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Review

Microbial Cell Factories for the Management of Pharmaceutical Micropollutants

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ABSTRACT

Extensive use of pharmaceutical drugs and its disposal in soil and water reservoirs leads to serious environmental pollution. These pharmaceutical micropollutants are highly water soluble, low biodegradable and easily accumulated in the food chain. Thus, these micropollutants persist in the environment and may cause a serious threat to ecosystem. This review highlights the sources of pharmaceutical micropollutants and adverse effects on ecosystem. The pharmaceutical drugs such as anti-convulsive drugs, antidepressants and cytostatic drugs are more ecotoxic, hence need to remove them from contaminated environments. Further, review also insights the importance of microbial degradation in management of pharmaceutical pollutions.

Key words: Bioremediation, ecotoxicity, micro pollutants, bioaccumulation, Covid-19

INTRODUCTION

Increasing multidrug resistance in microorganisms and development of several diseases which leads to increasing drug usage. During COVID-19 situation, several antiviral drugs, steroids and painkillers are used which results into discharge of drugs in the environment (Nippes et al. 2021, Gwenzi et al. 2022). Environmentally acquired drug resistance in human pathogens has been observed. For example, Oseltamevir and Tamiflu developed Influenza A virus resistance in wild fowl reported previously (Fick et al. 2007, Singer et al. 2007, Kuroda et al. 2021). Domestic, industrial and hospital activities are responsible for discharge of several pharma micropollutants in the aquatic environment (Ribeiro et al. 2015). The existence of active ingredients of pharmaceuticals and personal care products (PCPs) in the environment are also detected (Brausch and Rand 2011, Montesdeoca et al. 2018). It is investigated that both steroidal and non-steroidal drugs are detected in water and soil environment (Ghlichloo and Gerriets 2021).

The drugs such as diclofenac, azithromycin, clarithromycin and erythromycin are considered as emerging contaminants in the environment (Ribeiro et al. 2015). The diclofenac has been detected in drinking water in range of 0.02 ng/L to 20.00 µg/L (Simazaki et al. 2015). It was also studied that diclofenac and its metabolites such as 42 -hydroxy-DCF and 5-hydroxy-DCF are found in wastewater (Bouju et al. 2016). Other contaminants mixture of non-steroidal anti-inflammatory drugs like diclofenac, ibuprofen, naproxen, and acetylsalicylic acid are considered as serious threat to the environment and human health (Cleuvers 2004). Therefore, management of such harmful contaminants is of prime importance. The techniques such as nanofiltration and reverse osmosis are suggested by several researchers for the treatment of contaminated water bodies (Radjenovic et al. 2008). Some conventional methods such as sewer, combustion, or land disposal are used for disposal of pharma products (Ivshina et al. 2006).

Recently, other processes like advanced oxidation and solar photodegradation are recommended for removal of diclofenac from surface water (Leónidas et al. 2005). Implementation of physicochemical methods for the removal of cytostatic compounds (ecotoxic) at the site of origin and utilization is difficult as compared to biological method (Bhattacharyya et al. 2022).

Impact of Pharmaceutical Micropollutants on Ecosystem

Pharmaceutical products are the primary concern in aquatic environment (Patel et al. 2019). They have many adverse effects on human embryo cells, fish, birds, algae and microorganisms (Bessa et al. 2017). Subinhibitory level of antibiotics showed effect on phenotype, genotype and signaling pathway (Andersson et al. 2014). The toxicity of ciprofloxacin is studied due to its occurrence in manure compost (Lan-jia Pan et al. 2017). Naproxen has been detected about 55 $\mu g\ L^{-1}$ in aquatic system (Marco et al. 2010). About 11 therapeutic drugs used for COVID-19 treatment were detected in aquatic environments (Kuroda et al. 2021). In Arkhangelsk, Russian North, Umifenovir and its 29 transformed chlorinated or brominated metabolites are detected in river bottom sediment and sludge (Ul'yanovskii et al. 2021). During COVID-19 situation, use of hydroxychloroquine and paracetamol was enhanced (Hernandez et al. 2021, Galani et al. 2021). This hydroxychloroquine is highly soluble as well as low biodegradable. Therefore, remain persist in food chain (Tuo et al. 2012, Neuwoehner et al. 2009).

