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Filamentous fungi for pharmaceutical compounds degradation in the environment: A sustainable approach

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ABSTRACT

Pharmaceutical compounds play an important role in enhancing the quality of human life. They substantially increase the life expectancy of humans and the well-being of livestock. The expansion in the global human population has increased the usage of pharmaceuticals in an enormous way. This has led to the emergence of pharmaceutical compounds as environmental pollutants because these components are continuously released to various water sources and terrestrial ecosystems. The pharmaceutical components are released during their synthesis, as waste from human and veterinary healthcare sectors, and dumping of drugs that are not used. Pharmaceutical components are known to persist in their potential even at lower concentrations and can create serious issues for ecosystems, especially aquatic systems. Various efforts are being made to remove or reduce the toxicity of pharmaceutical components in aquatic systems.

Bioremediation using fungi is one of the most secure and sustainable ways of decontaminating polluted environments. With their strong morphology and diverse metabolic abilities, Fungi employ different methods including fungal enzymes to clear pollutants. Studies have proven that fungi and fungal enzymes can transform these pharmaceutical compounds into less toxic components. This review highlights the role of fungi in the bioremediation of pharmaceutical compounds.

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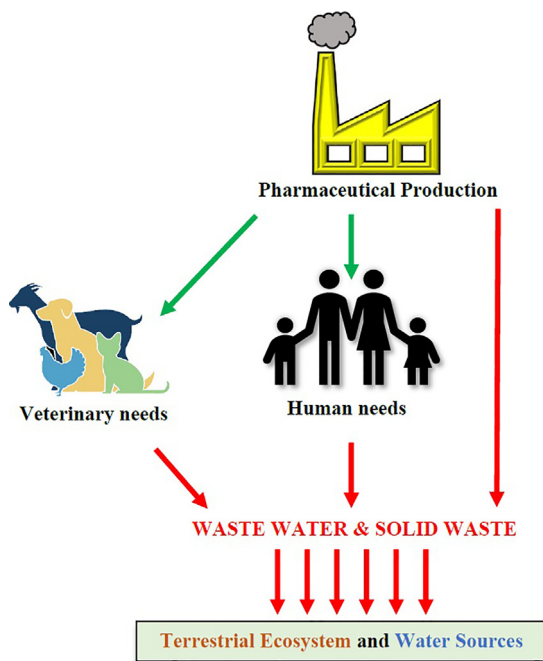


Fig. 1. Release of pharmaceutical components to the environment.

1. Introduction

Nature is rich in pharmacologically active plant, fungal, and animal chemical substances. These compounds are produced by the organisms mainly for protection from predators. Since ancient times, humans have been using these substances, especially from plants to relieve pain, heal wounds, and treat various illnesses (Jones, 2011).

Pharmaceutical compounds are chemical substances that are used for the treatment, prevention, or diagnosis of diseases. They play a significant role in increasing the life expectancy of humans (Olicón-Hernández et al., 2017). These compounds contain active ingredients of natural or synthetic origin with various therapeutic potentials such as antibiotics, analgesics, antidiabetics, antihypertensives, anticancer, immunosuppressants, and many more (Afonso-Olivares et al., 2013). The worldwide pharmaceuticals market is projected to reach approximately 2135 billion dollars in the year 2026 (Report Linker, 2022). Along with the expansion in population, the usage of pharmaceutical compounds has also increased simultaneously. Its implication in contemporary life cannot be underrated; on the other hand, their usage and disposal create enormous environmental pollution.

In the ecosystem, particularly in water sources, emerging pollutants with a pharmaceutical origin have been found (Vasilachi et al., 2021). Pharmaceutical components have risen as rapidly dispersed environmental pollutants which are hazardous to some species, cause hormonal imbalance, reproductive failures in fish, and the development of drug-resistant pathogens. Awareness about the effects of poor disposal of pharmaceuticals and chemicals on human health, animal health, and the environment are getting well-recognized these days. The different ways by which pharmaceutical components are released into the environment are depicted in Fig. 1. By implementing rules and regulations and with proper pharmaceutical waste disposal practices the pollution caused by pharmaceutical compounds can be reduced.

Most of the organic chemicals found in the environment are known to be broken down by fungi.

