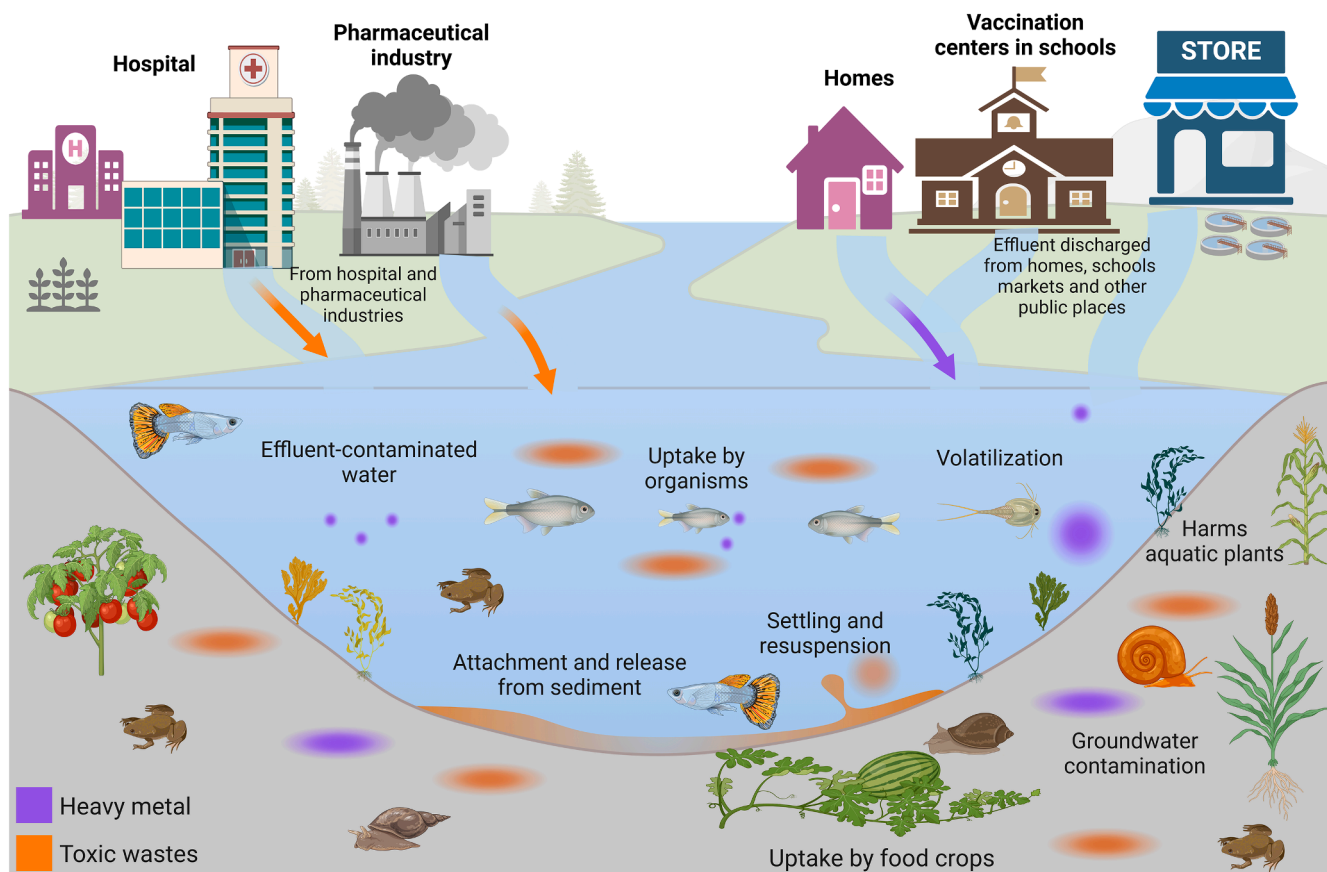


Fig. 4. Pharmaceutical wastewater effluent management techniques and hypothetical selection of pollutants group.

