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Promising approaches and kinetic prospects of the microbial degradation of pharmaceutical contaminants

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Pharmaceutical pollutants are released into the environment due to their direct outflow from waste disposal, animal discharge, and drug manufacturing. The long-term health effects on humans and animals due to their biological activity are the negative impacts of pharmaceutical pollutants. Microbial degradation is an effective remediation strategy for removing harmful contaminants from contaminated zones by breaking down foreign substances into smaller useable materials. The novel aspect of the review deals with the advancements and kinetic prospects of the microbial degradation of pharmaceutical pollutants. This review illustrates the classifications, toxic effects on health, occurrences and sources of pharmaceutical pollutants. The interaction mechanism between microbes and pollutants and the molecular mechanism under aerobic and anaerobic conditions are clearly demonstrated in this review. This review discusses in depth the advancements in the field of microbial degradation, such as the utilization of genetically engineered microbes and enzyme immobilization techniques for enhancing the degradation of pollutants. The purpose of this review is to describe the microbial degradation kinetics in order to efficiently supervise the pharmaceutical-contaminated sites. Recent advancements and future prospects for the effective removal of pharmaceutical contaminants are also discussed in depth.

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Environmental significance

Environmental significance statement for the paper "Promising approaches and kinetic prospects of the microbial degradation of pharmaceutical contaminants." 1. What is the problem/situation? The release of pharmaceutical pollutants has increased worldwide through improper disposal of medicines, drugs and other used compounds from drug manufacturing units. This hinders the biological activity of many living organisms and has a long-term effect on the ecosystem. 2. Why is it important to address/understand this? The remediation of pharmaceutical contaminants is essential for mitigating the negative effects caused by the compounds in the ecological system. Microbial degradation is considered to be one of the effective remediation strategies due to its lack of toxic byproduct release during the process. Micro-organisms have the ability to degrade complex pharmaceutical compounds into simpler substances in the presence of enzymes. Hence, a clear understanding of the mechanisms and advancements in microbe-based degradation of pharmaceutical pollutants is essential for effectively addressing the pollution problems. 3. What is the key finding and what are the implications of this in relation to 1 and 2 above. The molecular mechanism in the microbial degradation of pharmaceutical pollutants is one of the key findings in this review. The interaction of micro-organisms with pollutants adds on for the better understanding of the degradation process. The factors that need to be optimized during the microbial degradation process have been discussed in detail, of which the type of microbial inoculum, pH, and temperature are crucial for better degradation. Advances such as genetic engineering and immobilization enable the complete degradation of pharmaceutical compounds and also inhibit the release of toxic compounds.

1. Introduction

Humans have created a plethora of synthetic compounds for use in a variety of sectors. Some new pollutants have a significant impact on the ecology, as they are not effectively monitored prior to disposal. Pharmaceuticals play a critical role in improving the quality and expectancy of life of people across the globe. Several medications are used each year to treat infections, illnesses, and other health issues.[1] Antibiotic consumption is remarkably high in developing countries, such as India, Russia, and South Africa. Following treatment processes, these residual pharmaceutical substances are released into the environment, causing major medical risks. Pharmaceutical chemicals are classified as emerging pollutants due to their continued use, uncertain environmental and health impacts, and resistance to complete degradation.

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Pharmaceuticals have been found in surface and ground water at concentrations of parts per trillion and billion.[2] Most medications are partially metabolised by organisms into inactive forms. Approximately 75% of antibiotics are excreted as active metabolites. Nonsteroidal medications are highly water-soluble chemicals that are partially destroyed and have a negative influence on the environment.[3,4]

Extensive pharmaceutical distribution is a major concern as it poses serious threats worldwide.[5] Active chemicals, such as hormone receptors are detrimental to marine organisms in the setting of an aquatic system. To control the hazardous pharmaceutical pollution, certain discharge regulations are required under standard settings. High aqueous-based discharges must be closely monitored and recognised in order to hypothesise on the best ways for removing and degrading pharmaceutical compounds from water sources. Apart from these, pharmaceutical contaminants also come in the form of agricultural runoff, which might include pesticides.[6–8]

Pharmaceutical pollutants, including high COD concentrations, vary depending on industrial discharge. Nitrogen usage in antibiotic manufacturing increases nitrogen concentrations, but no legally controlled legislation or system is in place to mitigate these pollutants.[9,10] In general, chlorination is the most commonly used procedure for purifying drinking water. Overall, physicochemical methods are used first, followed by secondary treatment processes involving biological reactions. Adsorption is favoured in fundamental physicochemical processes for the elimination of some medicinal substances, and organic and inorganic pollutants. Advanced oxidation and precipitation procedures can be used to eliminate bio-organic substances. However, certain residual medications such as ibuprofen, iopromide, and sulfamethoxazole are still present in the effluent and must be treated using subsequent biological processes.[11,12]

Microbial species are important xenobiotic degraders that aid in the maintenance of correct ecological balance. Microbial degradation is a highly effective approach for removing dangerous pharmaceutical pollutants from the environment (Ramesh *et al.*, 2023). The pharmaceutical breakdown rates are primarily determined by factors such as the composition of the microbial culture, medicines, pH, and temperature. Microorganisms play an important role in the environment *via* several biodegradation pathways involving enzymes, metabolites, and co-metabolites.[13–15] Furthermore, the use of microbial breakdown mechanisms can greatly lower the toxicity of active medicinal compounds. In nature, the interaction between microorganisms and drugs is non-inhibitory. Basic molecular biology and engineering principles are used in preliminary procedures that provide an imperfect solution to metabolic mechanisms.[16]

Recent innovations in genetic engineering domains, such as recombinant techniques, allow for a shift in practical applications. Microbial systems are built in such a way that enzyme switching to mineralization of medicinal substances is possible. Synthetic biology and system biology, two topics related to systemic biology, aid in reducing the obstacles and drawbacks connected with earlier conventional microbial degradation processes.[17,18] The principles of sustainable metabolic and synthetic engineering help maximise the sustainability of pharmaceutical degradation. Current studies have resulted in the successful rebuilding of metabolic pathways. Another recent breakthrough is the immobilisation of microbial cells in an appropriate carrier material. The immobilisation of biodegrading organisms in biofilm systems has advantages in terms of ease of use, operation, and economics. Enzymes or bacteria/fungi with degrading capacity can be immobilised in an intact system with an inert carrier material. As a result, microbial immobilisation contributes to being a prospective candidate in recent improvements. Different kinetic models can be used to predict the mechanism of biodegradation.[19–21] The literature previously has not focused on the recent advancements with the kinetic aspects of the microbial mediated remediation of pharmaceutical pollutants. This review article specifically focusses on the kinetic prospects and advances like metabolic or genetic engineering with immobilization for the microbial degradation of pharmaceuticals.