Diclofenac is non-steroidal anti-inflammatory drug (NSAID) has been reported in Pakistan and Nepal for its increasing mortality rates due to renal failure caused by diclofenac (Nambirajan et al. 2018). It was studied that about 62.28 to 272.20 ng/g of diclofenac was detected in kidney and liver tissues and gut content of dead Indian white-backed vulture. It was also noticed that the toxic range of diclofenac (70-908 ng/g) was found in the kidney of white-backed vultures (Nambirajan et al. 2018). Thus, death of vultures was due to diclofenac reported earlier (Das et al. 2011, Cuthbert et al. 2011b). Further studies revealed that Diclofenac can be possible reason for decline in Steppe eagles and freshwater fish species such as rainbow trout (Schwaiger et al. 2004). Thus, there is a serious risk of diclofenace the environment has been reported. Transformation of Venlafaxine into O-desmethyl venlafaxine and its carcinogenic by-product, N-nitrosodimethylamine in wastewater treatment plants suggests the safe removal of such drugs with the aid of biological method (Llorca et al. 2019). The biodegradability index (BI) is used to check the efficacy of biological treatment which is the ratio of BOD5 and COD (Abdalla and Hammam 2014). The Pilot study has been carried out for the applicability of disinfection process for the more than 50% removal of residual concentration of anti-inflammatory and anti-convulsive drugs before the biological treatment process (Gagnon et al. 2008).

Major sources of pharmaceutical pollutants are pharma industries wastewater, hospital wastewater and municipal wastewater treatment plants (Larsso et al. 2007, Yakubu 2017, Lenzet et al. 2007, Asimakopoulos and Kannan 2016). These pollutants include drugs, heavy metals and microplastics (Zhou et al. 2020, Pico et al. 2020). Emission of these pollutants in soil, water and air are causing fish toxicity (behavioural changes induced by methamphetamine and psychiatric drugs), phytotoxicity (imposed by paracetamol on wheat and metronidazole on soybean) and Avian toxicity (by diclofenac)(Horky et al. 2021, Brodin et al. 2013, Parrot and Blunt 2005, Jing et al. 2009, Yakubu 2017, Nambirajan et al. 2018).

Effect of pharmaceutical micropollutants on microbial community

Effect of pharmaceutical micropollutants on bacteria

The pharmaceutical drugs and their intermediates have some impact on the microbial community such as changes in the morphological features, change in population size, and development of drug resistance characteristics. For example, development of carbapenem resistance in Enterobacteriaceae has been observed. Thus, development of antibiotic resistance in the pathogens was observed due to discharge of several pharma micropollutants in the environment (Sholeh et al. 2020).

Hydroquinone is considered as the most toxic due to its adverse effect on microbial cell numbers. Therefore, the soil contaminated with hydroquinone, reflects decreasing activity of â-glucosidase and dehydrogenase in microbial community (Chen et al. 2009). Hydroquinone also arrests the cell cycle at the G2/M transition due to the activation of Hog1-Swe1 pathway in *Saccharomyces cerevisiae* reported previously (Shiga et al. 2010). Further study revealed the changes in cell integrity, electrokinetic properties and catalase activity in *Rhodococcus cercidiphylli IEGM 1184* and *R. ruber IEGM 346* in presence of 50 mg/L diclofenac and 100 mg/L ibuprofen

(Tyumina et al. 2022). The aggregation based cooperative behavior was observed in *R. ruber* IEGM 346 in presence of diclofenac (Ivshina et al. 2019).