Fungus is known to play a role in the bioremediation of toxic compounds. Diverse species, including filamentous fungi (*Fusarium*, *Aspergillus*), and basidiomycetes are widely utilized for bioremediation purposes (Ghosh et al., 2023). The fungi can be easily cultured as per our needs and their potential to degrade a wide range of pollutants to non-toxic or less toxic compounds made them suitable for bioremediation (Yang and Peng, 2022). The enzymes produced by lignin-degrading fungi are known to degrade antibiotic and pharmaceutical pollutants (Akerman-Sanchez and Rojas-Jimenez, 2021). In this article, the authors have reviewed

- (i) the types of pharmaceutical compounds which may result in environmental pollution,
- (ii) the role of fungi and fungal enzymes in the degradation of these pharmaceutical compounds,
- (iii) how engineered fungi enhance the bioremediation of pharmaceutical compounds, and finally
- (iv) challenges and prospects in using fungi for bioremediation of pharmaceutical compounds.

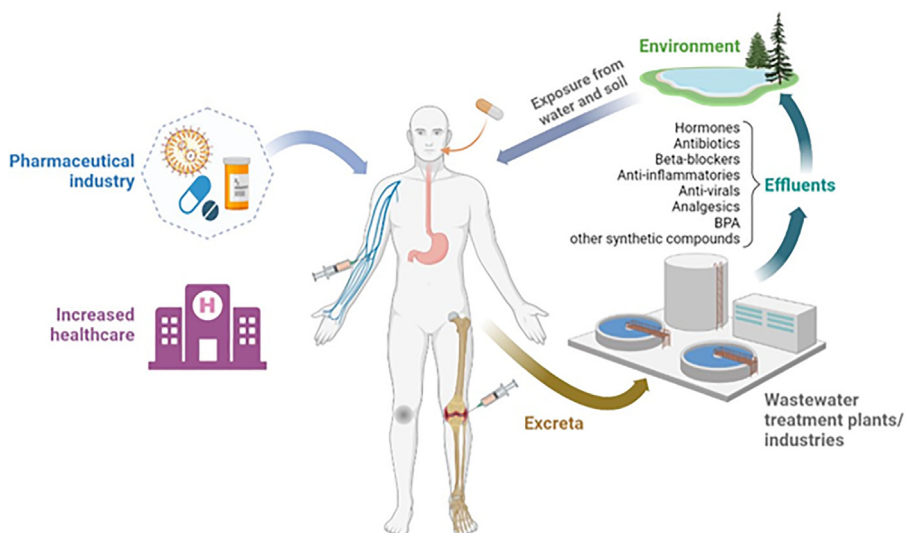


Fig. 2. Different categories of pharmaceutical compounds and their entry route in the water cycle and human body.

2. Pharmaceutical compounds in the environment

Intensification in medical care especially during the pandemic period has led to a drastic increase in the presence of pharmaceutically active compounds in the environment. These compounds have long been considered environmental pollutants and have presented themselves in the form of antivirals, antibiotics, antiparasitic, antiprotozoals, β -blockers, anaesthetics, non-steroidal anti-inflammatory and anticancer drugs, X-ray contrast media, and glucocorticoids, among many others (Lian et al., 2017). The major source of entry of these compounds is through the water cycle as they are not fully consumed in the human body and are excreted out resulting in their emergence as an aquatic contaminant (Fig. 2).

Studies have proved that analgesics and NSAIDs, which are known to cause ulcers, and problems in gastro intestine and kidney, are detected in water sources (Świacka et al., 2021).

In general, the literature reports that several pharmaceutical compounds can be detected in freshwater and wastewater streams derived from hospitals, urban areas, treatment plant effluents, and pharmaceutical industries (Chander et al. 2016, Perini et al. 2018). For instance, Al Aukidy et al. (2012) reported the occurrence of 22 pharmaceutical compounds in the effluents of wastewater treatment plants in Italy that included antibiotics sulfamethoxazole, clarithromycin, and azithromycin, etc. Among these, diclofenac (533–800 ng/L) and hydrochlorothiazide (520 ng/L) showed their presence in high concentrations followed by atenolol (264 ng/L) and sotalol (262 ng/L). The investigation highlighted that β -blockers, anti-inflammatories, antibiotics, analgesics, and antihypertensives were among the top five classes of pharmaceutical compounds detected in the effluents which showed a high environmental risk quotient ($RQ > 1$).