The primary concern of the review has been on the mechanisms and advances in the microbial degradation of pharmaceuticals. The paper provides a comprehensive summary of several pharmaceutical pollutant groups, their sources, and the accompanying health impacts. The interaction of microorganisms and pharmaceutical pollutants, as well as their chemical mechanism, has been described. The review discusses the recent advances in the microbial realm, such as metabolic engineering and cell immobilisation. The description of the degradation kinetic analysis aids in the determination of the mechanisms involved in pharmaceutical contaminant elimination.

2. Pharmaceutical pollutants

2.1 Classifications

Antivirals, anti-inflammatories, anti-convulsants, antibiotics, and analgesics are the major prevalent pharmaceutical pollutants. Table 1 lists the classification and characteristics of pharmaceutical pollutants.[22–45] Antiviral medications are used to treat viral infections such as influenza, hepatitis, polio, measles, and small pox by inhibiting the pathogen growth. Antiviral medicines are more active in nature during viral propagation. Antiviral medications impede viral attachment entry into the cell, nucleic acid synthesis with protein synthesis, and eventually packaging and vital release into the environment. Amantadine, gancyclovir, zidovudine, nevirapine, and emtricitabine are examples of common antiviral medicines.[46,47] Antiviral medications are commonly found in aquatic systems such as wastewater, effluents, surface water, and ground water. Antibiotics are additional developing pharmaceutical contaminants that are widely used in the veterinary and health industries. Antibiotics are medication classes used to treat bacterial illnesses in humans and animals by inhibiting growth or metabolism and killing the bacterium. Antibiotics are primarily produced by microorganisms to accomplish a variety of activities. They can function as predators with an attacking mechanism or as a chemical weapon with a defensive mechanism.[48,49]

Table 1 Classification and characteristics of pharmaceutical pollutants

S. no.	Classification of pharmaceutical	Pharmaceutical compounds	Chemical formula	CAS ID	Molar mass (g mol^{-1})	Boiling point (°C)	Melting point (°C)	pK_a	References
1.	Antivirals	Acyclovir	$C_8H_{11}N_5O_3$	59277-89-3	225.21	595	256.6	2.52	22
		Adefovir	$C_8H_{12}N_5O_4P$	142340-99-6	273.186	632.5	102	1.35	23
		Amantadine	$C_{10}H_{17}N$	665-66-7	151.25	360	180	10.1	24
2.	Non-steroidal anti-inflammatory drug	Aspirin	$C_9H_8O_4$	50-78-2	180.158	140	136	2.97	25
		Ibuprofen	$C_{13}H_{18}O_2$	15687-27-1	206.29	157	75–77	5.2	26
		Naproxen	$C_{14}H_{13}NaO_3$	22204-53-1	230.26	403.9	153	4.2	27
		Diclofenac	$C_{14}H_{11}Cl_2NO_2$	15307-86-5	296.148	412	302–310	4	28
		Celecoxib	$C_{17}H_{14}F_3N_3O_2S$	169590-42-5	381.373	529	161–164	11.1	29
		Etoricoxib	$C_{18}H_{15}ClN_2O_2S$	202409-33-4	358.842	510	135–137	4.5	30
3.	Anti-convulsant	Pregabalin	$C_8H_{17}NO_2$	148553-50-8	159.23	85	196	4.2	31
		Phenytoin	$C_{15}H_{12}N_2O_2$	57-41-0	252.268	464	298	2.3, 8.3	32
		Ethosuximide	$C_7H_{11}NO_2$	77-67-8	141.168	265.3	64.5	8.2	33
		Topiramate	$C_{12}H_{21}NO_8S$	97240-79-4	339.363	438.7	125	1.4, 4.3	34
4.	Antibiotics	Erythromycin	$C_{37}H_{67}NO_{13}$	114-07-8	733.93	818.4	135–140	8.88	35
		Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	723-46-6	253.279	482.1	169	3.92	36
		Azithromycin	$C_{38}H_{72}N_2O_{12}$	83905-01-5	785	822.1	129–135	8.5	37
		Trimethoprim	$C_{14}H_{18}N_4O_3$	738-70-5	290.32	405.2	199–203	7.1	38
		Levofloxacin	$C_{18}H_{20}FN_3O_4$	100986-85-4	361.368	571.5	213–218	5.35	39
		Cephalexin	$C_{16}H_{17}N_3O_4S$	15686-71-2	347.39	727.4	326.8	3.45	40
5.	Analgesics	Codeine	$C_{18}H_{21}NO_3$	76-57-3	299.364	462	154	8.2	41
		Fentanyl	$C_{22}H_{28}N_2O$	437-38-7	336.471	466	87.5	8.05	42
		Hydrocodone	$C_{18}H_{21}NO_3$	125-29-1	299.368	65	118–128	8.9	43
		Meperidine	$C_{15}H_{21}NO_2$	57-42-1	247.33	328.9	186–189	8.63	44
		Methadone	$C_{21}H_{27}NO$	76-99-3	309.445	423.7	235.54	9.2	45

The first antibiotics are penicillin compounds produced from organic components *via* chemical synthesis or modification. Antibiotics are further categorised as bacteriostatic or bactericidal based on their method of action.[50]

Non-steroidal anti-inflammatory medications are a large class of therapeutics with a vast functional variety that is used to alleviate pain and inflammation. Aromatic groups with acidic functional moieties are common in anti-inflammatory medicines.[51] A broad classification based on chemical forms includes oxicams, salicylates, acid, indole derivatives, and anthranilates. The majority of anti-inflammatory medications are attached to plasma proteins, which improves the bioavailability by allowing them to cross the organ barrier. Anti-inflammatory medications have notable effects such as tumour cell induction, DNA damage protection, and neogenesis inhibition.[52]

Anticonvulsants, frequently referred to as antiseizure or antiepileptic medications, have the ability to regulate convulsions caused by electrical activity in the brain.[53] Antiepileptic medications give the necessary seizure relief. Phenytoin, benzodiazepine, primidone, and phenobarbital are examples of common anticonvulsants. More than 30% of persons are resistant to anticonvulsant medications that result in significant side effects during seizure management. Hormones are the most common drug classes in the pharmaceutical industry. Underactive hormone secretion will be treated with synthetic hormone replacement therapy.[54,55] Other pharmaceutical pollutants found in the environment include antidepressants and antipyretics. Certain classes of pesticides also come under such disinfectants, and wormicides also come under pharmaceutical class of contaminants. Fig. 1 represents the classification and health effects of pharmaceutical pollutants.