ecosystems, as well as both acute and long-term effects (Changotra et al., 2019) (Fig. 4). The non-emerging pollutants in pharmaceutical wastewater comprise a variety of complex chemicals that are differentially less biodegradable and more hazardous to the natural existence of living things (Qin et al., 2015). The natural processes invented by nature in the management of these pollutant compounds in their varying forms often result in transition and intermediate products due to their partial breakdown (Golovko et al., 2014). They may also facilitate the alteration of genetic and adaptation traits, cause a shift in the functional roles of exposed organisms over time, and create interspecific imbalances in ecosystems. Polynuclear aromatic hydrocarbons, benzene, and other refractory and dangerous chemicals in pharmaceutical wastewater have been reported by Malik et al. (2019). It also contains large amounts of antibiotic-resistant bacteria and genes as well as 80% organic substances that include residues of active medicinal substances (Hermine et al., 2021). Variable concentrations of heavy metals have also been reported in pharmaceutical effluents Che et al. (2018) observed that zinc, nickel, lead, cadmium, cobalt, copper, iron, chromium, arsenic, manganese, and mercury are the common brands of heavy metals linked to industrial effluents (Alslaibi et al., 2013). Overdosing the environment with effluents containing this group of pollutants has implications for human and animal health, genetic diversity, species diversity, and ecosystem functioning depending on exposure duration, composite nature, and spread dynamics of effluent released to the environment, and tolerance capacity of exposed organisms.

## 5. Biological management of pharmaceutical effluents

The recurrent effects of pollution, global warming, climate change, and the earth's forest covers have given impetus to the management of pharmaceutical effluents before discharging them into the environment (Adetunde and Ninkuu, 2016; Fernandes et al., 2021). Environmental safety legislation, physical, chemical, and biological methods formed the regular approaches of variable modifications to pharmaceutical effluent management in many countries. The upstream pharmaceutical production processes involve extraction, formulation, chemical synthesis, fermentation, and packing. Xueqing et al. (2017) observed that chemical synthesis and fermentation generate a larger amount of spent water containing higher levels of recalcitrant organics, pharmaceutical residues, and salts among the upstream processes. Conversely, downstream effluents efflux from storage, supply/transport, marketing, uses, and discard of unused pharmaceutical products are relatively lesser in volume, pollutant concentration, and diversity than those from the manufacturing processes. In practice, biological management of pharmaceutical effluents relied mostly on the action of various microorganisms (bacteria, fungi, yeast, algae), including nematodes in specially designed bioreactors to degrade, metabolize, or interact with dissolved, non-toxic micropollutants in effluents for reproduction, communication, and existence. Furthermore, bioremediation in this context may be used interchangeably with biological treatments and is a common phenomenon in wastewater management worldwide. The principle mimics the natural order by which microorganisms behave in nature to propel the recycling of elemental materials required for biogenesis (Chen et al., 2022). Even though the nature of the intersection between the physiological, biochemical, and physical processes in biologically removing pollutants is still not completely understood, the biological method cannot be ignored due to the advantages associated with its application in pharmaceutical wastewater treatment. While biological treatment techniques may be selective and incapable of completely removing all pollutants, some of its advantages over other standard treatments include their technological simplicity, cost-effectiveness (economic and energy), tractability, environment-friendliness, and stability (Guo et al., 2017). This has made the biological method more conventional and attractive as a treatment method that is amenable either for pharmaceutical wastewater pretreatment or tertiary treatment (Li and Li, 2015). However, the method's performance potential depends on a

combination of factors that include the nature of total organic carbon (TOC), physicochemical and biological parameters, the volume of discharge, and the thermodynamics of energy change. Unlike chemical and physical management of pharmaceutical wastewater, biological removal is sustainable and restores wastewater to its natural state without generating residues or significant amounts of toxic sludge (Bakare and Adeyinka, 2022; Liu et al., 2022). Despite this, conventional treatment has shown to be successful in lowering wastewater's carbon and nitrogen levels. The literature describes a variety of complex pollutants' removal mechanisms, such as sorption (absorption, adsorption), biodegradation (mineralization, metabolism, oxidation-reduction reaction, etc.), and other interactions, including precipitation (Ahmad et al., 2021).

