Review Article

Mycoremediation of Pharmaceutical Industrial Effluents

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ABSTRACT

The major environmental problem facing the world is the contamination due to toxic chemicals released by industries. When the industrial process increases rapidly, their chemical reactions to form harmful by-products continue to increase. The level of pollution is increased by industrial effluent, which is been identified as a major polluting agent. The remedy for industrial effluent is bioremediation. Bioremediation is the clean-up process of effluents by microbes and plant enzymes. Microorganisms like bacteria, algae, yeast, and fungus naturally can degrade toxic substances in the environment. Bioremediation techniques like phytoremediation, Phyto stabilization, hemofiltration, augmentation, biosorption, hyperaccumulation, mineralization, excavation, stabilization and mycoremediation, and so on. In this chapter, we are dealing with a promising technique of mycoremediation, where the toxic compounds are removed by fungus. Fungal enzymes like Peroxidase, catalases, and laccases can degrade heavy metals, paper, and pulp effluents, petroleum products, and sludge wastes. Fungus is the most powerful composer for secreting strong cellular enzymes due to their aggressive growth and biomass production. Here we discuss the role of fungal species in the remediation, yield, and tolerance capacity to reduce the influence of toxins.

Keywords: Bioremediation, Industrial effluent, Contamination, mycoremediation, Fungal Enzymes.

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INTRODUCTION

Pharmaceuticals have grown as an enormous business by enlarging the use of exhaustive livestock raising and a rise of the human population, which assure the standard of human life andwellbeing. However, the evolution of detachment technologies for these compounds is not keeping pace with the swift increase in their usage [1,2,3,4,5.] For the last decades, the analysis of environmental contamination was mainly concentrated on the effect of synthetic toxic waste released at high concentrations. Recently a dominant category of chemicals has been examined as an expected impurity for the environment, named emergingcontaminants. They are chemicals or products that are determined in the environment and characterized by a lack of particulars concerning their unfavorable contamination. They may be future dependent on the research about their health effects and their presence in the surrounding. Among the emerging contamination, pharmaceutical products need a special concern.

Pharmaceutically active components are a large and diverse group of mixtures designedto prevent, cure and treat disease and improve health. They have been used in a significant amount throughout the globe[6.] The drug in the pharma industry is used to serve, detect and help in preventing animal and human diseases. Various new and more effective pharmaceuticals product are being evolved to meet increasing demand throughout the world. According to the Institute for Healthcare Informatics, Worldwide media is predicted to be 4.4 trillion by 2020 [2.] The consumption of pharma products is grown regularly to the awareness of new drugs due to the increased population, continuous improvement of quality of life, as well as to the expiration of patents which make drugs additionally affordable[6.] With the immoderate manufacturing and successive utilization of pharmaceutical products, the components are automatically being liberated into waste streams. pharmaceutical components enter the environment through hospital effluents, industrial discharges, agricultural runoff, and human, as well as animal, excrete[3.] Besides, unutilized and scraped drugs eventually get into the ecosystem due to mishandling [4.] Hospitals sources are one of the leading sources of contamination. Hospital discharge comprises active drugs, their metabolites, expired pharmaceuticals products, hazardous chemicals, solvents, disinfectants, and heavy metals [5.] These pollutants have an intrinsic property to interrelate with the living system. As evidence, in 1992 the annual consumption of anti-inflammatory drugs like acetylsalicylic acid, paracetamol, ibuprofen, and diclofenac was approximately 900 tonnes in Spain [7.] The increase in consumption of new antibioticsoutweighed the decreased use of obsolete antibiotics [8,9.]

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Due to the excessive production of pharmaceutical drugs which are wasted, disposal ofdrugs leftover in sewage and trash is another source, in many countries which are estimated that tons of pharmaceutical were disposed of every year from medical care and approximately 60-70% of them were either flushed down the toilets or disposed of with normal household waste[10].

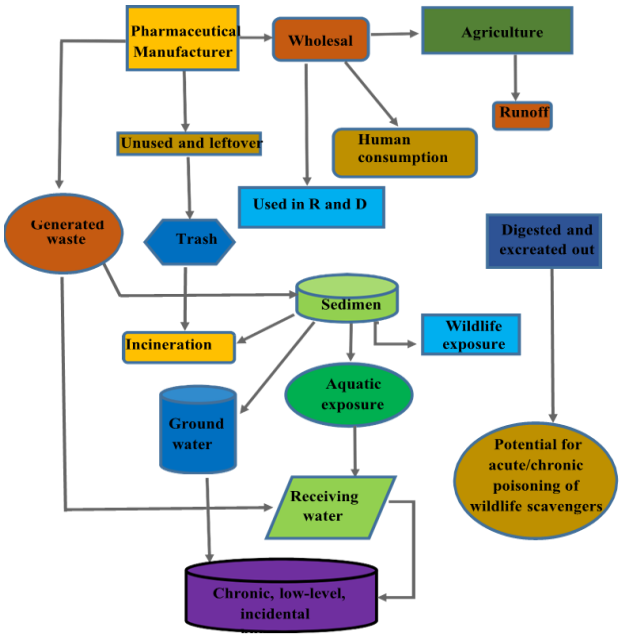

Figure 1: Fate of Pharmaceuticals

In addition, several publications reported the ineffective method for conventional wastewater treatment plants in the detachment of pharmaceutically active components [11,12,13]. These chemicals are not entirely cursing and are either removed by absorption, which is released to surface water bodies [14,15]. On the other hand, the sewage sludge produced in the treatmentof wastewater which had considered a source of contamination, the pharmaceutically active components are adsorbed in the sludge and disposed to landfill.