2.2 Health effects

Pharmaceuticals react biologically differently to various particular and non-specific species. Pharmaceuticals with low concentrations can be found in the environment for extended periods of time. The bioavailability of pharmaceuticals and their associated health ailments are tabulated in Table 2.[56–67] The toxic effects on aquatic organisms exposed to pharmaceutical contaminants alter their lifetime. Analgesic exposure in the environment causes kidney diseases and morphological abnormalities in the gills. Pollutants at 1000–3000 g L^{-1} concentrations might cause acute renal failures with changes in foetal anomalies.[68,69] Fish are noteworthy organisms harmed by excessive pharmacological concentrations. Pharmaceutical pollutants cause structural disturbance with changes in gene expression and the reproductive system, which are the major governing mechanisms. Aside from fish, several algae are vulnerable to the negative effects of medications.[70] In plants, fatty acid production is a critical step in the photosynthetic process. Chronic toxicity in the photosynthetic machinery of both algae and plants has been found, impairing chloroplast function. Because of their active nature, hormones, even at low doses, can pose substantial health risks. This causes considerable endocrine disturbance in fish, resulting in estrogenic

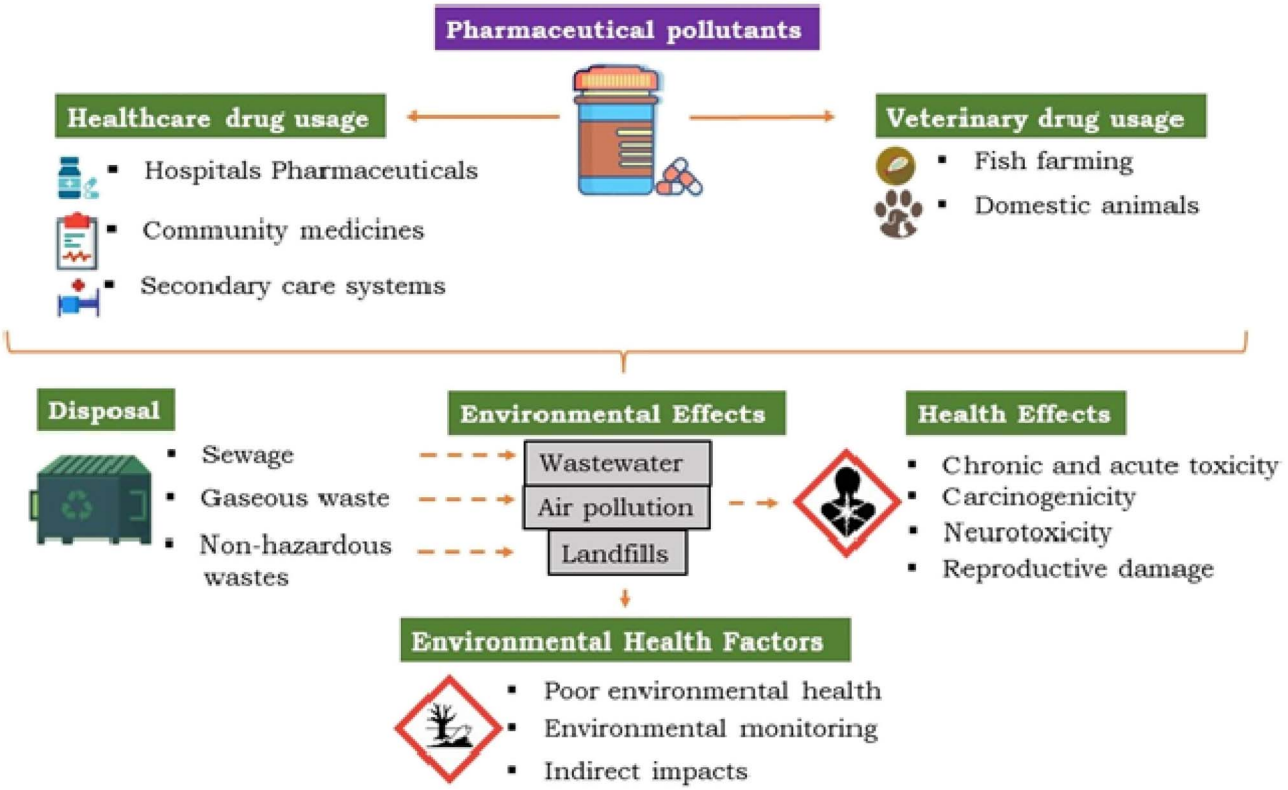

Fig. 1 Classification and health effects of pharmaceutical pollutants.

Table 2 Bioavailability of the pharmaceutical and their associated health ailments

S. no.	Pharmaceuticals	ChEMBL Id	Bioavailability	Administrative route	Dosage	Health ailments	References
1.	Acetaminophen	112	70–90%	Oral, rectal, and intravenous	150 mg kg^{-1}	Abdominal pain, diarrhea, irritability, and vomiting	56
2.	Cimetidine	30	60%	Oral, and intravenous	400 mg/per day	Reversible impotence or gynecomastia	57
3.	Digoxigenin	1153	70–80%	Oral	0.25 mg/per day	Ventricular arrhythmias, hypotension, symptomatic bradycardia	58
4.	Carbamazepine	108	75–85%	Oral	200 mg/per day	Coma, imbalance, dizziness, and drowsiness	59
5.	Warfarin	1464	100%	Oral	7.5 mg/per day	Joint pain, bleeding, vision change, significant hemorrhage	60
6.	Albuterol	714	21–27%	Inhalation route	4 mg/3–4 times a day	Cough, throat irritation, vomiting	61
7.	Ciprofloxacin	8	70%	Oral, and intravenous	1000 mg/per day	Tendinitis, tendon rupture	62
8.	Codeine	485	60%	Oral	240 mg/per day	Acute pancreatitis, liver damage	63
9.	Dehydro nifedipine	193	45–68%	Oral, and intravenous	120 mg/per day	Flushing, peripheral edema, dizziness, and headache	64
10.	Diltiazem	23	40%	Oral	240 mg/per day	Headache, allergic reactions	65
11.	Doxycycline	1433	73–95%	Oral	200 mg/per day	Bloating, blistering, decreased appetite	66
12.	Metformin	1431	40–60%	Oral	500 mg/per day	Lactic acidosis	67

effects. Cyanobacteria and algae have a higher histopathological index and are more antibiotic resistant.[71,72] When exposed to tetracycline chemicals, oxidative DNA damage with metal complex formation has been reported. Atorvastatin exposure had a significant impact on lipid regulators with beta blockers in both target and non-target organisms. Because of their high sorption nature and affinity in sediments, enzymes involved in the beta receptor activity represent a risk to aquatic animals. Neurotoxicity is the most common health problem associated with psychiatric medicines in effluents or municipal wastewater systems. Anticancer drugs at concentrations ranging from 0.1 to 0.3 mg L^{-1} have an effect on optical acuity and mutagenicity. Endocrine disruptors induce reproductive and digestive system disruption. Males experience hypogonadism as a result of ibuprofen contraindications.[73–75] These pesticide compounds may enter into water systems through surface run-off or leaching. Indirect toxic effects on the fishes with impairment in the metabolic system of primary producers are few ailments related to aquatic species. Hormonal imbalance, neurological dysfunction, blood disorders, and immune impairment are the known effects of pesticides in the health system.[76] As a result, pharmaceutical exposure leads to expanding health and environmental problems.