Biological treatment methods may traditionally be subdivided into aerobic and anaerobic techniques. Aerobic techniques include activated sludge, membrane batch reactors, and sequence batch reactors. Anaerobic methods include anaerobic sludge reactors, anaerobic film reactors, and anaerobic filters (Deegan et al., 2011). Pharmaceutical sector effluents have traditionally been treated using conventional activated sludge with a lengthy hydraulic retention time (HRT). It is generally more environmentally friendly than chlorination and has a lower capital cost per unit than other sophisticated treatment systems. It also has a limited operating demand. Pharmaceutical production facilities' batch operations, temperature, HRT, pH, dissolved oxygen (DO), organic load, microbial population, and presence of toxic or recalcitrant compounds all impact how well-activated sludge facilities remediate pharmaceutical effluent (Roy et al., 2020). However, anaerobic treatments are more amenable to high-strength wastewater with low energy inputs, sludge yield, nutrients, operating cost, space requirement, and improved biogas recovery (Ahmad et al., 2021).

### 5.1. Microbial treatment of pharmaceutical effluents

The traditional concept of anaerobic biodegradation is hinged on four stages: hydrolysis, acidogenesis, acetogenesis, and methanogenesis. Therefore, the first essential component in enabling this process is the bacteria that can hydrolyze polymeric organics into monomers and then disintegrate the monomers into smaller organic fragments (such as volatile fatty acids and alcohols). Second, the anaerobic biological treatment of pharmaceutical wastewater depends on the role of archaea, also known as methanogens, in the use and conversion of fermentation metabolites to methane gas (Fernandes et al., 2021).

Anaerobic degradation involves a complicated network of interactions between several microbial groups, and any imbalance in this network can lead to the accumulation of metabolic intermediates and the eventual failure of the system. For this reason, a balanced microbial community structure is just as important to the anaerobic treatment process as the appropriate design of the system operating parameters. Bacteroidetes, Firmicutes, and Proteobacteria are commonly reported groupings of bacteria that comprise the microbial populations found in anaerobic pharmaceutical treatment plants. While *Methanomicrobia*, *Thermoplasmata*, and *Methanobacteria* were the main archaeal groupings, Clostridia (Firmicutes) and  $\beta$ -Proteobacteria (Proteobacteria) were the dominating bacteria identified in numerous biological processes. These anaerobic system archaea are metabolically versatile in converting anaerobic digestion metabolites into methane gas and relatively resilient in highly toxic environments [66]. Aerobic biological treatments, unlike the anaerobic bioprocesses, have wider acceptance in low-economic countries and are reported by Mullai et al. (2017) to involve microorganisms like *Aspergillus*, *Bacillus*, *Enterococcus*, *Pichia*, *Pseudomonas*, *Shewanella*, *Staphylococcus*, protozoans, and yeasts. The complexity of determining the chemical dosage appropriate for wastewater treatment and the simple reactor design configuration for passive oxidation of organic and inorganic impurities also makes aerobic processes attractive (Fig. 4).

Given their structural dissimilarities from naturally occurring

chemicals, hazardous and poisonous xenobiotics produced from medications may generally be more difficult to degrade. Current research has revealed a range of bacteria that rely on some of these toxins to survive (Bhatt et al., 2007).

Depending on the microbial ability to grow in specific conditions, organic material can be degraded aerobically or anaerobically (Shah et al., 2008). For instance, aerobic and anaerobic microorganisms can degrade phenol, but conventionally aerobic processes are preferred (Lika and Papadakis, 2009). Aerobes often convert organic molecules into inorganic compounds (CO<sub>2</sub>, H<sub>2</sub>O) and proliferate more quickly than other microorganisms, making them more effective at breaking down harmful substances (Mrozik et al., 2010). Because they are less expensive, aerobic biodegradative techniques are also favoured (Ruiz-Ordaz et al., 2001).