Non-steroidal and anti-inflammatory drugs are one of the causes of contamination fromthe pharmaceutical industry activity and the inappropriate discarding of unexploited or expired drugs, squander generated in hospitals and stock raising farms [16]. In recent years,an enlarged consumption of the counter drugs such as ibuprofen, naproxen, paracetamol, ketoprofen, diclofenac, and acetylsalicylate had been observed [17,18]. Among these anti-inflammatory drugs, the use of ibuprofen is the most highly consumed pharmaceutical in the world [19]. This drug belongs among the most frequently detected pharmaceuticals in the aquatic environment [20]. Although ibuprofen and naproxen are detected on the water surface, and ground surface in a certain range, they may accumulate in the aquatic organism [21,22,23]. It was shown that ibuprofen, as a non-selective cyclooxygenase inhibitor, reveals ecotoxic effects in the aquatic environment [24]. In distinction, photo derivatives of the drug naproxen tend to be endotoxin in chronic and acute conditions [25]. In the territory condition, naproxen and ibuprofen underdo surface assimilation, desorption, and abiotic transformation belong to biological transformation [26]. The physical and chemical transformations help in the degradation of pharmaceutically active components but lead to the evolution of toxic intermediate [25,22]. Therefore, the bioremediation process is an alternative method for the degradation of toxic components. Bioremediation strategies are effective and able to mineralize the pharma products into safer products [27]. Major release of components is in water bodies, now a day wastewater repetition contains many components such as aromatic components, organic solvents, synthetic polymers components contaminated from industries[28].

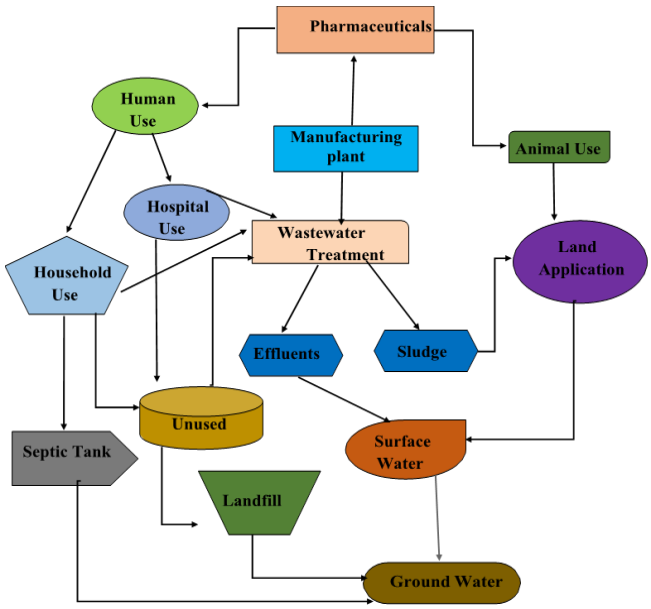

Figure 2: Source of Pharmaceuticals in the environment

However, the degradation of components is difficult by biological process and the efficiency is not satisfactory [29,21]. They had found that theyneed to isolate a microorganism that could degrade the anti-inflammatory and non-steroidal drugs at a higher rate. The feasible defeatist ecotoxicological consequence produced by the presence of chemicals in the environment is a serious issue for the environment. Nowadays theresearchers have focused on the detachment of pharmaceutically active components, Although,chronic ecotoxicity data are scarcely contrasted to drastic incremental reactions that have been shownto damage some ecosystems [33]. Standard treatment of pharmaceutical wastewater can be moved out using contrasting methods such as physical, chemical, and biological methods. Then some of the popular methods such as membrane bioreactor, activated sludge, chlorination, activated carbon, and ozonation[30]. The efficiency of all methods is not up to the range, still, the degradation rate varies from method to method. Hence, there is an emerging technology that now plays an important role such as microalgal consortia, bacterial consortia, or microalgal-bacterial consortia are attracting many researchers to mineralized pharmaceutical components. consequently, the development of processes

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for the removal of active components is required. Among the different alternative methods, biological treatment is more desired because they are continual and environmentally friendly. Therefore, new biological treatments must be studied for effective removal of the pharmaceutical active complexes, which would help to reduce the environmental impact of these chemicals in the environment. In this study, we are mainly dealing with the biological treatment for the degradation of the pharmaceutical active complex.

Major pharmaceutical pollution to the environment

Worldwide, the use of pharmaceutical products is rapidly increasing, at the same time pharmaceutical pollution is one of the causes of major pollution across the world. The pessimistic clash of the construction of pharmaceutical results on the instinctive environment is well known. However, this persists largely uncontrollable, which provides an extremely toxic collision. It has on both animals and humans continues with the unclear end in sight, The pollution caused at any stages of the production can be at end products, by-products of various types and classes are released into the environment is a major cause[31].

Over the last 30 years, international organization and the pharmaceutical industry has begun to notice the determined impact pharma products have on the environmental impact pharma products have on the environment on a global scale. Pharmaceutical products throw themselves into the environment at numerous phases of their life cycle but particularly during the production phase, one of the vital threats is that discharging antibiotics into the surroundings can assist the natural expansion of antibiotic-resistant pathogens that are harder to treat. Pharmaceutically active compounds are realized as the significantly emerging micropollutants,some of the components are Antibiotics, psychiatric drugs, beta-blocker, anti-inflammatory, lipid regulators, antihypertensives, analgesics, antiepileptics, antiseptics, hormones and steroids, contraceptive which is widely used by the world[32]. These active compounds have certain physicochemical properties, such as volatility, hydrophobicity, and absorbability and it's a complex structure, which induces different fates when exposed to surroundings, leading to high persistence[33].

Over recent years, the use of pharmaceutical products such as antibiotics has increased. The main categories of antibiotics used day by day are aminoglycosides, beta-lactam,glycopeptide, sulphonamides, and tetracycline are worldwide increased their use for the treatment of infectious diseases, the world without such types of antibiotics looks very different from the world we live in now[34]. Due to the rapid use of pharmaceutical products, their production has increased in recent decades. The use of pharmaceutically active components has been ubiquitously detected in abiotic and biotic media often in low concentrations [35,36,37]. The excessive consumption and improper disposal of products lead to pharmaceuticals build-up in municipal sewage, due to dumping in lands, where finished dose antibiotics are concentrated in a specific location,which leads to a source of pollution that enters the food chain from the surface, groundwater and sediments, which leads to emerging organic pollution are known as micropollutants. Micropollutants are one of the challenging environmental issues[38,39]. Occurrence and removal of multiple classes of antibiotics and antimicrobial agents in biological wastewater treatment.