2.3 Sources and occurrence

Without suitable treatment techniques, pharmaceutical chemicals are widely discharged into the environment. Pharmaceuticals are also used in different agricultural elements for disease prevention and treatment. Pharmaceutical use has increased in recent years due to its physicochemical and biochemical action modes. Certain molecules are metabolised during drug delivery, while others stay intact prior to elimination. Because of their low volatile and highly polar character, these metabolites remain stern and are not excreted into systems or disposed of in waste effluents. Pharmaceutical contaminants are unlikely to enter the environment *via* industrial disposal channels.[77,78] Pharmaceutical chemicals are classified into two types: point sources and non-point sources. Pharmaceuticals are most typically introduced into the environment by sewage sludge dumping, groundwater leaching, and surface run off. Medical chemicals have been found in municipal and hospital effluent sewage. Hospital sludge has a higher concentration than that of municipal sludge. Expired medications are dumped in home sewage. Pharmaceuticals are also present in landfills; however, they are less concentrated due to their sorption or breakdown capabilities. Primary and secondary point sources of pharmaceutical pollution are landfills and wastewater. Sewage treatment plants contain considerable amounts of medicines that remain unmetabolized for extended periods of time.[79] Duan *et al.* (2021) investigated the occurrence and source analysis of pharmaceutically active components in China City's aquatic systems. Diclofenac acid, carbamazepine, and caffeine are the most commonly detected substances. Besides, high lincomycin concentrations (81.1 ng L^{-1}) are frequent in the antibiotic class. Other medications detected in average concentrations (16 to 21 ng L^{-1}) include sulfamethoxazole, roxithromycin, and erythromycin.[80,81] The investigation also revealed that the target compounds were detected in low amounts and that non-antibiotics were more frequent in the ecosystems.

3. Microbial degradation

3.1 Molecular mechanism and interaction of microbes with pharmaceutical pollutants

Many organic and inorganic compounds are degraded significantly by microorganisms. Microbial systems play a significant role in ecosystem functioning since they are a key community. When medicines enter the ecosystem, many processes such as sorption, hydrolysis, and biodegradation occur, which prevents ecotoxicity in environmental systems. Microbial degradation is the best strategy in the environmental aspect for effective harmful pollutant removal.[82] Natural creatures in water and soil are significant players in environmental process management. They also control the release of drugs into the environment. Microbial species participate in the degradation and purification processes *via* metabolic and co-metabolic pathways. The two primary biodegradation pathways are bio-oxidation and hydrolysis. The enzymes involved in metabolic and co-metabolic pathways aid in pharmacological transformation.[83] Fig. 2 depicts the interaction mechanism between microbes and pharmaceutical pollutants.

Microbial biodegradation can be categorised into three stages: bioattenuation, biostimulation, and bioaugmentation.[84] Bioattenuation is the inclusiveness of organisms to improve metabolic activity and pharmaceutical breakdown. Limited nutrients are added to enable the microbial species to degrade harmful contaminants. Supplementary organisms are added to microflora for specific impurities during the bioaugmentation process. By metabolising pollutants, microorganisms use pharmaceutical contaminants as their sole source of growth. Pharmaceutical contaminants can be completely mineralized during the biodegradation process.[85,86] The biodegradation of pharmaceuticals has the benefit of both aerobic and anaerobic mineralization. In terms of bacteria-based biodegradation, a mixed bacterial consortium is favoured since it has a variety of enzymes capable of degrading the chemicals. Several investigations have been conducted on the breakdown of particular medicinal components by specific bacterial species. In one investigation, the *Achromobacter* sp. destroyed sulfamethoxazole. Pharmaceutical wastewater sediments were used to isolate the bacterial species. The bacterial culture must first adjust to its new habitat before beginning the degradation process. For strain growth, sulfamethoxazole was used as an electron donor and carbon source.[87,88]

Diclofenac was also subjected to biodegradation by *Labrys portucalensis* sp. in another investigation. This mechanism was primarily identified by the detection of metabolites. The reaction begins with hydroxylation reactions, which result in isomer formation. The hydroxylation reaction takes place using mono and dioxygenase enzymes released by *Labrys* sp. as the first step in the microbial degradation process. The enzyme methyl transferase adds a methyl group to 4-hydroxy diclofenac molecules. The decarboxylase enzymes then participate in the

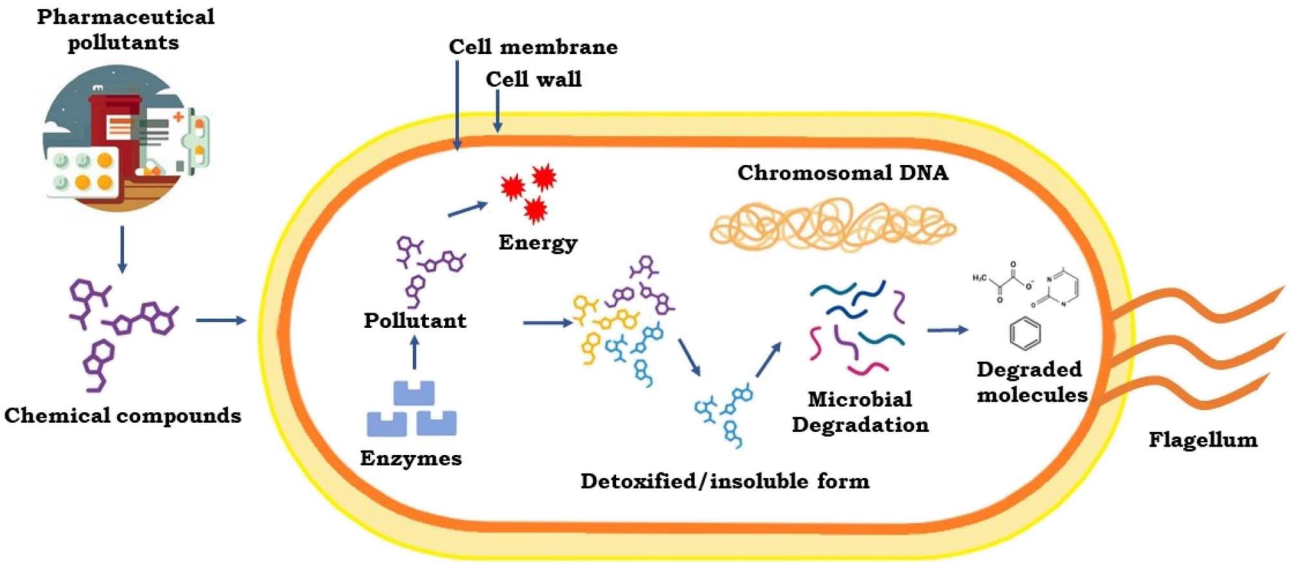

Fig. 2 Interaction mechanism between microbes and pharmaceutical pollutants.