Rivera-Jaimes et al. (2018) have detected significantly high amounts of diclofenac, naproxen, and acetaminophen in water from wastewater treatment plants. Balakrishna et al. (2017) investigated the presence of personal care products and pharmaceutical compounds in Indian water bodies. They reported that carbamazepine (anti-psychoactive), trimethoprim and sulfamethoxazole (antibacterial), atenolol (antihypertensive), ibuprofen and acetaminophen (analgesics), triclocarban and triclosan (antimicrobials), and caffeine (stimulant) are the commonly occurring compounds in effluents from the wastewater treatment plant and pharmaceutical industry. The concentration of some of the above-mentioned compounds is 40 times higher in Indian water bodies than those observed in water bodies of other countries in Asia, Australia, Europe, and Africa. Several investigations have also shown very high concentrations of antivirals, especially during the pandemic period which persists to date in water bodies. Lopinavir (730 ng/L), Favipiravir (4231 ng/L), Ribavirin (7402 ng/L), and Remdesivir (319 ng/L), used for the manufacture of drugs during the COVID-19 pandemic have infiltrated domestic water sources and have been reported to show high ecotoxicity (Kuroda et al., 2021).

The occurrence of anticancer drugs in hospital wastewater effluents, surface water, activated sludge, groundwater and even drinking water is another emerging threat to the environment and human health. These drugs have been majorly classified as antimetabolites, cytotoxic antibiotics, alkylating agents, plant alkaloids, immunosuppressants, protein kinase inhibitors, endocrine therapy agents, and platinum complexes (Castellano-Hinojosa et al., 2023). There has also been evidence of the presence of these compounds in soil (Khan et al., 2022) where its half-life ranges anywhere from 30–360 days. In contrast, the half-life of anticancer drugs in water spans the range of 15–180 days. However, in sediments, the half-life of certain anticancer drugs can be as high as 135–1620 days (Azuma, 2018). A study in Japan showed that the sewage treatment plant effluent and, river waters and sediments were contaminated with bicalutamide (an anticancer

drug) in high concentrations (254 ng/L) which had serious negative implications on crustaceans, algae, rotifers, and fish (Azuma, 2018).

Apart from the threat posed to aquatic biota, the pharmaceutical compounds occurring in the drinking water and soil can enter the human body and accumulate there even when exposed to concentration at the ng/L level (Zhang et al., 2023). These compounds can cause mutagenic, carcinogenic, and reproductive disorders. In this regard, several studies provide conclusive evidence of the presence of endocrine-disrupting compounds (EDCs) in the environment. Several classes of EDCs have been identified that include hormones (17β -estradiol, estrones, estriol), pesticides, and plastic-derived compounds (bisphenol A, phthalates) (Pironti et al., 2021). To cite an example, testosterone, estrone, and estriol are some of the most frequently occurring hormones that are found in the freshwaters of African and European countries. In Africa, most of the hormones were detected in animal farms, and untreated domestic wastewater was discharged at 3,000–20,000 times higher concentrations than that in Europe (Olaturunji and Adekola, 2017). Celic et al. (2020) analyzed the risk posed by 13 different EDCs of which, bisphenol A (BPA) was found at the maximum concentration of 338 ng/L in Serbian surface, drinking, and wastewater. However, they reported higher RQ of estrogens E2 and E1 in general than BPA. Ismail et al. (2019) also reported the presence of testosterone hormone, caffeine, and BPA in estuaries of Malaysia with 17α -ethynylestradiol (EE2) (<0.30–7.67 ng/L) and 17β -estradiol (E2) (<5.28–31.43 ng/L) exhibiting high concentrations, second only to diclofenac (<0.47–79.89 ng/L).