Anaerobic bacteria are not widely used for the biodegradation of certain pharmaceutical contaminants, including phenols, for these reasons. We concentrate on aerobic biodegradation in this study because aerobic biomasses have been used in the majority of biotreatment research. Pharmaceutical pollutants, such as substances containing phenol, can be broken down by a variety of microorganisms, such as bacteria, fungi, and algae (Lika and Papadakis, 2009). Numerous phenol-degrading bacteria have been identified and characterized at the physiological and genetic levels as a result of the substantial research conducted on the biodegradation of phenolic compounds by bacteria (Wang et al., 2007). The most common biomass for breaking down phenols is *Pseudomonas* mixed and pure cultures, which have been shown to have significant potential for various biotechnological uses (Stoilova et al., 2007). *Pseudomonas putida* has been the preferred microorganism for the biodegradation of phenol because of its exceptional elimination efficiency (Hsieh et al., 2008). *P. putida*'s reaction to chemical stressors suggests that its cells may employ a variety of defence mechanisms to survive in a range of harsh settings. Some of the biological agents reported as used in pharmaceutical industry wastewater treatment are as follows:

#### 5.1.1. Bacteria

Pharmaceutical effluents have been treated with bacterial biotreatment on a large scale. An adaptable microbial consortium used in bacterial biotreatment produces an efficiency of roughly 70–80%. Several bacterial species, such as *Bacillus subtilis* and *Pseudomonas*, have been used in the treatment procedure.

#### 5.1.2. Higher plants

Higher plants are more frequently employed to rid contaminated soils of hazardous materials than to remove pharmaceutical contaminants. It depended on interactions between the soil microbial populations and the harmful pollutants that were *in-situ* in terms of physical, chemical, biochemical, microbiological, and biological aspects (Azubuike et al., 2016). *Helianthus annuus* (Sunflower) has been reported by Gai et al. (2020) to be effective in removing oxytetracycline and tetracycline from aqueous media. The bioaccumulation of poisons and the elimination of heavy metals like lead and cadmium are two more uses for this technique.

#### 5.1.3. Fungi

A strain of the White Rot fungus, *Bjerkandera adusta* MUT 2295, was investigated by Bardi et al. (2017) in relation to its ability to remove synthetic refractory effluents from certain sample conditions. The findings indicated that the elimination of biological oxygen demand (BOD) in tannic and humic acid solutions was 89% and 75%, respectively. Additionally, it demonstrated a reduction of 61% of the chemical oxygen demand (COD) in the tannic acid effluent. Fungal species (Ascomycetes and Basidiomycetes) have the potential to remove pollutants through enzymatic biodegradation and sorption; however, their use in pharmaceutical wastewater treatments is less common than that of bacteria, despite the fact that more research is being done in this area (Mrozik,

2021; Olicón-Hernández et al., 2017).

#### 5.1.4. Algae

In order to selectively remove heavy metals like chromium from wastewater, Arumugam et al. [89] examined the use of microalgae, macroalgae, and cyanobacteria like *Chlorella*, *Spirulina*, and *Scenedesmus*. Algae are naturally able to make use of the metals and nutrients found in wastewater. Additionally, Arumugam et al. (2018) have listed the origins and uses of all seaweed varieties (red, brown, and green) and their functions in each industry that produces wastewater. These investigations confirmed the seaweeds' adaptability and efficacy in eliminating phenol, biphenyls, hydrocarbons, nutrients, heavy metals, and colors from wastewater with industrial origins, including medicines. Also, Sarmah and Rout (2019) observed that *Nostoc carneum* causes frailty and perforation to low-density polyethylene (PE) in a study.

When FT-IR and NMR techniques were used to investigate the biodegraded products, the peaks showed the presence of carbonyl groups, which were created when polyethene was cleaved. This study affirmed the potential of the cyanobacterium in the biodegradation of PE, which is an important tertiary packaging material used in the pharmaceutical industry.