intermediate process. The auto-oxidation of hydroxylated metabolites occurs *via* an alternative pathway, resulting in benzoquinone molecules. Diol dehydrogenases fission rings, resulting in Kreb's cycle intermediates and simpler metabolite molecules.[89] After 24 hours of treatment, diclofenac had a comparable response to *Chlamydomonas reinhardtii*. The concentration of metabolites was also observed to rise with the cell biomass.[90]

Other microbial species that participate in the pharmaceutical breakdown process include fungi. Pharmaceutical substances are broken down by extracellular multi-enzyme complexes. Olicon-Hernandez *et al.* (2019)[91] investigated ascomycete fungus species' degradation of diclofenac compounds. *Penicillium oxalicum* was isolated from hydrocarbon-polluted materials and employed in flask and bench scale reactors for biodegradation. For free *Penicillium* sp., the clearance rate was greater than 99%. During biodegradation mechanisms, hydroxylated metabolites linked with phase 1 and phase 2 detoxification pathways are formed concurrently. The inclusion of transferase enzyme in the process mechanism facilitates the formation of high conjugate metabolites – diclofenac acyl glucuronide.[91] *Trametes pubescens* was used to breakdown clofibric acid, another pharmaceutically active molecule. *Trametes* sp. consumes clofibric acid as a substrate, which has both antagonistic and synergistic effects. *Trametes*, a white rot fungal, undergoes oxidation followed by the production of metabolite intermediates. The fungal-based microbial degradation reached around 30% degradation.[92] In the microbial degradation of pesticides, pesticides are utilized as microbial nutrient sources, which are consequently degraded into small compounds. Mechanisms involved in the degradable pathways are hydrolysis, reduction, decarboxylation, condensation, dehydrogenation, and oxidation. Initially, adsorption of pesticides occurs on the cell membrane surface. Second, mineralization of the organic compounds to simple inorganic compounds takes place under the influence of enzymatic action. In addition, microbial pesticide degradation includes co-metabolism as a primary mechanism.[93,94] Chen *et al.*[93] explored the metabolic pathway for the chloracetamide degradation by microbial species. Different biological and physiological reactions such as hydroxylation, dechlorination, and dealkylation have been observed in the microbial degradation of chloracetamide pesticides.[93] Different microbial remediation studies on the removal efficiency of pharmaceutical pollutants are listed in Table 3.[95–119]

3.2 Influencing factors

Certain biotic and abiotic variables generally influence the biodegradation process. In terms of microbial degradation, the factors associated with microbial growth and processing are growth source, temperature, pH, and nutrient source. Besides, pharmaceutical features and microbial culture incubation with medicines have an important influence on the degradation process.[120]

pH is a vital component in the microbe-based degradation process because it influences enzymatic activity, proliferation, adaptability, shape, and certain membrane properties. The acidic and alkaline pH values are intimately related to the ionic form of medicinal substances, which influences the degradation process indirectly.[121] In a study of ibuprofen degradation by *Bacillus thuringiensis*, it was discovered that a pH in the range of 6 to 7 was optimal for maximum ibuprofen degradation. The bacterial enzymes hydroquinone monooxygenase and hydroxyquinol 1,2-dioxygenase are most active at pH levels between 7 and 8, which may have altered the breakdown process. The uncharged form of ibuprofen interacts with the bacterial cell surface releasing enzymes, leading to disintegration.[122]

Temperature is an essential factor that influences the microbial breakdown process. The chemical reaction doubles

Table 3 Microbial remediation studies on the removal efficiency of pharmaceutical pollutants

S. no.	Microbes	Pharmaceuticals	Operating condition	Technique used	Efficiency	Time	References
Bacteria							
1.	*Geobacter*, and *Acetoanaerobium*	Erythromycin	500 mV, 27 °C	SEM	99%	4 days	95
2.	*Bacillus cereus* H38	Sulfamethazine	25 °C, pH 7.0, and inoculation amount 5%	LCMS, whole genome sequencing	100%	3 days	96
3.	*Pseudomonas stutzeri*, and *Shewanella putrefaciens*	Sulfamethoxazole	30 ± 1 °C, 180 rpm, 24 h	HPLC-MS	61.79%, and 68.67%	5 days	97
4.	*Delftia lacustris*	Erythromycin	37 °C, 180 rpm, 18 h	—	45.18%	5 days	98
5.	*Providencia stuartii*	Tylosin	15 h, 40 °C, pH 7.0, and 1% (v/v) inoculation	Whole-genome sequencing	100%	3.5 days	99
6.	*Sphingomonas* sp.	Thiamphenicol	25 °C, 150 rpm	Proteomic and metabolomic analysis	93.9%	1.5 days	100
7.	*Bacillus clausii*	Cefuroxime, cefotaxime, and cefpirome mixture	37 °C, 220 rpm	Uv-spec, RT-PCR	100%	0.5 day	101
8.	*Klebsiella* sp.	Tetracycline	25 °C, 5 min, 630 W	UPLC-Q-TOF, UPLC-UV	58.64%	6 days	102
9.	*Pseudomonas aeruginosa*	Dicloxacillin	30 °C, 2 h	UV, PCR, HPLC	100%	2.2 days	103
10.	*Micrococcus luteus* N.ISM.1	Gabapentin	35 °C, 120 rpm, 72 h	FE-SEM, LC-ESI-MS	47%	40 days	104
11.	*Klebsiella* sp.	Diclofenac sodium	30 °C, 120 rpm	LCMS	79.14%	3 days	105
Fungus							
12.	*Lentinula edodes* and *Imleria badia*	Cephalosporin	Ultrasound at 49 kHz, 20 min	UPLC/MS	100%	7 days	106
13.	*Leptosphaerulina* sp.	Oxacillin	28 °C, pH 5.6, and 160 rpm for 15 days	Biotransformation and MTT assay	100%	6 days	107
14.	*L. edodes*	Testosterone	25 °C ± 2 °C, 140 rpm	UPLC	100%	21 days	108
15.	*L. edodes*	17α-Ethinylestradiol	25 °C ± 2 °C, 100 rpm	HPLC, UV-Spec	100%	21 days	109
16.	*Penicillium oxalicum*	Diclofenac	28 °C, 120 rpm	HPLC, UPLC	100%	1 day	110
17.	*Penicillium commune*	Oxytetracycline	27 °C, pH 7.3	Optical and scanning electron microscopy	78%	15 days	111
18.	*Penicillium oxalicum* RJJ-2	Erythromycin	35 °C, pH 6.0, 96 h	HPLC-MS	84%	4 days	112
19.	*Trichoderma citrinoviride* AJAC3	17-β-estradiol (E2)	28 °C ± 2 °C, 120 rpm	HPLC, GCMS, SEM, FTIR	100%	4 days	113
20.	*Trichoderma* sp.	Ciprofloxacin	25 °C, 135 rpm	LCMS	81%	13 days	114
21.	*Phanerochaete chrysosporium*	Sulfadiazine	30 °C, pH 5.7	Q-Exactive-MS, RNA sequencing	100%	6 days	115
22.	*Trametes versicolor*	Diclofenac	4 pH, 1 mL min^{-1} flow, 33 h (hydraulic retention time)	Q-TOF LC/MS	98%	7 days	116
Algea							
23.	*Chlorella* sp.	Florfenicol	5000 ± 100 lux illumination intensity, 30 ± 1 °C	HPLC-UV	97%	7 days	117
24.	*Chlorella* sp.	Thiamphenicol	4 °C, 5000 rpm, 10 min	Uv, HPLC	97%	5 days	118
Microbial consortium—bacteria, fungus and yeast							
25.	*Klebsiella pneumoniae*, *Achromobacter* sp., *Candida manassasensis*, *Trichosporon asahii*	Ofloxacin, and norfloxacin	30 °C, 120 rpm, 48 h	PCR	80%	20 days	119