It seems that there is substantial evidence to establish that antibiotics, β -blockers, and antivirals are the major threats to life on Earth as these compounds can facilitate the growth of resistant pathogens and viruses that could be the very reason for another pandemic. Antibiotics such as tetracyclines, sulfonamides, nitroimidazoles, fluoroquinolones, and quinolones are detected in water bodies throughout the world (Bilal et al., 2020). The presence of high concentrations of hormones in drinking water is another major concern, the consequences of which are clearly visible in the increase in reproductive disorders and early maturity in adolescents. Therefore, this issue needs to be tackled carefully and through economical routes for higher propagation of the scientifically woven package of practices to be adopted worldwide for the biotransformation of the said compounds.

3. Fungus in the biotransformation of pharmaceutical compounds

Fungi are known to adapt to harsh environmental conditions and they can accumulate many compounds which are xenobiotic in nature (Jiao and Lu, 2020; Braeuer et al., 2020). Due to their capacity to create a wide range of enzymes that can change chemical molecules, fungi are frequently used in the biotransformation of pharmaceutical substances. These enzymes can be employed to create new substances, alter already-existing substances, or break down undesirable substances. More often these fungal enzymes can convert pharmaceutical compounds to less toxic compounds. Fungi can produce a wide range of enzymes that catalyze a wide range of reactions and this is one of the major advantages of using them in biotransformation. As a result, the biotransformation procedure can be more flexible because different enzymes can be used to focus on different regions of the pharmaceutical compound.

The white rot fungus can decompose different pollutants with the help of its enzymes such as laccase, peroxidase, and cytochrome P450 (Park and Choi, 2020). Most of these enzymes can act on a wide range of substrates which make them suitable for the bioremediation of diverse class of pharmaceutical compounds (El-Gendi et al., 2021).

Fungi can be grown in bulk quantity which enables enormous production of enzymes required for biotransformation. Akerman-Sanchez and Rojas-Jimenez (2021) has summarized the major mechanisms used by fungi to bioremediate pharmaceutical substances. The morphology of hyphae is suitable for the absorption and immobilization of pharmaceutical compounds. The reactive oxygen species produced by fungi help in the oxidation of pharmaceutical compounds. Moreover, due to the low specificity of the extracellular and intracellular fungal enzymes, they can extensively degrade pharmaceutical compounds other than their normal substrates. Hence, bioremediation of pollutants using fungi is one of the effective, environment-friendly, and profitable strategies (Akhtar and Mannan, 2020). In this section, different types of fungi and fungal enzymes used in the biotransformation of pharmaceutical compounds were discussed.

3.1. Types of fungi involved in pharmaceutical degradation

Fungi are chemoheterotrophic organisms found in both terrestrial and aquatic habitats and the latest appraises from taxonomy confirm 19 important phyla in the fungal kingdom (Zeghal et al., 2021; Wijayawardene et al., 2020). Among the different phyla of fungi, *Ascomycota*, *Basidiomycota*, and *Zygomycota* are known to degrade various pharmaceutical compounds. *Basidiomycota* fungi are well known for maintaining the balance of the ecosystem by helping in the recycling of carbon and nitrogen from various sources (Theradimani and Ramamoorthy, 2022). The study by Dalecka et al. (2019) showed that a three-hour treatment of wastewater using *T. versicolor* eliminates diclofenac completely. The enzyme machinery of *Basidiomycota* is suitable to act on various substrates including pharmaceutical compounds (Mendonça Maciel et al., 2010; Olicón-Hernández et al., 2017). Complete elimination of a mixture of NSAIDs (celecoxib, diclofenac, ibuprofen) in 72 h was achieved by treating with a consortium of *Ganoderma applanatum* and *Laetiporus sulphureus* (Bankole et al., 2020).

The intra and extracellular enzymes of *Basidiomycota* species especially cytochrome P450 have a significant role in the biotransformation of pharmaceutical compounds. *Ascomycota* is yet another class of fungi that has the ability

for the biotransformation of pharmaceutical compounds. The various fungal strains used for the biotransformation of pharmaceutical compounds are summarized in Table 1. *Trametes versicolor* is an important species under Basidiomycota division. This strain is widely used for the biotransformation of various types of pharmaceutical and other chemical compounds. Jureczko et al. (2021) studied five different strains of white-rot fungi – *Trametes versicolor*, *Hypholoma fasciculare*, *Pleurotus ostreatus*, *Fomes fomentarius*, and *Phyllotopsis nidulans*, for its potential in degrading the anticancer drug vincristine. The results showed that after four days of treatment with *T. versicolor*, *H. fasciculare*, and *F. fomentarius* can significantly remove vincristine.