## 6. Prospects of wetlands in the treatment of pharmaceutical wastes

Conventional contaminants in a variety of wastewaters, such as residential wastewater, industrial effluent, mine drainage, leachate, contaminated groundwater, and urban runoff, have been demonstrated to be effectively treated by constructed wetlands (Choudhary et al., 2011). On the other hand, a novel application area is the treatment of pharmaceutical pollutants in wastewater by artificial wetlands. A thorough understanding of the removal mechanisms, efficiencies, environmental and design impacts, and toxicity risks is necessary to effectively remove pharmaceuticals from wastewater through engineered wetlands. The four kinds of artificial wetlands that are used to filter out medications from wastewater are surface-free water-constructed wetlands (SF-CWs), vertical subsurface flow-constructed wetlands (VSSF-CWs), horizontal subsurface flow-constructed wetlands (HSSF-CWs), and hybrid constructed wetlands (hybrid CWs).

There is a dearth of research papers on the use of artificial wetlands as a secondary wastewater treatment system alternative for pharmaceutical removal compared to the number of publications on this use. Diclofenac, ibuprofen, ketoprofen, triclosan, and atenolol are among the medications that created wetlands can readily remove (mean removal efficiency > 70%), except the poor or inconsistent removal efficiencies recorded (Breitholtz et al., 2012; Matamoros and Salvadó, 2012; Verlicchi et al., 2013). Whereas sulfamethoxazole, clofibrac acid, and carbamazepine have low removal efficiencies in constructed wetlands (mean removal efficiency between 20 and 50%), naproxen and caffeine are moderately removed pharmaceuticals by these wetlands (mean removal efficiency between 50 and 70% (Breitholtz et al., 2012) used four full-scale hybrid SF-CW systems with various design configurations to study the removal of pharmaceutical chemicals from four sewage treatment plants. It was found that the quantities of several medications in effluent water were higher than in influent water.

A process known as competitive sorption may arise in the presence of several pharmaceutical chemicals and other wastewater contaminants in the water at the same time (Conkle et al., 2010; Dordio et al., 2009). In artificial wetlands, competing pharmaceutical compounds may limit the sorption capacity of one another or other contaminants due to the competition for preferential binding sites on the solid matrix. Therefore, in artificial wetland systems that include a wide variety of pharmaceutical chemicals, this competing impact may be concerning. Additionally, plants in artificial wetlands are crucial in promoting the growth and activity of microbial populations, which are bolstered by exudates, mucigels, dead cell matter, and other products of rhizodeposition. This

leads to a multitude of biological processes occurring in the rhizosphere (Calheiros et al., 2009). According to Matamoros and Salvadó (2012), microbial degradation was the main method of removing ibuprofen, and it was most likely connected to biofilms on the surface of plant roots. Certain plant exudates may function as catalytic agents for the breakdown of organic compounds in addition to biological activities (Dordio and Carvalho, 2013) [98].

Microbes in constructed wetlands are also important in the transformation and mineralization of nutrients and organic pollutants (Zhu et al., 2010; Zhu et al., 2011; Zhu et al., 2013). A range of microorganisms, including heterotrophic and autotrophic bacteria, fungi (basidiomycetes and yeasts), and certain protozoa, can break down organic molecules in artificial wetlands both aerobically and anaerobically (Kadlec, 2009). The microbial breakdown process is significantly influenced by the chemical structures of organic molecules (Dua et al., 2002; Reddy and DeLaune, 2003).

## 7. Dynamics of survival of the microbiome in pharmaceutical effluents

Wastewater from rivers, lakes, groundwater, and the ocean is where prescription medications and their metabolites end up polluting the environment. Overflowing sewage systems, agricultural runoff, and outdated infrastructure all contribute to higher pollution levels in pharmaceutical effluents.

Pharmaceutical products, generally, drugs and chemical-based personal care products have remained increasingly common as the world's population grows. Their importance in contemporary life cannot be overstated, yet how they are used and disposed of raises serious questions about environmental contamination.