Effect of Pharmaceutical Micropollutants on Algae

The microalgal growth was adversely affected by wastewater contaminated with some pharmaceutical micropollutants like sulfonamides and fluoroquinolones and anti-depressants such as sertraline, fluoxetine and the fluoxetine metabolite norfluoxetine (Yan et al. 2018). Antibiotics such as tetracycline, sulfamethoxazole and ciprofloxacin showed significant effect on growth of cyanobacteria *Nostoc* sp. PCC 7120 by stimulating nitrogen fixation activity reported earlier (Liu and Zhang 2021). These three antibiotics also downregulated the phosphonate ABC transporter and a methionine aminopeptidase (Liu and Zhang, 2021). Amoxicillin drug was reported for its hormesis effect i.e. low-dose stimulation and high-dose inhibition on *Microcystis aeruginosa* (Liu et al. 2016).

Antibiotic residues in animal products and wastes

The possible impact of pharmaceutical micropollutants on humans is still unclear and further study is needed. The pharmaceutical micropollutants have been detected in leaf crops, root crops, fishery products, dairy products, and meat. Traces of the ophylline and paracetamol have been found in breast-fed infants might be due to the consumption of drugs by nursing mothers or via milk powders (FAO 2014).

The National Dairy Research Institute (NDRI) in India studied that some antibiotics like oxytetracycline, gentamicin, tetracycline, amoxicillin, ampicillin, cloxacillin, and penicillin are extensively used in India (Grover and Bhavadesan 2016). Further study also revealed that untreated animal waste is a major source contamination of antibiotics such enrofloxacin and oxytetracycline. These antibiotics are continuously discharged as micropollutants into environment (Jindal et al. 2020). The antibiotic like oxytetracycline was also detected in the milk beyond the permissible limit in Kerala, India (Hebbal et al. 2020).

Control measures of pharmaceutical micropollutants

The drugs responsible for pollution should be properly disposed off by classifying or labeling them as expired, unused, and unwanted medicines (Campos et al. 2021). Misuse of antibiotics is the main cause to acquire antibiotic resistance in pathogens, high health care cost, and ecotoxic effects of drug. Therefore, there is a great need of surveillance systems should be employed for the monitoring of antibiotics management (Shapiro et al. 2014, Demirjian et al. 2015). It was observed that restricted use of carbapenem in some institutes, resulted in control of *P. aeruginosa* resistance to carbapenems and effective in prevention of *Clostridium difficile* infections reported previously (Wong and Brad 2017). The National Health Policy mentioned that antimicrobial resistance is a major issue in India and therefore suggested pharmaco-vigilance via the implementation of Antimicrobial Stewardship Program (AMSP) (AMSP Guidelines 2017) includes 5 measures like 4D's (right drug, dose, duration and interval), prospective audit of drug, formulators restriction, use of microbiology lab, and patient specific clinical practice (MacDougall and Polk 2005, Walia et al. 2015).

Use of microorganisms in detoxification of pharma micropollutants

The microbial models of mammalian metabolism revealed that microorganisms have systems alike to mammal's cytochrome P450, which could detoxify the pharma products. Therefore, for microbial degradation study, it is important to classify the medicines into different categories such as expired, faked or rejected (Ivshina et al. 2019). It has been reported that several microorganisms have the ability to detoxify toxic compounds using enzyme such as oxidoreducatse and exopolysaccharide assisted mechanism reported previously (Rao et al. 2010, Gadkari et al. 2022). Bacterial degradation of drugs with their product is given in Table 1.

Algal degradation of pharmaceutical micropollutants

Algae are widely accepted for the treatment of wastewater contaminated with pharmaceutical micropollutants. Bioremediation of pharmaceutical wastewater is carried out via photosynthetic organisms in photobiorector system by optimizing the factors of cost and efficiency (Katarzyna et al. 2022). Feasibility of algae in remediation is considered due to its photosynthetic and ecofriendly nature (Jiu et al. 2018). Detoxification of pharmaceutical micropollutants is achieved by