The data from various studies proved that the whole-cell fungal treatment is better than the cell-free treatment (using enzymes alone) for the biotransformation of pharmaceutical compounds. This can be related to the synergistic effect of various mechanisms for bioremediation adopted by fungal strain – bioabsorption and immobilization, the effect of ROS, and fungal enzymes (Hofmann and Schlosser, 2016).

3.2. Role of fungal enzymes in the biotransformation of pharmaceutical compounds

One of the most diverse groups of microorganisms is the fungus, which is important to nature as a decomposer, a mutualist, or a pathogen. Fungi employ several defense mechanisms to deal with a wide range of harmful substances, including pesticides and refractory polycyclic aromatic hydrocarbons (PAHs) (Olicón-Hernández et al., 2017). These tactics do not involve enzymatic processes like bio adsorption biomineralization (bio-precipitation), as well as biotransformation and biodegradation carried out by the enzyme systems (Harms et al., 2011). The cell wall composition, such as chitosan or chitin, mediates bio adsorption. Until this bio adsorption achieves equilibrium, bisphenol A, 17-ethinylestradiol, and triclosan elimination play a significant role in certain fungi, such as *Phoma* sp. UHH 5-1-03. Pharmaceuticals can be biotransformed by processes such as hydroxylation, oxidation, sulfoxidation, and dealkylation that have been seen in fungi. Since hydroxylation can lower the solubility of contaminants and hence limit their potential for bioaccumulation, hydroxylation can be thought of as a biotransformation method for bioremediation procedures.

The non-specific lignin-modifying enzymes such as laccases and peroxidases produced by white-rot fungi extracellularly can degrade a wide range of pharmaceutical compounds (Akerman-Sanchez and Rojas-Jimenez, 2021). Basidiomycota fungus employs extra- and intracellular oxidoreductases (laccases, peroxidases, CYPs, etc.) to change and break down the bonds of various substances like pharmaceuticals and aromatic compounds, mostly through extracellular routes (Schmid and Schmidt-Dannert, 2016). In this regard, various fungal intermediates have been studied for the biodegradation of pharmaceuticals in the white rot fungi *Phanerochaete chrysosporium*, *Phlebia ochraceofulva*, *Pycnoporus sanguineus*, *Pleurotus ostreatus*, and *T. versicolor* (Dí az Cruz et al., 2015). Fungi isolated from *Plantago lanceolata*, including *Aspergillus niger*, *Eurotium repens*, *Leptosphaerulina chartatum*, *A. nidulans*, *E. amstelodami*, *Cladosporium pseudocladosporioides*, *Penicillium chrysogenum*, *Bipolaris* sp., and *Epicoccum nigrum*, and their enzymes α -l-rhamnohydrolase, β -N-acetylhexosaminidase, and urease can decompose non-steroidal anti-inflammatory drugs, such as diclofenac, diflunisal, ibuprofen, mefenamic, and piroxicam *in vitro* (Gonda et al., 2016). Kang et al. (2023) have developed a fungal wheel reactor containing a microbial population high in *T. versicolor* for the removal of acetaminophen, bisphenol A, and carbamazepine from wastewater. A report showed that the effluents from wastewater treatment plants contain Bisphenol A, acetaminophen, carbamazepine, and sulfamethoxazole. Among these pollutants, bisphenol A and acetaminophen were completely removed by Lac enzyme treatment (Kang et al., 2021). *T. versicolor* is reported to remove the anticancer drug vincristine (Jureczko et al., 2021). The fungal consortium of *Cladosporium cladosporioides*, *Alternaria alternata*, and *Penicillium raistrickii* was found effective in removing carbamazepine, ketoprofen, and diclofenac from sewage water (Ledezma-Villanueva et al., 2022).