Even though many urban and rural groundwater sources are pure and clean enough to drink, they may include traces of pharmaceutical chemicals such as coffee, antidepressants, birth control pills, painkillers, shampoos, and anti-epileptic medications. There is an increased prevalence of pharmaceutical waste and its by-products in ecosystems, landfills, and dumping places due to pharmaceutical industries occasionally discharging untreated wastewater into the open environment and adjacent aquatic bodies. As a result of their adaptability to a wide variety of environmental circumstances, microorganisms are found throughout the biosphere and are highly prevalent. Microbes' widely distributed and accepted role in the biodegradation of environmental contaminants might also be attributed to their adaptability as a dietary agent. Pathogenic contaminants are transformed, altered, and utilized by microbes to generate biomass and energy (Barra Caracciolo et al., 2015; Ninkuu et al., 2022). Instead of simply absorbing the pollutants and storing them, bioprocessing them into non-toxic products or compounds in well-organized biological phenomena that include metabolism, acclimatization, bioaccumulation, and energy generation.

### 7.1. Biological degradation of pharmaceutical compounds

Biological degradation or biodegradation is the breakdown of complex, toxic chemical compounds into simpler, less toxic products by the action of the enzymes secreted by the microorganisms. The primary process in wastewater treatment that removes organic micropollutants to the greatest extent possible is biodegradation. The solubility of pharmaceutical contaminants in wastewater is a major determinant of their biodegradation efficiency. Sewage sludge will retain micropollutants (hydrophobic compounds) if their solubility is low. These substances stay in the sludge longer, meaning the micropollutant is either employed as a carbon source or as a substrate for a catabolic microbial enzyme (Samal et al., 2022).

### 7.2. Bioremediation processes as a new remediation technology

Microbial communities are crucial for breaking down organic

materials and supplying nutrients to higher-up food chain creatures (Barra Caracciolo et al., 2015). As a result, they are crucial for the environment's natural purification as well as its upkeep, renewal, stability, and health. When xenobiotics invade an area and upset its natural equilibrium, the microbial communities there are affected, which in turn affects the ecosystem functions that are essential to the ecosystem's ability to provide services (Lahti and Oikari, 2011). Through metabolic and co-metabolic processes, microbial communities can break down organic contaminants; the latter is particularly crucial for the removal of pollutants (Caracciolo et al., 2015; Lahti and Oikari, 2011). The utilization of natural detoxification processes by microorganisms to break down contaminants is the foundation of bioremediation technology (Megharaj et al., 2011). In order to create a microbial inocula capable of degrading target contaminants with the least long-term impact on the microbial biomass of the polluted locations, it is essential to select and isolate indigenous degrading bacteria (Paul et al., 2005). The diversity and richness of microorganisms in nature are increasing, which has drawn attention to this technology. Their ability to function in and adapt to a wide range of situations and their varied catalytic processes (Megharaj et al., 2011; Wang and Wang, 2016).

A group of microorganisms is always more efficient for the breakdown of pollutants than a single bacterial strain because cooperative interactions or synergistic effects among various bacteria play a significant role in the biodegradation of harmful chemicals (Paul et al., 2005; Wang and Wang, 2016). However, bioremediation of a polluted site may only be carried out provided the microbial activity is not rendered inactive by the contaminant's toxicity (Caracciolo et al., 2015).