A major consequence of insufficient treatment is the direct discharge of active pharmaceutical products into water bodies, causing diffusion in almost all aquatic environments and even in drinking water sources [40,41]. Mostly discharge of antibiotics is a major pollutant, for example, some of the environmentally persistent pharmaceutical pollutants, are analgesics and non-steroidal anti-inflammatory drugs, which cause serious environmental issues worldwide, most problems are in natural water systems and groundwater. This type of pollutant reaches water effluents through emit from industries and secretion of none metabolized drugs by humans or animals through urine and feces, anti-inflammatory drugs such as diclofenac and fluoxetine are common, among this diclofenac is usually found in hospitals and sewage water bodies and even in septic tanks which are released in the aquatic surface which results in various problems.

Structural chemical diversity among pharmaceutical compounds

Pharmaceutical active components cover an extensive span of chemical structure. They are generally confidential according to their medicinal functions such as lipid regulation, anti-inflammatory/analgesic drugs, Psychiatric drugs, antibiotics, estrogen, and indicated contrast media[42]. Mostly they are calmed by heterocyclic aromatics containing heteroatoms nitrogen, oxygen, or sulfur of 3or4 or fused rings, and macrocycles [43]. The existence of aromatic structures confers to these substances' properties related to aromaticity, electrophilic substitution reaction, and resonance stabilization [44]. which consequences in low stabilization, based on their water partition coefficient. These characteristics decrease their degradation efficiency since they are less bioavailable to microbial species. In addition, in the case of antibiotics, which are transformed with bacteria or fungi could represent a challenge since the antimicrobial properties hinder their use as a carbon source. These aromatic compounds contain molecules that had a functional group of electron-donating groups such as hydroxyl group(paracetamol); Carbonyl groups (Quinolones) and some amine groups (Carbamazepine, trimethoprim); fluorine groups (Ciprofloxacin) in their structures; even many molecules is being constituted of complex structure (diclofenac, diazepam, sulfamethoxazole). Excluding the existence of aromatic components, we also found linear once such as carboxylic acids (Valproic acid). Finally, they concluded that because of the complex structure, it is

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difficult to rule out the conduct and extensive pathways for microbial transformation.

BIOLOGICAL TREATMENT FOR THE BIOREMEDIATION OF PHARMACEUTICAL EFFLUENCE

A biological system is methodical in transmuting defiant and racist pharmaceutical antidote toreduced destructive form or leading it to complete mineralization[45]. Bioremediation is the biotic process of reclaiming wastes into a different form that can be utilized and reutilized by other organisms, nowadays the earth is a facade of the suffix difficulties. We know that microorganisms are extensively spread in the biosphere because of their ability to assist in a wide range of environmental circumstances. microorganisms play analternative solution to overcome these challenges. The microbes release a well-organized procedural activity that was applied to disintegrate or modify to none toxic forms. The processof bioremediation is carried out by biological agents to clean up contaminated sites. Some of the bioremediations are bacteria, archaea, and fungus. At present, separate practices and plans of action are implemented in different parts of the world. For example, biostimulation, bioventing, and bio attenuation are common.

Fungi as an agent of bioremediation

Fungi can exist in a variety of environments with a complex soil network as a major location for the fungal region along with freshwater as an aquatic environment which also shows a stable region. Fungai can mostly flourish in soils of different environmental conditions together with the maximum proportion through the dispersion of spores in the ecosystem, which helps in maintaining an equilibrium biosphere [46]. Fungi are employed in the biodegradation of disagreeable materials or compounds and transmute them into non-toxic, manageable, or utilitarian products. Fungi had a unique capacity to degrade the effluents and also had a capacity for producing extracellular proteins, organic acids, and some metabolites [47]. In this chapter, we are explaining different fungus species and their efficiency in the bioremediation of effluents.

The role of fungus in the biodegradation of pharmaceutically active components

Fungi are composed of different groups of microorganisms with their character in nature as composers, mutualists, or pathogens [48]. In worldwide fungal species,abundance is disputed since most of the species are not yet described [48,49,50]. Whereas it is consensual that the most fungalspecies in the characters involve terrestrial ascomycetes and basidiomycetes [51].Both phyla hold hazardous waste that deteriorates [52]. where Zygomycota is a sub-classification of fungal species of inverter sides, some of them are well responded in the metabolized xenobiotics [53,54]. Fungi had a diverse plan of action to prevent a myriad of toxic materials such as pesticides and polycyclic aromatic hydrocarbons. This action includes non-enzymatic operations such as mineralization, bio adsorption, and some enzymatic operations such as biodegradation and biotransformation[52]. Bio adsorption is referee by the particular configuration of cell walls suchas chitin [55]. In addition, fungi had a capacity for constructing biosurfactants, and amphiphilic surface active components with hydrophobic and hydrophilic portions that attract between different phases of polarities, which results in increasing tension reductions and capacity to interact with molecules [56,57]. It isconcluded that structural biosurfactants involve some the components such as sophorolipids, polysaccharide complex networks, glycolipids, and glycolipoproteins. This component plays animportant role in the bioremediation activity [58]. In the property of pharmaceutically active components, the aromatic structural condition increases the possibility of biosurfactants, which improves the mobility of active components and increases their bioavailability, as observed in polycyclic aromatic hydrocarbons [59].

White-rot fungi

White-rot fungi are handed down for biodegradation of lignivorous material inthe atmosphere that is assigned to carbon recovery. Due to the accumulation of endocrine-disrupting chemicals, TrOCs, and heavy metals released from the pharmaceutical and personalcare products when they are released into water resources, there is a development of acute and chronic toxicity to aquatic species and also anxiety for human health which is remediated bywhite-rot fungi, there are many white-rot species like *Phanerochaete chysosporium, Bjerkandera adjusts* and *Pleurotus species* which can produce different types of ligninolytic enzymes such as laccases and peroxide [60,61]. In fastidiouswhite-rot fungi, the wood secondary cell wall is delignified and coercivity begins from the lumenthen followed by delignification of the lamella, As white-rot fungi are effective in degradation of lignin prefers hemicellulose as a carbon source, the cell of wood is enriched by cellulose[62]. Exacting delignification can occur inadequate throughout the wood substance, restricting the area of complete lignin removal, which is called white pocket rot. selectively the degradation of wood is based on the physical and chemical environment of the wood, such conditions are temperature, oxygen, nitrogen, and moisture content of wood [63] and also based on the wood species [64]. White rot fungi could degrade wood extractive [65,66]. That enzyme is used for the biological transformation of organic pollutants from the contaminated wastewater by assisting microbial activity by the bio purification system [68]. The extracellular enzyme-like ligninolytic enzyme of white-rot fungi had a capacity for decolorization and adsorption of effluents. The probable basement of the pollutant would be carried by a lignocellulosic enzyme for degradation. such type of treatment is possibleby white-rot fungi [68,61]. The polycyclic none steroidal and anti-inflammatory drugs are biotransformed by microbial species, white-rot fungus plays a rolein the degradation but the biotransformation for selected drugs is not completely degraded, sotstill requires further studies [18].