or rises four times for every 10 °C temperature increase. The temperature is directly related to the operation of cell enzymes and cell membranes. High temperatures cause protein denaturation, whereas low temperatures affect the cell viscosity and stiffness, limiting the enzyme performance. Temperature has also been shown to have a considerable impact on the metabolic development and activity of cultures.[122–124] In a study by Yu *et al.*,[125] the effect of different parameters on sulfamethoxazole degradation by *Pseudomonas koreensis* and *Paenarthrobacter ureafaciens* was analysed. The effects of temperatures ranging from 10 to 50 °C have been investigated. The bacterial consortium grew better at temperatures ranging from 20 to 40 degrees Celsius. The ideal temperature for maximum sulfamethoxazole was found to be 30 °C. Microbial development was not possible at low temperatures. Similarly, no pharmacological decrease was observed at high temperatures.[125]

Microbial inoculum is a key aspect in the degradation of medicinal substances. When the inoculum is large, it can occasionally hinder the degrading capacity due to poisonous material release. The ageing of the inoculum affects the organism's ability to degrade.[126] Yang *et al.*[97] studied the impact of several parameters on the degradation of chloramphenicol by *Pseudomonas* and *Shewanella* sp. For maximum breakdown ability, bacterial inoculation amounts of 1, 2, and 3% were changed. The effectiveness of biodegradation increased, as the bacterial count increased from 1% to 2%. Yet, at 3% bacterial concentration, the degradation remains steady without further rise. At a bacterial load of 2%, a maximum of 60–65% degradation efficiency was achieved.[98] The nature and characteristics of medicinal compounds play an additional role in biodegradation. The more stable and complex pharmacological substances are more difficult to breakdown.[127]

4. Recent advancements

4.1 Metabolic or genetic engineering

Genetic and metabolic engineering is a rapidly growing discipline globally for the production of novel microbes with desired features. In general, genetically modified organisms are bacteria that have had their genetic code altered *via* the recombinant DNA process. Designing genetic and metabolically modified organisms is required for creating new metabolism pathways for pharmaceutical degradation, reducing hazardous metabolite accumulation, increasing metabolic catabolism, and improving organism substrate flux. The introduction of novel genes aids in the adaptation of microorganisms to pharmaceutical pollutants.[128,129] The steps involved in the production of metabolically engineered microbes are shown in Fig. 3. The recombinant DNA field enables improved energy generating methods, increased copy number, and inclusion of desired genes. The metabolic engineering method has included novel aspects relevant to limiting factors and pathways. Various genetic methods have been used to reinforce optimal gene expression and change the metabolic pathways of enzymes.[130] Some fundamental elements must be present in order to regulate the complicated enzyme system and metabolism. Four parameters must be observed when it comes to the breakdown of pharmaceutical contaminants: enzyme nature, metabolic management of the breakdown pathway, creation with metabolic pathway regulation, and lastly, overall process development for improved genetic modification. Fungal genetic engineering plays a significant role in modifying enzyme targets and affinity for medicinal drugs.[131,132]

Another new subject that offers potential solutions for pharmaceutical degradation is metabolic engineering. *In vitro*

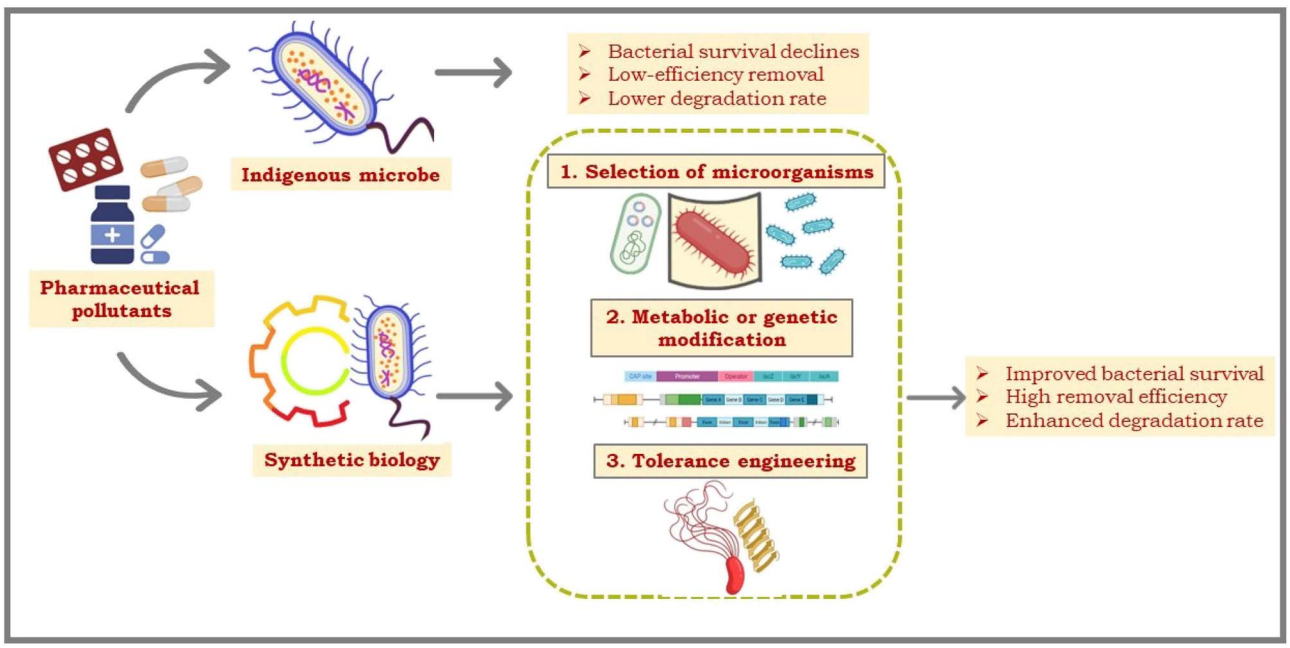

Fig. 3 Steps involved in the production of metabolically engineered microbes.