### 7.3. Factors affecting biodegradation process

During biological treatment, several processes, including as volatilization, adsorption, and biodegradation, may occur (Paul et al., 2005). In facilities that treat wastewater, the processes of biodegradation/biotransformation and adsorption play a more significant part in the degradation of medicines during biological treatment (Zhao et al., 2015). The ability of pharmaceutical chemicals to be either adsorbed or destroyed by the sludge depends on their physicochemical characteristics. These compounds' ability to biodegrade also depends on how many microbial degraders are present in the treatment system; in systems with few microbial degraders, the biodegradation of these compounds may be very low (Paul et al., 2005). Additionally, interactions with other chemicals (antagonistic effect) can have an impact on the breakdown of pharmaceuticals (Santos et al., 2013) or microorganism interactions (synergistic effect) (Wang and Wang, 2016). The degradation of the pharmaceuticals may be enhanced or inhibited by these actions, which may account for the varying clearance efficiencies attained with comparable treatments. Pharmaceuticals' inherent chemical structures differ from one another, making it important to analyze and assess each compound's biodegradability. For example, a compound's structure may contain halogens or sugar moieties, which can make it more biodegradable (Vasquez et al., 2014). Due to the chemically specific enzyme reactions involved in biodegradation processes, drugs that are part of the same therapeutic class but have different chemical structures may degrade at different rates (Kümmerer and Al-Ahmad, 1997). Apart from the previously listed variables, additional factors may impact the biodegradation of medicines and account for variations in the clearance rates noted for identical compounds. The pharmacological concentration is the first and most significant one. Distinct concentrations result in disparate clearance efficiencies that are incomparable. Furthermore, excessively high drug concentrations can kill microbes and hinder microbial ecology (Ninkuu et al., 2023; Ninkuu et al., 2022; Onesios et al., 2009). The pharmaceutical concentration as the main substrate is another element that is connected to the first one. Depending on their concentration, pharmaceuticals may be used as a primary substrate, meaning that microbial communities can use them as a carbon and energy source. However, if the concentration is too low, it

might not be enough to trigger the right enzymes, which would lead to the compound's preferential biodegradation through co-metabolism (Ternes and Joss, 2007). The potential for medicines to function as either a primary or a co-substrate could account for variations in biodegradation rates. Thirdly, while incubation duration is typically arbitrary, it can impact biodegradation rates and highlight variations in the amount of medication removed.

Various incubation durations can result in varying clearance rates for an identical chemical component. Finally, the origin, concentration, and degree of pre-adaptation of the microbial inoculum can affect the rate of biodegradation. These variables can have an impact on the lag times and removal efficiency based on how the microbial population reacts to them (Kümmerer and Al-Ahmad, 1997). The microbial community included in the inoculum, for example, may recognize the substance more quickly if it has previously been exposed to medications. This would enable the community to adjust to the new conditions more quickly.

In conclusion, a variety of internal and external variables can influence the processes of biotransformation and biodegradation in both *in-situ* and *ex-situ* systems. Thorough research is necessary to comprehend and mitigate potential obstacles to the advancement of bioremediation technology. Notwithstanding potential drawbacks, such as with any method, bioremediation technology is a viable option that ought to be considered for the cleanup of pharmaceutical and other polluted sites (Shishir et al., 2019). These consist of minimal implementation-related side effects, long-term viability, great efficiency, and no need for further construction during implementation.

#### 7.4. Application of microbial fuel cells in pharmaceutical waste remediation

Due to the cathode processes' driving force, numerous studies have demonstrated that using MFCs as a remediation technique can accelerate the degradation of pharmaceutical contaminants and shorten reaction times (Ceconet et al., 2017). Certain research suggests that penicillin may break down during the process of producing energy. It was surprising to learn that certain mixtures of penicillin and glucose were used to produce energy. 1 g L<sup>-1</sup> glucose (14.7 W m<sup>-3</sup>) and 50 mg L<sup>-1</sup> penicillin (2.1 W m<sup>-3</sup>) together produced a power density six times lower in a single-chamber MFC than 1 g L<sup>-1</sup> glucose + 50 mg L<sup>-1</sup> penicillin (101.2 W m<sup>-3</sup>). The peak current density (10.73 A m<sup>-2</sup>) was 3.5 times higher when 50 mg L<sup>-1</sup> penicillin was administered than when it was not (3.03 A m<sup>-2</sup>). By decreasing the internal resistance of the MFC and raising power density, penicillin seems to increase the permeability of the bacterial cell membranes, enabling electron transport from the microbe to the anode via cell membranes. According to these findings, several dangerous and biorefractory organic substances, including antibiotic effluents, may be useful resources for the production of energy using MFCs (Wen et al., 2011).