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Basidiomycota fungi

The *Basidiomycota* is the distribution of fungi is a class of micro and macro-organism are distributed by the development of basidia, it like a bottle-shaped cell structured which havehaploid and is sexually basidiospores [1]. Due to their surrounding relations, the *Basidiomycota fungi* have grown and developed into different processes associatedwith carbon and nitrogen sources, as well as for a balanced environmental condition. which provides a sequence of pathways such as intracellular and extracellular processes. It effectively interacts with varied substances, mainly the fungus capable of producing lignin [69]. One of the conditions in Basidiomycota *fungi* is a degradation of the pharmaceutical active complex substance, which can degrade under effective metabolizing conditions. From an eco-physiological extremity perspective, *basidiomycetes* from macroscopic fruiting bodies can be predominantly confidential into wood-decaying, mycorrhiza-forming, and litter-decomposing fungi. Wood-decomposing fungi. Populated on dead or dying tree trunks and stumps use cellulose while changing the hemicellulose and lignin elector causes any brown rot or more commonly, white rot via the useof hemicellulose and cellulose throughout the deterioration of lignin. Wood rot fungi are the dominant deterioration of the main plant polymers lignin, cellulose, and hemicellulose in the earth [70,71,72]. Wood rot fungi entirely mineralize these polymers to CO2, whereas *brown-rot fungi* competently decompose cellulose and hemicellulose components of wood but clarified lignin only to a limited extent [71]. Mushrooms are cultivated worldwide for their nutritional attributes and possible applications in industries [73]. In inclusion, they have many medical uses and are a good agent for remediation [74,75]. The major implement in the deterioration of PhAcs and aromatic components by Basidiomycota fungi by extra and intracellular oxidoreductases suchas laccase, peroxidases, etc. which alter and break down the bonds of a different substance, mostly by extracellular pathways [69]. There are many kinds of fungal mediators that have been studied on the deterioration of PhACs in the white-rot fungi such as *Phanerochaete chrysosporium, Phlebia ochraceofulva, Pynoporus sanguineus, Pleurotus ostreatus and T. Versicolor* [78,79]. However, in all cases the participation of Cytochromes P450 in the deterioration of PhACs transformation, usually deterioration is measured by the inhibition with cytochromes enzymes such as 1-aminobenzotriazole and piperonly butoxide. The main role of *Basidiomycota fungi* in the degradation of pharmaceutically active components along with aromatic components including some extra and intracellular oxidoreductase enzymes, which could break down the bondsof components and modify its pharmaceutical active components by pathways [69].

Brown-rot fungi

Brown-rot fungi are a part of wood-rotting *basidiomycetes*, they are esteemed from white-rot fungi by their defective ability to detach lignin and cellulose degradation [80,64]. Brown rot fungi could wood darken, shrink and break into a different shaped piece of wood [76,79]. The researcher had made a chemical analysis and concluded that brown rot fungi do not utilize lignin to an appreciable extent [77,80]. The main role of fungi on lignin is the demethylationof aryl methoxy groups [81]. Halder and Trojanowsk reported that fungi could metabolize lignin at an extent rate. Which had shown that isolated lignin was decomposed carbon dioxide only at a limited total in liquid culture.

Litter decomposing fungi

Fungi that are populated on soil litter, particularly *litter degrading fungus*, comprise basidiomycetes and ascomycetes on the upper surface of the soil and the surface ofgrasslands, and the humus layer of forests. Generally, the decomposition of litter is brought about by the combined activity with the help of bacterial, fungal, and animal populations, litter decomposing fungi had able to produce lignocellulolytic enzymes [82]. *Basidiomycetous litter*-decomposer is in the class of agarics, but it also belongs to basidiomycetes for example pores and boletes. Furthermore, many macroscopic fruiting bodies form ascomycetes. This fungus is considered in a broader sense. The lignocellulosiccomplex in specific lignin that pounces by the number of enzymes by laccase and manganese peroxide. Litter decomposing fungi could degrade lignin and cellulose which also could produce hydrolytic and oxidative enzymes. some of them are protease, cellulose, and phenoloxidase [83]. Which releases nitrogen during the degradation of leaf litter. As such, it is clear that the crash of this fungal group is exceptionally important in forestsand grads, and the ecosystem. Litter is often populated by the fungus during their accumulation ofrecalcitrant materials which is completely minimized. These fungi had an important role in recycling carbon in the soil.

***Ascomycota* fungi**

Ascomycota comprises the major varying phylum of the fungal group, considered for above 65% of the recently described fungi [52]. This group includes the existenceof both the state of reproduction such as anamorphic and teleomorph and constructing theircategory is especially difficult [84]. This species contains all lifestyles such as parasitic, symbiotic, or saprotrophic and even in morphologies such as unicellular, multicellular, and dimorphic fungi. The biological variety of fungal communities in wastewater treatment plants has been mostly ignored [85,89]. The investigation on the difference in anthropogenically polluted samples, such as wastewater treatment plants by *Ascomycota* fungi [85,86,87]. Their high conversion is supported by various advantages to environments, such as their ability to detoxify, which are extremely persistently in wastewater [88,89]. The capabilities of Ascomycota fungi in theobservation performed for the degradation of non-sterile wastewater using *Ascomycota,* after 7-15 days in unsterilized condition on the bioreactor, show their higher contribution tothe deterioration of

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pharmaceutically active components.

The use of *Ascomycota* fungi, in the active component degradation at a lower rate. The degradation efficiency of this species by some of the components of aromatic substances such as diverse xenobiotic components and chlorinated hydrocarbons [90,92,91,93.] They are distinguished by the collaboration of the intracellular enzymatic system carried by CYP, by secreting some enzymes such as manganese,and laccase which involves in the degradation of drug metabolites [94,95.]