Table 1. Bacterial degradation of drugs and their end products

Name of the drug	Microorganisms	End products	References
Diclofenac	*Rhodococcus ruber* IEGM 34650µg/L, 6 days	DCF monohydroxy metabolites 2-[2-(22, 62-dichloro-42 hydroxyanilino) phenyl] -acetic acid (42 -OH-DCF), 2-[2-22, 62-dichloroanilino)-5-hydroxyphenyl] acetic acid (5-OH-DCF), and also of the benzoquinonimine-type and its dihydroxy derivative	Ivshina et al. (2019)
	*Consortia of Alcaligenes faecalis, Staphylococcus aureus, Staphylococcushemolyticus, Proteus mirabilis*150 mg/L, 5 Days	Hydroxy sodium diclofenac	Murshid and Dhakshina-moorthy (2019)
	Enterobacter hormaechei	1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one	Aissaoui et al. (2017)
	Klebsiella sp. WAH179. 14% degradation,3 days10 mg/L		Sharma et al. (2021)
	BrevibacteriumD4 10 mg/L, 30 days		Bessa et al. (2017)
	Actinoplanes ATCC 537715mM; 318 mg (for shake flask studies); 500 µM (for hollow fiber cartridge (HFC) reactors) 1 Day	4-hydroxy, 5-hydroxy, and 4,5-dihydroxy metabolites of diclofenac	Osorio-Lozada et al. (2008)
Paracetamol (acetaminophen)	*Rhodococcus ruber*	*p*-aminophenol, pyrocatechol, and hydroquinone	Ivshina et al. (2006)
	Stenotrophomonas sp. f1 400 mg/l	4-aminophenol, and hydroquinone	Zhang et al. (2012)
	Pseudomonas sp. f2 2,500 mg/l, 70 h	4-aminophenol, and hydroquinone	Zhang et al. (2012)
	Pseudomonas sp. fg-22,000 mg/l, 45 h	4-aminophenol, and hydroquinone	Zhang et al. (2012)
	Delftia tsuruhatensis, Pseudomonas aeruginosa 100 mg/l, 40 h	Hydroquinone	Bart et al. (2011)

Name of the drug	Microorganisms	End products	References
	Brevibacterium] frigoritolerans, Corynebacterium nuruki and *Enterococcus faecium, Bacillus cereus*200 mg/L,144 h	4-aminophenol, hydroquinone and 2-hexenoic acid	Palma et al. (2021)
	Flavobacterium, Dokdonella and *Methylophilus* 50 mg/L in municipal wastewater, 2 days	4-aminophenol , hydroquinone,One unknown compound	Palma et al. (2018)
	Cunninghamella echinulata	*N-acetyl-p-benzoquinoneimine (NAPQI)*	Ratna Kumari et al. (2009)
	Staphylococcus sciuri strain DPP1 (MN744326), Bacillus subtilis strain DPP3 (MN744327), Bacillus paralicheniformis strain DKP1 (MN744324), Enterococcus faecium strain DKP2 (MN744325) and *DDP2 (MT705211),*1200 mg/L of APAP, 70 Hrs	4-aminophenol, benzamide, (R)-2-methylpentanoic acid, methylene-3-vinyl cyclohexane, and 1,5-hexadiene	Chopra and Kumar (2020)
	Shinella sp. HZA2100 mg/L, 12 Hrs	4 Aminophenol and Hydroquinone	Chen and Ma (2022)
Naproxen [(S) 6-methoxy-á-methyl-2-naphthalene acetic acid]	*Phanerochaete chrysosporium*, *Funalia trogii*, *Aspergillus niger*, and *Yarrowia lipolytica*	*O*-desmethylnaproxen and 7-hydroxynaproxen	Aracagök et al. **(**2017)
	White-rot fungus *Trametes vesicolor* 6Hr.	2-(6-hydroxynaphthalen-2-yl) propanoic acid and 1-(6-methoxynaphthalen -2-yl) ethanone	Marco et al. (2010)
Carbamazepine	*Starkeya* sp. C11 and *Rhizobium* sp. C12		Bessa et al. (2017)
	Trichoderma harzianum	-	Buchicchio et al. (2016)
Clarithromycin	*Trichoderma harzianum*	14 Hydroxy clarithromycin and N-Desmethyl clarithromycin	Buchicchio et al. (2016)