Zhang et al. (2017) employed a double-celled MFC to remove metronidazole and chloramphenicol. Within 24 h, metronidazole degradation in the MFCs was 85.4%, but in open circuits, it was only 35.2%. It was found that the MFCs might be used to break down antibiotics like metronidazole, which has been used in the treatment of tainted water. Zhang et al. (2017) also investigated CAP degradation using MFCs and were able to achieve 80% degradation of 50 mg/L concentration of the antibiotics. The possibility of employing MFCs for antibiotic biodegradation was investigated (Song et al., 2013). MFCs were inoculated with sludge supernatant mixtures and artificial wastewater, including animal feces. Moreover, the MFC efficiency (0.51–0.41 V) was reduced by supplementing the reactors with aureomycin, roxithromycin, sulfadimidine, and norfloxacin, whereas the output voltage was raised by lowering the antibiotic concentration. Norfloxacin, roxithromycin, and aureomycin all had 100% degradation efficacy according to LC-MS analysis. However, sulfadimidine had a 99.9% degradation efficiency.

Another study by Ondon et al. (2020) found that the effectiveness of COD removal and norfloxacin degradation using MFCs was 94.5% and 65.5 percent, respectively. The research also found that electricity production was effective, but that the efficacy of norfloxacin biodegradation, COD elimination, and MFC voltage output were unaffected by an increase in norfloxacin concentration (128 mg L<sup>-1</sup>).

Some advantages of MFCs are direct power production, energy-efficient processes, anaerobic treatment due to reduced sludge output, centralized and decentralized applications, and the lack of expensive aeration. However, one of the most difficult issues facing the commercialization of MFCs is coming up with a cheap and efficient design for larger-scale versions of laboratory-scale reactors. Laboratory-scale MFCs have shown exceptional achievements in the production of power and decontamination. To replicate these outcomes on a larger scale, though, a number of factors need to be taken into consideration, such as the design of the separator, its mechanical strength, the cost of the electrode, the method of supplying oxidant, the amount of energy and space needed, and so forth (Zhou et al., 2018).

## 8. Conclusion and recommendation

Pharmaceutical wastewater exerts crucial hazards on the ecosystem (Fig. 4) that require urgent attention and innovative management skills. These effluent pollutants are a complex composition of both emerging and non-emerging contaminants, and their treatment warrants a combinatorial approach. Bioremediation techniques have shown considerable promise owing to their ecological sustainability and efficacy. However, exploring other technologies, such as microbial fuel cells, could drive advancements in the field, enabling the dual benefit of pollution mitigation and energy recovery. Moreover, the success of this field hinges on multidisciplinary collaborative efforts involving regulatory bodies, and environmental stakeholders in establishing effective treatment protocols to ensure the long-term safety of the ecosystems and public health.

Comprehensive research focusing on the identification of contaminants of specific biological pathways and optimizing treatment processes is crucial to the effective management of pharmaceutical wastewater effluents. Additionally, educating and improving effluent disposal practices will mitigate the pollution risks caused by pharmaceutical effluent. Through such multifaceted strategies, we can balance pharmaceutical use with environmental safety, ensuring a cleaner and healthier future for all living organisms. The management and treatment of pharmaceutical wastewater represent a growing area of concern and innovation. With sustainable research and practices, it is possible to transform these hazardous effluents into manageable resources that benefit society and the environment.

### CRedit authorship contribution statement

**Lawrence Adelani Adetunde:** Writing – original draft, Conceptualization. **Osarenkhoe Omorefosa Osemwegie:** Writing – review & editing. **Bolanle Adenike Akinsanola:** Writing – review & editing. **Adebowale Toba Odeyemi:** Writing – review & editing. **Vincent Ninkuu:** Writing – original draft, Visualization.

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No data was used for the research described in the article.

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