The deterioration of nonsteroid anti-inflammatory drugs, such as diclofenac has been used byAscomycota fungi to catalyze the diclofenac which transformed to 4-hydroxydiclofenac 90%. The deterioration of antibiotics such as fluoroquinolones and quinolones is done by Ascomycota. A preparatory observation was carried out by [96.] The samplesare isolated from artificially contaminated soil with antibiotic ciprofloxacin with the strains of penicillin notatum, aspergillus fumigatus, penicillin frequent and, the researcher had reported the degradation rate is very low, even though, the metabolites were not observed.

Although *Ascomycetes* fungi could degrade a more number of components, this complexity and variability of pharmaceutically active components require another method to increase the degradation rates. The work of native fungi should be widespread in the use of allochthonous microbes for bioremediation purposes. In the current year, the use of fungal species autochthonous group belonging to Ascomycota has been used for industrial purposes for increasing the deterioration of several pollutants [97.]

Mucoromycotina fungi

Mucoromycotina incertae sedis considered a heterogeneous group of fungi, there is adiscussion that it is monophyly or Zygomycota, but this fungal characteristic is like a zygospore in the sexual phase and aplanospores in its asexual phase [98.] Among all the lifestyles this fungus can act as saprophytes, mutualists, and pathogens, which comes under the member of Mucorales and Zygomycota, it is characterized by saprobes or facultative parasites in nature. Thus, they mean emulating mammal drug metabolism and manufacturing metabolites of process interest [54.] The fungus had a great ability to transform the components which were studied on a small scale, some of the components such as diuretic furosemide [99,] anti-inflammatory meloxicam [100], antibiotics, pro hormonal adrenosterone [101]. The anticoagulant and the antidepressant mirtazapine [102,] which has been verified by spectra of pharmaceutically active compounds by cunninghamella elegant strain. The biotransformation of pharmaceutically active components by cunninghamella elegant, under the condition of two phases of reaction, under the phase 1 condition where reduction, hydrolysis, and oxidation, which converted into oxidized, reduced, and hydrolyzed components. These reactions are highly regioselective and stereoselective. The other phase of reactions is a rare condition. The potential of this class of these fungi for the separation of several factors, the increased level of this condition has not yet been developed, so the competition capability against other microorganisms remains still unknown.

Trametes Versicolor

The fungus *Trametes Versicolor* is a filamentous species of white-rot fungi that come under the family of Polyporaceae. It is an astrict aerobic fungus frequently found on stumps, tree trunks, and branches. The fungus mostly occurs in certain zones of Europe, Asia, and North America. A common shelf fungus in the northern hemisphere. Its role is to degrade wood andit is a type of tree parasite. Numerous names have been used in the composition such as *Agaricus Versicolor, Boletus Versicolor, Polyporous Versicolor*, and so on, more than 100 strains of *Trametes Versicolor* are known [103.] The morphology of this fungus is used in industrial applications. These strains had capable of secreting many enzymes like lignin peroxidase, manganese peroxidase, laccase, and cytochrome P450 were secreted at contrasting proportions based on the composition of the medium [104,105.] The pharmaceutical product like anti-inflammatory drugs are nonsteroidal agents that are used enormously as non-prescription drugs, and the remainder of these composite have beendetermined everywhere in wastewater treatment plants, which are released into an aquatic environment, [106,107.] In a conclusion, they have found the degradation of pharmaceuticals by a fungal transformation. For the degradation of anti-inflammatory drugs that as ibuprofen, the process of degradation is screened using white-rot fungi such as *TrametesVersicolor, Ganoderma lucidum*, *irpex lacteus, and phanerochaete chrysosporium* for the separation of ibuprofen, it has concluded that the degradation by Trametes Versicolor can degrade the contamination by a very fast rate when compared to other species of white-rot fungi. other anti-inflammatory drugs such as fenoprofen, indomethacin, and propyphenazone, this component are degraded by cultures of Trametes Versicolor, they observed complete degradation of fenoprofen indomethacin and nearly 75% of propyphenazone are degraded. Thesum up, the anti-inflammatory drugs studied are degraded at a higher rate by this fungus, finally, this degradation leads the components to decrease their toxicity, and the materials are completely mineralized.

According to Tran et.al, 2010, research work on the degradation of the drug Gemfibrozil (lipid regulation) which included familiar drug groups such as fibrates, the studies had been investigated the degradation of gemfibrozil by T. *Versicolor* activity and its LAC. The scientists acquired a result of degrading capacity of *T. Versicolor* above 75% within incubation of a week with the whole fungus. By further inspection, less than 35% was degraded by using crude and mercantile LAC, and they found that only intracellular enzymes target the

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gemfibrozil degradation by oxidation. By Garcia-Garcia et.al.2011, research work on the deterioration of certain antibiotics known as sulphonamides using a whole-cell fungal system. It was found that the deterioration of Sulfamethazine by *T. Versicolor* pellets in a medium, It was found that entire sulphonamide degraded in 20 hours. Even other antibiotics such as desulphonated, and formylated are degraded by an enzymatic system produced by *T. Versicolor*. By Marco-Urrea et.al. (2010d), degradation of therapeutic agent Beta-blockers, which is usedto treat cardiac arrhythmias, cardioprotection after myocardial infarction, and hypertension. where propranolol, a successfully developed beta-blocker, and atenolol are commercially used beta-blocker for cardiovascular disease. The most commonly used drugs were discharged into the aquatic environment, so they selected to degrade such drugs by biological Fenton like a system which is resolved by *T. Versicolor* based on the degradation ofcontamination. The initial concentration is 10 mg L^-1, and the deterioration rate is achieved above 80% only by 6 hours of incubation with propanol and atenolol. Estrogen is another kind of therapeutic agent. Which deteriorated by the means of the enzymatic method by some fungal species such as P. chrysosporium and *T. Versicolor* the degradation rate is above 80%. Extending the treatment for 8 hours the entire estrogen has been removed [109,110,] common results are found by [111,131] with the enzyme manganese peroxidase with *P. sordida* and Lactose enzyme with *T. Versicolor* the deterioration take is at a faster rate, which takes only 2hours for degradation of estrogens.