and *in vivo* approaches are used to create a synthetic metabolic pathway. *In silico* technologies can be used to anticipate probable metabolic pathway paths. Another emerging subject is enzyme engineering, which involves the development of novel enzymes with activating/deactivating roles in the metabolic breakdown pathway.[133,134] Aulestia *et al.*[135] applied genetic characterisation to determine the metabolic pathway for ibuprofen degradation in a recent research study. *Rhizorhabdus wittichii* eliminates the pharmaceutical pollutant ibuprofen by the generation of metabolites. Genetic approaches have been used to identify IBU genes with non-colored and leaky mutants. For a better understanding of pathways, molecular biology methods such as mutant insertion and sequence analysis were used.[135] A research study employed *Escherichia coli* metabolic engineering to complete naphthalene breakdown. A total of 17 genes involved in the degradation pathway were optimized and rebuilt. It is possible to recreate the metabolic modules involved in the conversion of naphthalene into catechol and other metabolites. In that study, consecutive naphthalene degradation was achieved by altering the BL-CA-cat genes.[136] Similarly, recent studies have focused on the genetic and metabolic alteration of microbial species for improved pharmaceutical contaminant breakdown.

4.2 Immobilization

Enzymes play a crucial role in the microbial breakdown of medications by metabolising the complex compounds. These enzymes can be used directly to degrade the substances. The enzymes can be introduced into the degradation medium as free cells or immobilized. Because enzymes in their free state are difficult to separate, they can be immobilized into solid support materials that only enable the transfer of degrading chemicals into it.[137,138] The immobilization procedure will also considerably increase the enzymes' stability and reusability. The two ways for immobilizing enzymes onto solid substrates are physical and chemical. Chemical approaches include cross-linking and covalent bonding, whereas physical methods include encapsulation, entrapment, and adsorption. Physical or ionic attachment of enzymes to solid supports is one way of immobilization *via* adsorption. Fig. 4 denotes the microbial immobilization for the removal of pharmaceutical pollutants. Silica gel, activated carbon, porous glass, biomass, and other organic porous substances are the commonly utilized support materials.[139,140] Because adsorption does not necessitate the use of expensive materials, enzyme or cell structure will not be altered, resulting in high enzymatic activity. Encapsulation encompasses immobilizing enzymes in a spherical shaped non-permeable membrane, whereas entrapment involves enclosing enzymes or cells in a closed fiber-like network. Because physical trapping of enzymes is sometimes ineffective, resulting in enzyme leakage, chemical methods of immobilization are used. Partially deformed enzyme structures and molecular networks produce a stable and strong bond with the support matrix. Chemical immobilisation techniques such as covalent, disulphide, and ionic bonding allow many treatment and reuse cycles.[141–143]

Cross linking is another type of immobilisation in which enzymes can be immobilised as crystals or aggregates. Primozic *et al.*[144] immobilised a laccase enzyme as a cross-linked aggregate for diclofenac biodegradation. Laccase precipitation in propanol and aminosilane magnetic nanoparticle solutions was used to form the aggregates. The degradation process was carried out in a stirred batch reactor. The ability to remove diclofenac was approximately 13–16 g diclofenac/g laccase. Even after the fourth regeneration cycle, the immobilised enzyme's half-life remained constant. Immobilised laccases also exhibit good stability.[144] Laccase was immobilised in a polyvinylidene fluoride

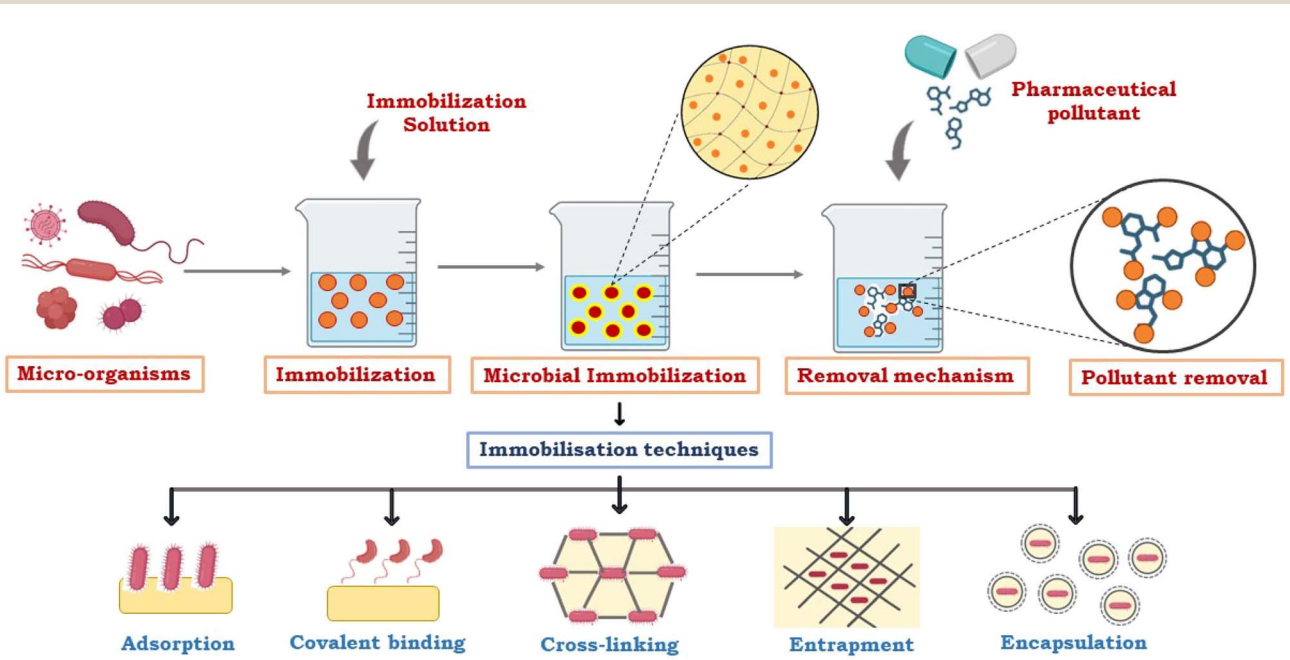

Fig. 4 Microbial immobilization for the removal of pharmaceutical pollutants.

nanocomposite and nanotube containing diclofenac and carbamazepine for breakdown in another recent investigation by Masjoudi *et al.*[141] Initially, phase inversion was used to create multiwalled carbon nanotubes using polyvinylidene fluoride nanocomposites. The laccase enzyme was immobilised in the produced samples and used as a catalyst in pharmaceutical degradation. In the membrane reactor, an activity recovery of 38.31% was recorded with immobilised laccase, with a removal efficiency of 27%.[141] Whole cells can also be immobilised for pharmacological degradation. Zur *et al.*[145] immobilised the entire Pseudomonas moorei strain in bacterial cellulose for degrading purposes. Immobilisation was performed for 72 hours in order to improve its effectiveness, and it was examined for auto aggregation and co-aggregation capacity. This complete cell immobilised system decomposed around 150 mg L^{-1} of paracetamol. Hydroquinone 1,2-dioxygenase, deaminase, and acyl amidohydrolase are major enzymes implicated in the paracetamol breakdown route *via* entire immobilisation.[145] As a result, an immobilised enzyme system with reusable capacity can be successfully used for pharmaceutical degradation.