An investigation reported that the extracellular enzymes lignin peroxidase, manganese peroxidase, and laccase produced from two strains of fungi, *B. adusta* and *F. meliae*, were able to degrade 91%–93% of broad-spectrum xenobiotics such as diclofenac (Dhiman et al., 2022). Bond-cleavage and hydroxylation were found as the major mechanisms responsible for diclofenac disintegration. In another investigation, laccase-producing thermophilic *Chaetomium* sp. was shown to degrade 60% and 35% of the EDCs 4-tert-butylphenol and EE2 in two hours (Daâssi and Alharbi, 2023). An erythromycin-degrading strain *Aspergillus sydowii* W1 was used by Ren et al. (2023) where it was revealed that esterase and glucoside hydrolase were the major extracellular fungal enzymes that were involved in the biodegradation process. About 84% degradation of erythromycin was observed within seven days of treatment at optimal conditions (6.0 pH, 30 °C, 100 mg/L erythromycin).

3.3. Fungal genetic engineering for bioremediation

Fungal genetic engineering plays an important role to enhance bioremediation to alter the enzymatic action and binding affinities of target drugs and to advance novel technologies for fungal strain development. This needs the advancement of potent genome manipulation techniques to get fungi equipped to intermingle with many contaminants, decrease highly toxic decomposition end products, and create enhanced components that can be employed (Tahri et al., 2013). Also, the likelihood of constructing all the characteristics of fungi in one organism is a potential option, which is highly economical (Arun et al., 2023; Madhavan et al., 2023, 2017; Madhavan and Sukumaran, 2014).

Various types of research articles have been published on the application of genetic engineering for contaminants removal, one such example is within the expression of lignin-modifying enzymes, like fusion laccase of *P. eryngii* heterologously expressed in *S. cerevisiae*, which enhanced the activation, substrate binding, and action of the enzyme, by

Table 1
Fungal strains used for bioremediation of various pharmaceutical compounds.

Pharmaceutical compounds type	Examples	Fungi for bioremediation	References
Antibiotic	Azithromycin, Ciprofloxacin, Tetracycline, Cephalexin	<i>Trametes versicolor</i>	Badia-Fabregat et al. (2016)
	Ciprofloxacin and Ofloxacin		Cruz-Morató et al. (2014)
	Erythromycin		Cruz-Morató et al. (2013)
	Sulfamethoxazole		del Álamo et al. (2018)
	Sulfamethoxazole	<i>Bjerkandera</i> sp. R1, <i>Bjerkandera adusta</i> and <i>Phanerochaete chrysosporium</i>	Rodarte-Morales et al. (2011)
	Sulfamethoxazole	<i>Aspergillus niger</i>	Bodin et al. (2016)
β -Blockers	Clarithromycin	<i>Trichoderma harzianum</i> <i>Pleurotus ostreatus</i>	Buchicchio et al. (2016)
	Amoxicillin	<i>Trichoderma pubescens</i>	Cai et al. (2023)
	Metoprolol, Carazolol	<i>Trametes versicolor</i>	Badia-Fabregat et al. (2016)
Psychiatric drug	Metoprolol	<i>Aspergillus niger</i>	Bodin et al. (2016)
	Diazepam		Badia-Fabregat et al. (2016)
	Carbamazepine	<i>Trametes versicolor</i>	Tran et al. (2010)
	Diazepam	<i>Bjerkandera</i> sp. R1, <i>Bjerkandera adusta</i> and <i>Phanerochaete chrysosporium</i> <i>Phanerochaete chrysosporium</i>	Cruz-Morató et al. (2014) del Álamo et al. (2018) Rodarte-Morales et al. (2011) Rodarte-Morales et al. (2012)
Keratolytic agent	Salicylic acid	<i>Trametes versicolor</i>	Cruz-Morató et al. (2013)
Analgesic	Codeine, Acetaminophen		Cruz-Morató et al. (2013)
	Antipyrine	<i>Trametes versicolor</i>	del Álamo et al. (2018)
	Propyphenazone		Tran et al. (2010)
Anti-inflammatory	Acetaminophen	<i>Aspergillus niger</i>	Bodin et al. (2016)
	Ibuprofen, Ketoprofen		Cruz-Morató et al. (2013)
	Fenoprofen, Naproxen, Ketoprofen, Indomethacin	<i>Trametes versicolor</i>	Tran et al. (2010)
	Acetaminophen, Ibuprofen, Ketoprofen		Cruz-Morató et al. (2014)
	Sodium diclofenac		Marco-Urrea et al. (2010)
	Ibuprofen, Naproxen, and Diclofenac	<i>Bjerkandera</i> sp. R1, <i>Bjerkandera adusta</i> and <i>Phanerochaete chrysosporium</i>	Rodarte-Morales et al. (2011)
	Diclofenac and Naproxen	<i>Aspergillus niger</i>	Bodin et al. (2016)
	Ibuprofen, Diclofenac, and Naproxen	<i>Phanerochaete chrysosporium</i>	Rodarte-Morales et al. (2012)
	Diclofenac and Ketoprofen	<i>Pleurotus ostreatus</i>	Palli et al. (2017)
Antilipidemic	Sodium diclofenac	<i>Bjerkandera adusta</i> <i>Fomitopsis meliae</i>	Dhiman et al. (2022)
	Clofibrilic acid		Tran et al. (2010)
Lipid regulation	Clofibrilic acid	<i>Trametes versicolor</i>	del Álamo et al. (2018)
	Gemfibrozil	<i>Trametes versicolor</i>	Tran et al. (2010)
Endocrine disrupting chemicals	Bisphenol A, Nonylphenol, Parabens, Phthalates	<i>Trametes versicolor</i>	Pezzella et al. (2017)
Antihypertensive	Atenolol	<i>Trametes versicolor</i> <i>Pleurotus ostreatus</i>	del Álamo et al. (2018) Palli et al. (2017)