Phanerochaete chrysosporium

Phanerochaete chrysosporium is a type of white rot fungi. It can degrade the aromatic polymer lignin. The extracellular enzymes released by *P. chrysosporium* could degrade complex structural lignin into components that can be utilized for its mechanism. So, seeking a way of utilizing *P. chrysosporium* in the biodegradation of a reverse range of pollutants. Which belongs to the member of basidiomycetes. The removal of pharmaceutically active components by the fungal treatment which is performed under an in-vitro condition, under a controlled condition of PH and Temperature, the experimental degradation is started by milligram per liter on wastewater treatment plant effluents. A few works were performed in an unsterilized condition with many contaminations and the microorganism even present but the efficiency of removal capacity is hindered by fungus. Zhang and Geiben 2012, have reported the degradation of Carbamazepine is above % under a none arterial condition, by utilizing *P. chrysosporium* in immobilized form while treating.

By Cruz-Morato et.al., 2013, reported the removal of 8 pharmaceutical activecomponents out of 10 components that are screened under the unsterile condition in that they had obtained by the utilization of the fungi in the wastewater treatment. Under a batch reactorcondition, it is employed the removal of pharmaceutical components from wastewater by fungal treatment. To Rodarte-Morales et.al., 2011, the deterioration of diclofenac, NPX(Naproxen sodium), and IBP (Ibuprofen and paracetamol) in a concentration of 1 mg L^{-1} degraded by *P. chrysosporium* in a fed-batch reactor with proper conditions such as desired temperature, optimum pH and sufficient oxygen supply for one day. Remove triclosan under batch bed packed reactor by using immobilized laccase and *P. chrysosporium*. Li et.al., 2015, reported that the target components such as Naproxen and carbamazepine, these components are dissolved by methanol deionized water, which is prepared into 1.0g L^{-1} stock solution is incubated for 4°c along with *P. chrysosporium*, the efficiency of deterioration has shown for one week, which is 34% efficiency of carbamazepineand 86% efficiency of naproxen under an unsterile condition. By the immobilized system, the removal efficiency for a week was around 62% for carbamazepine and 90% for naproxen.

Table 1: Rate of pharmaceutical drug degradation using fungus

Drug Category	Drug	Fungus	Treatment	Initial Concentration	Removal Rate	Reference
Anti inflammatory	Diclofenac	*P. sordida*	Mycelium Incubation in Flask Shaked at 150 rpm and30•C	30 mg L^{-1}	Completely disappeared after 4 days.	[128]
	Fenoprofen	*T. Versicolor*	Incubation at 30•C in shaken condition for 48 hours	10 ug L^{-1}	Completely disappeared within 48 hours	[108]
	Ibuprofen	*B. adusta*	Erlenmeyer'sa flask containing defined and contamination were statically incubated at 30• C for 2weeks	1 mg L^{-1}	Total degradation in 1 week	[114]
Antibiotics	Ciprofloxacin	*T. viride*	Incubation of mycelium for 16 days	300 uM	31% had been transformed into the product	[132]

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	Enrofloxacin	*G. striatum*	Mycelia suspended in a defined liquid medium with contamination were Shakedat 150pm during 6 weeks	10 mg L^{-1}	Production of 27.3%CO_2 from [C] enrofloxacin	[133]
	Erythromycin	*P.chrysosporium*	Inoculation of granular bioplastic formulation	10 ug mL^{-1}	98 % after 30 days	[134]
	Norfloxacin	*P. guepini*	Incubation of mycelium for 18 days	313 uM	68.9%removed after 18 days	[132]
	Sarafloxacin	*M.ramannianus*	Cultures grown in sucrose peptone broth were closed with sarafloxacin	260 uM	59 % of the starting material remained.	[132]
	Sulfamethoxazole	*P.chryosorium*	Inoculation of granular bioplastic formulation Entrapping propagules of *P.chrysosporium* in wastewater	10 ug mL^{-1}	98%degraded after 30 days	[134]
Anti hypertensive	Atenolol	T. Versicolor	Degradation of contaminant by induction of oxidizing agents in T. *Versicolor* via quinone redoxcycling	10 mg L^{-1}	80% reached after 6 hours of incubation.	[90]
	Clofibric acid	*I.lacteus*	Cultures wereincubated in serum bottles Shaked at 135	10 mg L^{-1}	Only at low degradation	[90]

Zhang et al., 2019, performed a deterioration of sulfadiazine by *P. chrysosporium*, the experiments were performed by taking 2.5g of *P. chrysosporium* pellets and metabolic solution for 15ml with fresh medium for 5ml along with sulfadiazine. The estimation of the degradation efficiency is found to be 90% of degradation of sulfadiazine under a condition of 30°C. [115,129,130]

Whole-cell fungal treatment

These varieties of fungi are used for the treatment of pharmaceutical effluents with theconstruction and betterment of bioreactors along with the help of wastewater from industrial and hospital effluents. A whole-cell of *T. Versicolor* a *Basidiomycota* fungus is executing several new techniques of pharma effluent treatment as per a review of researchers [112,113,120,127,124,126.] Various bioreactors such as fluidized bed, batch, and membrane reactor are used for the removal of pharma effluents under sterile as well as unsterile conditions with the help of T. Versicolor and with the collaboration of laccase and CYPs. The mixture of contaminants from industrial water makes it difficult to degrade all toxic substances in the reactor [121,68,125.] Degradability rate of the experiment results in 70 % - 100 %. It is also necessaryfor the organism to achieve consistent COD and toxic or destructive reducibility, along with that there is another parameter of fungi is to coexist with an autochthonous organism present in the reactor. In some cases, the toxic reducibility is achieved sooner but there is not anyother comparison of CODs reduction efficiency with conventional treatment and then some other fungal and bacterial populations in the unsterilized condition of the reactor lead to the funguswhich we inoculated were displaced [120.]

The fungus *P. ostreatus* which is another kind of *Basidiomycota* is also used for bioremediation of pharma effluents. For example, in the diverse oxidative process of *P. ostreatus* along with a nanoparticle (gamma) r – Fe2O3 the degradation of bisphenol A removes 32 % greater while combine with biotransformation and Fenton-like reaction of oxidation [122,119.] For evaluating the metabolic products, biotransformation of liquid culture of carbamazepine is compared with lignocellulosic substance in solid-state fermentation. The metabolic products are differing in both case results, it indicates the formation of 2 and 24 metabolites in submerged and solid-state fermentation [118,123.] Environmental conditions are also playing a vital role in pharma effluent degradation. Comparability was made between the solid-state culture of *Pycnoporus sp., T. Versicolor, and Hymenochaete* spritebyeliminating (Beta) B – oestradiol and optimizing enzyme to addingcitric acid and lignocellulosic biomass. Improvement is happening at different levels of laccase secretion by adding these substances and eliminating up to 80 % [117.] The negative impact in the environmental application of this type of inductor is linked to degradation because for instance formation of dark spots formation.