5. Microbial degradation: kinetic models

The kinetics section is critical for determining the breakdown of pharmaceutical contaminants. Microbial degradation kinetics aids in the accurate evaluation of microorganisms and their environments for pollutant degradation. Besides, model building is critical in regulatory considerations for predicting biodegradation at different time intervals. For the microbe-based degradation of pharmaceutical contaminants, many kinetic models have been developed.[146–148] One such model for determining degradation kinetics is the Haldane equation. This equation addresses the kinetics of cell development on hazardous substrates. The Haldane equation can be represented as follows:[149]

$$\mu = \frac{\mu_{\max} S_0}{K_S + S_0 + \left(\frac{{S_0}^2}{K_i}\right)} \quad (1)$$

When the inhibition phenomenon occurs, the Haldane equation is more appropriate. The significant parameters are max, K_S, and K_i. Certain investigations show that low values of max are due to low biomass concentrations. At high pharmacological concentrations, substrate inhibition can occur, resulting in the incomplete mineralization of intermediates.[150] Calero-Diaz *et al.*[151] used kinetic modelling analysis to better understand the biodegradation of ibuprofen, ciprofloxacin, and carbamazepine in a membrane bioreactor system. The following equation was used in the investigation to determine the decay coefficient and kinetics.

$$b_H = \frac{k_d}{1 - Y_H(1 - f_P)} \quad (2)$$

where the decay efficient is represented by b_H and the volatile biomass fraction is denoted by the term $1 - f_P$. The addition of pharmaceuticals ibuprofen, ciprofloxacin, and carbamazepine to the membrane bioreactor system resulted in a higher biodegradation rate, which doubled as the cell growth rate increased. With various pharmacological concentrations and an average decay rate of 1–80 g (h^{-1} mg^{-1}), 83–100% elimination was obtained.[151] In addition to the proposed models, the pseudo-first-order kinetic model is a commonly utilised technique of pharmacological degradation. In the first-order kinetics, the reaction rate can be calculated and is proportional to the change in initial pharmaceutical concentration with time. Ciprofloxacin biodegradation has also been studied in another study using *Thermus* sp. A bacterium that degrades pharmaceuticals has been identified from the pharmaceutical sludge. The linear relationship between time and diminishing medication concentration can be described as follows:

$$\ln C_t = -kt + \ln C_0 \quad (3)$$

The first-order kinetic model agreed well with the experimental data, indicating that microorganisms were responsible for the majority of the deterioration. Sodium acetate increased *Thermus* sp. biomass production by acting as an electron donor in the non-growth factor metabolism.[152] As a result, various kinetic models have been created and confirmed by researchers based on their research.

6. Future outlooks and challenges

One of the key challenges facing pharmaceutical microbial degradation is the lack of standard methodologies for assessing and comparing the degrading ability of different microbial species. Some typical biodegrading analysis methods are inaccurate, which have to be investigated further. The presence of many pollutants in the system reduces the degrading ability. The effect of antibiotics, for example, on the pharmaceutical transport behaviour is critical for successful clearance. This effect's hazy concept needs to be researched further. To anticipate the optimum period for degradation, the microbial species' adaptation time to the pharmaceutical wastewater environment must be well characterised. The mineralization process mostly degrades pharmaceutical substances. However, certain microorganisms biotransform pharmaceutical components, producing intermediates that are more dangerous than the primary pollutants. As a result, a mixed microbial consortium might be used for complete pollutant mineralization rather than a single pure culture, which lacks this potential. The utilisation of extra substrates, which aids in biodegradation *via* cometabolic processes, can also improve the biodegradation efficiency. The adoption of optimum statistical approaches can improve the growth conditions of microbial cultures. The incorporation of statistics and bioinformatics fields facilitates process condition optimisation. While the subject of genetic engineering has been developed for the alteration of microbial strains to aid in enhanced biodegradation processes, there is a dearth of research studies focusing on this issue. As a result, the scope of genetic engineering should be properly studied, and pathways should be clarified. To gain a better

understanding, various biodegradation routes used by microorganisms must be precisely identified. The reusability of enzymes or entire cells involved in the pharmaceutical degradation process can now be achieved because of the recent advances in immobilisation. However, some mass transfer constraints impact the movement of intermediates and metabolites into and out of the immobilised support system. The discovery of microbial degradation pathways enables modern developments such as metabolic or genetic engineering and immobilisation to significantly increase pharmaceutical biodegradation. A few numbers of kinetic investigations on pharmaceutical biodegradation have been conducted. As a result, additional research incorporating other process parameters is required for a better prediction of degradation rate and kinetic mechanism.

7. Conclusion

Substantial progress in the field of microbial remediation has been the focus in recent years. The presence of microbial communities determines the capacity and efficiency with which medicinal substances can be destroyed. Persistent pharmaceutical pollutants in the environment can be minimised *via* several metabolic and co-metabolic transformation processes. Hydrolysis and bio-oxidation are the two major degradation pathways for the microbe-mediated pharmaceutical remediation. The use of mixed microbial cultures is desirable for improving THE biodegradation activity. Advanced statistical and bioinformatics tools have been used to optimize the factors impacting the microbial degradation process. The advancement of immobilization techniques with various solid supports improves the reusability of materials used in the remediation processes. The ideal support systems should overcome the mass transfer constraint in the immobilised system. The field of metabolic and genetic engineering is a recent development in the microbial breakdown of pharmaceutical contaminants. Metabolic engineering approaches aid in developing new degradation pathways of metabolism, which enhance the ecological pharmaceutical removal. Of the different kinetic models facilitating the selection of several optimum techniques for polluted sites, the pseudo-first-order model is the best suited due to its better coherence with the process conditions. The future prospects for enzyme engineering improve the aspect of pharmaceutical degradation. Novel *in silico* techniques in the metabolic engineering field could enhance the contaminant removal from the ecosystem.

Conflicts of interest

There are no conflicts to declare.

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