(continued on next page)

Table 1 (continued).

Pharmaceutical compounds type	Examples	Fungi for bioremediation	References
Diuretic	Hydrochlorothiazide	<i>Trametes versicolor</i>	del Álamo et al. (2018)
Histamine 2 blocker	Ranitidine	<i>Aspergillus niger</i>	Bodin et al. (2016)
Hormones	17 α -ethinylestradiol, 17 β -estradiol	<i>Trametes versicolor</i>	Blánquez and Guieysse (2008)
	17 α -ethinyl-estradiol, 17 β -estradiol, Estriol, Estrone	<i>Trametes versicolor</i> <i>Myceliophthora thermophila</i>	Becker et al. (2017)
Antidepressant	Citalopram, Fluoxetine	<i>Bjerkandera</i> sp. R1, <i>Bjerkandera adusta</i> and <i>Phanerochaete chrysosporium</i>	Rodarte-Morales et al. (2011)
Fragrance	-Galaxolide, Celestolide, Tonalide,	<i>Bjerkandera</i> sp. R1, <i>Bjerkandera adusta</i> and <i>Phanerochaete chrysosporium</i>	Rodarte-Morales et al. (2011)
		<i>Bjerkandera</i> sp. R1, <i>Bjerkandera adusta</i> and <i>Phanerochaete chrysosporium</i>	Rodarte-Morales et al. (2011)
Anti-epileptic	Carbamazepine	<i>Aspergillus niger</i>	Bodin et al. (2016)
		<i>Phanerochaete chrysosporium</i>	Rodarte-Morales et al. (2012)
		<i>Trichoderma harzianum</i> <i>Pleurotus ostreatus</i>	Buchicchio et al. (2016)

N- or/and C-terminal engineering. The synthesized enzyme had been evaluated in the removal of hydroxylated polychlorinated biphenyl, with elimination rates between 11 and 65%, depending on the congeners applied (Macellaro et al., 2014). In another study, the immobilization of the recombinant expression of laccases onto the cellular wall of the expression host signifies a novel technique, which permits quick growth of *S. cerevisiae* (Bleve et al., 2014). Yeast cell surface display of laccases has been successfully employed for the transformation of bisphenol A and sulfamethoxazole, with more than 70 and 40% as elimination rates, correspondingly; with an enhancement in the elimination efficacy in the presence of enzymatic inducers and more than 85% of recycle efficacy after several cycles (Chen et al., 2016). The efficient heterologous expression of laccases from the basidiomycete fungus *Pycnoporus cinnabarinus* in *Aspergillus oryzae* and *A. niger* by the introduction of *lacI* gene, to advance an industrial process without applying laccase inducers (Sigoillot et al., 2004). The developed strain also provides the benefit of having good potential for the remediation of PhACs (Corso and Maganha de Almeida, 2009; Lubertozzi and Keasling, 2009). The laccase gene from *Trametes sanguineus* has been also heterologously expressed in *Trichoderma viride*, a fungus that exhibited an improved ability for the elimination of bisphenol A than the native strain (Balcázar-López et al., 2016). Manganese peroxidase enzyme was also recombinantly produced in *Aspergillus* to enhance its efficacy as a bioremediation agent. *A. niger* was modified using a manganese peroxidase containing (*mnp1*) expression from *P. chrysosporium*, with *A. nidulans* constitutive promoter glyceraldehyde 3-phosphate dehydrogenase (*gpdA*) and transcriptional terminator from *A. awamori* to enhance PAH decomposition by the recombinant expression of this biocatalyst. The new genetically engineered strain can report degrading PAHs in large concentrations in comparison to other lignocellulose degrading and non-lignocellulose degrading fungi (Balcázar-López et al., 2016), opens the new vista aromatic compounds degradation by fungus.