All the fungal mechanism that takes part is the main enhancement of whole-cell fungal treatment.For example, to compare the enzymatic extract of Phoma sp., whole-cell fungal treatment is much more effective because it involves its whole mechanism to eliminate effluents like

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diclofenacand carbamazepine [116]. The major disadvantage is the filamentous growth of fungi leads to clogging, fouling, and biomass separation.

BACTERIA AS AN AGENT FOR THE REMOVAL OF PHARMACEUTICAL CONTAMINANTS

The ecological diversity of microbial species occupies the sphere is assessed to have more thanone trillion species [135]. We know that bacteria are the most lavish microorganism and the aged life existing on the globe. Bacteria living in the human body are millions in the count. [136,137]. Bacterial species inhabited an ascendant position on the earth, due to their various metabolic proportions, assist the metabolic pattern that is needed for all life on the planet. Bacteria impact all research-based regulation counting in fields such as biology, cell biology, climatology, alternative energy production, and its role in bioremediation [138]. As an outcome of this feature, the biotechnological perspective of bacteria is nearly inexhaustible in all zones of science.

Technologies that utilize activated, granular, aerobic, etc. have been victorious in the care of domestic wastewater [139]. A work evaluated the dynamics of the bacterialsection in the detachment of pharmaceuticals such as alprenolol, bisoprolol, metoprolol, propranolol, venlafaxine, salbutamol, fluoxetine by an anaerobic sludge membrane reactor found a diverse bacterial circle, the most generous phyla being proteobacteria, *Bacteroidetes* and *Actinobacteria* as well as some bacterial groups such as *Acidobacteria, Chlamydiae, Chloroflexi, Cyanobacteria, Epsilonproteobacteria, Firmicutes, Gemmatimonadetes, Tenericutes and verrucomicrobia* [140]. Another study had shown that estimated the detached efficiency of pharmaceuticals by a bacterial efficiency is higher, the bacterial communities and physiological process shows remarkable proportions for degrading pharmaceutical contaminants. Further, we can see individual bacterial efficiency in the degradation of pharmaceutical contaminants.

Pseudomonas species

Pseudomonas is a genus of gram-positive, belongs to gammaproteobacteria, which come under the family of *pseudomonas* and have more than 191 validly described species. Their ease of culture invitro and accessibility of the enlarged numeral of the pseudomonad strain genome sequence. The exiguous extremity of the genus can process chemical pollutantsin the habitat and as a result, can be used for bioremediation. some pseudomonas species demonstrated acceptable use as bioremediation agents include. The species *P. alcaligenes*, which can degrade polycyclic aromatic hydrocarbons, *P. veronii*, which has been shown to degrade aromatic organic compounds, *P. putida* used to degrade organic solvents, and so on. An antibiotic-degrading microorganism was explored and secluded from the activated sludge,and their degradation capabilities were evaluated.

According to Lin et al, two strains of cefalexin-degrading bacteria CE21 and CE22 were isolated and it is examined that it comes under *Pseudomonas* species. In the collected activatedsludge, strain CE22 could degrade over 90% when compared to CE21 its efficiency is only 46.7% of cefalexin after the incubation duration of 24 hours. other than cefalexin, the strains CE21, and CE22 we're able to degrade caffeine, salicylic acid, and chloramphenicol, Furthermore, the CE21 strain had capable of degrading sulfamethoxazole and naproxen [141]. According to Bram Pauwels et.al, The species of *pseudomonas* involved in the 17alpha - ethinylestradiol metabolism, which is the energetic mix of the contraceptive pill, is a recalcitrant estrogen, which is encountered in wastewater treatment plants which causes feminization of aquatic species, they aimed to study microorganisms that could degrade ethinylestradiol and Oestradiol, they had concluded by an experiment the pseudomonas aeruginosa (gram) their degradation rate is nearly 99%, pharmaceutical active substances effective by bacterial species but still is not up to the rate.

Bacillus thuringiensis

Bacillus thuringiensis is a gram-positive, soil-dwelling bacterium, repeatedly used as an abiotic defoliant, also takes place needless to say in the gut of caterpillars of various types of moths and butterflies, in aquatic environments, animal feces, and grain storage facilities. Non-steroidal anti-inflammatory drugs enter the environment as a consequence of pharmaceutical industry activity and the improper disposal of unused or expired drugs, squandering gives rise to hospitals and stock-raising farms [16]. In current senility, an enlarging consumption of the above-the-counter medicines such as ibuprofen, naproxen, paracetamol, ketoprofen, diclofenac, and acetylsalicylate has been observed [17,18]. *Bacillus thuringiensis* used as an agent for degrading above mentioned drugs.

According to Marchlewick et.al, they had isolated a strain from the soil of the chemical factory "organic -Azot" in Jaworzno, Poland. Based on the gene sequencing analysis they had identified the strain Bacillus thuringiensis and examined whether it could degrade ibuprofen and naproxen, buta sufficient amount of carbon source is not enough. In the presence of a carbon source (i.e., Carbon), this strain had a le degrade ibuprofen and naproxen at greater efficiency. This strain efficiency of degradation is determined within 40days of their examination. The acquired outcome proposes that *Bacillus thuringiensis* materialized to be a strong and practical device in the bioremediation of non-steroidal anti-inflammatory drugs-contaminated environment [142].

According to Marchlewicz et.al, Ibuprofen is one of the determined frequently detected pollutants in the surrounding, especially dumped in landfill sites and wastewater. Corruption with pharmaceuticals is often gone by the presence of additional components which influencetheir degradation. Their work is described by a degrading pathway of ibuprofen by Bacillus thuringiensis, which is described in the enzymatic process. They had experimented that *B. thuringiensis* could degrade

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ibuprofen with the presence of other components such as phenol,benzoate, and chlorophenol [143]. This strain could degrade only certain pharmaceutical active components, but the efficiency is still at a decreased rate.

Bacillus subtilis strain

Bacillus species are a member of phylum firmicutes. It had the property of existing as obligate aerobic. This bacillus species generate certain enzymes which are used in various application, the enzyme activity in deterioration of pharmaceuticals active components, the deterioration of pharmaceutically active components in secondary discharge by bacillus subtilis, and by using beta-lactamase which is developed by response surface methodology design, with an initial concentration is (1-6mg L^-1) are taken with an incubation period of 2 weeks. The result has recovered by the researcher from 90%. Under a variable independent significant parameter, the deterioration rate is 95%, which was compared with other microbes such as E.coli and S.aureus against the amoxicillin and cephalexin, the efficiency of bacillus subtilis in the degradation is high[144].

Adel and Gheethi, 2014 made an investigation of the potential enzymes in the deteriorationof pharmaceutically active components (beta-lactam antibiotics) in sewage discharge. Thefunction of bacillus strain 1556WTNC in the production of beta-lactamase. They have selected four types of beta-lactam antibiotics such as amoxicillin, ampicillin, cephalexin, and cefuroxime. The enzymatic deterioration is performed they found a maximum degradation rate under the incubation for 12 days at 35°C with a pH of 6.5, for amoxicillin that rate is 25%with the initial concentration at 1 my mL^-1, then for ampicillin 16% at 0.8 my mL^-1, cephalexin is 22% at 1mg mL^-1, they concluded that bacillus subtilis 1556WTNC is suitablefor the deterioration of pharmaceutical effluents from the processed sewage effluents and higher quality of treating secondary effluents [144,145].

Adel et Al., 2015., made investigated the degradation of cephalexin antibiotics using strain, this effluent contains many toxins, which are highly toxic to humans and the surrounding. They were treated by many technologies but the result was found to be the release of products, so they aimed to investigate the capacity of bacillus species in the degradation of effluents of cephalexin. The results are found to be 26% at 10 mg mL^-1. Theyconcluded that the bacillus strain is the best alternative for the removal of certain antibiotics from pharmaceutical effluents [146].

PROSPECT, BARRIER, AND RESTRICTION OF MICROBIAL USE IN PHARMA DEGRADATION

The work of the providence of pharmaceutically active components in the surrounding is unmoving matter. Pharmaceutical components are known to be an uncooperative part, where the wastewater treatment plants decline to remove them efficiently [147]. The attentiveness of these substances is increasing around the world in the marine ecosystem. The expression of biopharmaceutical mention to the drug produced other than the extraction from a natural source. Due to such a case, only a few studies had been reported on the degradation of pharmaceutical components. Thus, the environmental significance of these components is not clear. However, the pharmaceutical components are called prions, which are very stable in an environment that causes diseases in animals [148,149]. The potential of pharmaceutical components, when exposed to the environment, causes several eco toxicities to health problems for humans, so a cost-effective and more effective method is needed for the removal of these components from the surrounding [150,151,152]. The toxic effect on the surrounding depends on the pollutants by pharmaceutical active components.

It is accepted that antibiotic resistance genes are generated by certain bacterial species by exposure to antibiotics. With the presence of such active components in wastewater discharge and the marine environment. So, the development of bioremediation is suitable for removing such components by using microbial species. The bioremediation by white-rot fungi carriedby their oxidative enzymes is a suitable alternative for wastewater treatment technologies,where the degradation efficiency is found to be high in the removal of effluents. Due to the excess production of pharmaceutical components, its accumulation on sewage sludge is at a higher concentration. The prescription for such active components does not exist[153]. So, the prescription is needed for developing the address for the safe content of this component in biosolids. It is reported that white-rot fungi had efficiency for removing pharmaceutical components from sewage sludge, mostly from hospital wastewater treatment plants.

The molecules derived from the parent components by structural changes may have anecological relevance. The presence of such partially degraded components is reported after thewastewater treatment practices. It is known that transformed components are considered to be less toxic even if they might be very toxic when compared to parent components which are naturally derived. The recovered components are not reported after the structural transformation, only reported that the components are removed. So, special care must be taken for effective treatment practices, by any treatment methods. Up to date, most of the procedures for the removal of active components by bacterial and fungal treatment under sterilized conditions are controlled by pH and temperature. The spiked concentration of components has been used with proper conditions and the effluents which are to be treated. The results of these study are revealed that the concentration of components is decreased fromthe range of milligrams to nanograms.

The additional concern in the fungal treatment is based on the scale-up considerations and designaspect of the reactor. Various reactor consideration has been taken for the rapid degradation of pharmaceutical components by fungi. Detailed work on determining the parameters is made for optimal temperature, pH, and dissolved concentration of

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oxygen for an effective degradation. However, for the waste of pharmaceutical manufacturers or industrial sewage, the use of bacterial and fungal treatment could be practical, and the attentiveness of the pharmaceutical components in the influent is high, and the capacity is comparatively lower when compared tothe influent of the wastewater treatment plants.

CONCLUSION

Researchers mainly focus on the biological process to treat the cases because, it is environment-friendly, cost-effective, and energy-saving. Naturally, some microorganisms have the potential to degrade high molecular weight substances to low molecular substances, withoutharming nature. The major part of pharma pollution is a lignocellulosic waste. This waste contains the complex composition of lignin, cellulose, and hemicellulose. Ligninolytic enzymes such as laccase, lignin peroxidase (LP), manganese peroxidase (MnP), and versatile peroxidase (VP) can degrade lignocellulosic waste. These enzymes can penetrateinside of structural unit on lignocellulosic waste material. Most unused pharmaceutical products are disposed o f environment. If there is any possible to reuse the products like donating them to poor nations or producing products in limited amounts.

Enzymes were identified over a century, but we have few strains of microbes to degrade pollution. The main drawback of enzymatic remediation is a relatively slow process. Research work with the enzyme going mainly under laboratory-scale level only. We may use mutualism microorganisms (different types of microorganisms work together without harmingthemselves) as a combination to get a better result. There is an alternative way to degrade pollution.By genetics, some specific degradative genes are artificially inserted into the microorganisms to produce strains against the pollutant. Apart from these some advanced oxidation processes like ozonation, solar photocatalysis, ultrasonic irradiation, and Fenton reactions notably increasethe biodegradability of pharma products.

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