Challenges and prospects in using fungi for the biodegradation of harmful pharmaceutical substances

Fungal metabolic pathways can utilize pharmaceutical compounds for their various requirements. Fungal bioremediation is one of the efficient and economically viable strategies for the removal and degradation of pharmaceutical compounds from polluted sites. The main challenge will be in identifying appropriate fungal strains for bioremediation purposes. Screening of polluted sites will help in identifying efficient fungal strains for bioremediation. For the successful application of fungal bioremediation, state-of-the-art techniques that give a thorough knowledge of the patterns of fungal functions, and persistence under stressful conditions are required. The biotechnological advancements in molecular biology, system biology, and bioinformatics can shed much light on the fungal bioremediation mechanisms. Different omics technologies can enhance the knowledge about enzymes and other proteins expressed by the fungi growing in polluted sites. More research must be done in developing fungal expression systems so that recombinant fungi exhibiting different types of efficient bioremediation mechanisms can be designed. A single fungal strain will not be adequate to remove different types of pharmaceutical compounds. To overcome this limitation, nowadays consortium of fungal strains is being used for better bioremediation. Novel fungal strains need to be isolated, that can work in a consortium so that a more significant number of pharmaceutical compounds can be removed or degraded. An interdisciplinary approach by implementing various advanced biotechnological techniques together will improve the bioremediation of pharmaceutical components from polluted sites using fungi. Research must be focused on utilizing cutting-edge gene editing tools such as CRISPR Cas9 system, ZFN, and TALEN in modifying fungal strains for better bioremediation.

4. Conclusion

Fungi belonging to *Basidiomycota*, and *Ascomycota* can eliminate and convert various pharmaceutical molecules at various rates, resulting in the production of various hydroxylated, conjugated, and oxidized compounds. So far, the data from various research showed that the potential of fungi in the bioremediation of pharmaceutical compounds has not been exploited to the fullest. For bioremediation of pharmaceutical compounds, there is still a higher incidence to use cell-whole white-rot fungi against non-lignin-modifying enzymes (p450 enzymes), and genetic manipulation techniques are employed in these systems to improve the secretion of extracellular lignin modifying enzymes. Nevertheless, it is essential to develop efficient fungal transformation and gene manipulation techniques for all fungi. However, this denotes a hindrance for many fungi which has the ability for bioremediation. In a way advancing, some research using fungus is united to a set of eco-toxicology tests and sex hormones research, the major alarm being to authenticate the implication of these technologies and to evaluate the destiny of the end-products generated predominantly conjugated compounds. Meanwhile, new geographical horizons must be explored to identify new potential fungal strains with better bioremediation activities.

CRedit authorship contribution statement

Arun K.B.: Data collection, Drafting the manuscript. **Aravind Madhavan:** Data collection, Drafting the manuscript. **Ayon Tarafdar:** Data collection, Drafting the manuscript. **Ranjna Sirohi:** Data collection. **Anoopkumar A.N.:** Data collection. **Laya Liz Kuriakose:** Data collection. **Mukesh Kumar Awasthi:** Data collection. **Parameswaran Binod:** Reviewing draft. **Sunita Varjani:** Reviewing draft. **Raveendran Sindhu:** Designing, Final drafting.

Declaration of competing interest

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

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