Name of the drug	Microorganisms	End products	References
Gentamicin C1a and C2a	Bacterial consortia; *Providencia vermicola, Brevundimonas diminuta*, *Alcaligenes* sp., *Acinetobacter* (Alkaline pH, 10% Inoculation (2.05x109 CFU/ml)	3' Acetyl gentamicin	Liu et al. (2017)
	Aspergillus terreus 100mg/L Biosorption and bioremediation mechanism	-	Liu et al. (2016)
Ciprofloxacin	*Thermus thermophilus* 20 mg/L	(7 metabolites) N-formylciprofloxacin, desethylene-N-acetylciprofloxacin, desethylene-N- formylciprofloxacin, desethylene-N-ciprofloxacin, e 7-amino-1-cyclopropyl-6- fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-amino-6-fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylic acid, 4-oxo-1,4-dihydroquinoline-3 -carboxylic acid	Lan-jia Pan et al. (2017)
	Pestalotiopsis guepini 300 µM	N-acetylciprofloxacin (52.0%), desethylene-N-acetylciprofloxacin (9.2%), N-formylciprofloxacin (4.2%), and 7-amino-1-cyclopropyl-6 -fluoro4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2.3%).	Parshikov et al. (2001)
	Labrys portucalensis F11	desethylene-N-ciprofloxacin	Amorim et al. (2014)
Cefdinir	*Ustilago* sp. SMN03 (Concentration 200 mg/L, 81% degradation within 6 days. pH 6.0, temperature 30°C, a shaking speed of 120 rpm, an inoculum dosage of 4 % (w/v)	5-Vinyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylic acid (M4) and Thiazol-2-amine (M5)	Selvi et al. (2014)
Oxytetracycline	*Pleurotus ostreatus*100 g/mL, 14 Days	ADOTC (2-acetyl-2-decarboxamido-oxytetracycline)	Migliore et al. (2012)
Sulfamethoxazole (SMX)	Consortia of *Bacillus licheniformis, Pseudomonas putida, Alcaligenes* sp. and *Aquamicrobium defluvium*	-	Islas-Espinoza et al. (2012)
	Bacterial consortia: *Bacillus subtilis, Pseudomonas aeruginosa, Pseudomonas putida,*	-	Larcher and Yargeau (2011)

Name of the drug	Microorganisms	End products	References
	Rhodococcus equi, Rhodococcus erythropolis, Rhodococcus rhodocrous, and *Rhodococcus zopfii*		
Sulfamethoxazole (SMX)	*Ochrobacterium* sp.SMX-PM1 -SA1 (45.2% biodegradation)	3-amino-5-methylisoxazole, 4-aminophenol and hydroquinone	Mulla et al. (2018)
	Labrys sp. SMX-W1-SC11 (62.2%) and *Gordonia* sp. SMX-W2-SCD14 (51.4%) 5 mg/L, 288 Hr.		
	Sphingobacterium mizutaii LLE5; 30.8°C, pH 7.2, 50 mg/L SMX 93.87%, 7 days.	sulfanilamide, 4-aminothiophenol, 5-amino-3-methylisoxazole, and aniline	Song et al. (2021)
Venlafaxine	*Trametes versicolor* 5 mg/L, 70% removal	N, N-didesmethylvenlafaxine	Llorca et al. (2019)
Progesterone	Algae: *Chlorella pyrenoidosa* and *Scenedesmus obliquus* 95% degradation, 5 days	3 â-hydroxy-5á-pregnan-20-one, 3, 20, Allopregnanediene-3, 20 dione and 6 major androgens	Peng et al. (2014)
Norgestrel	Algae: *Scenedesmus obliquus* 100 % degradation	4,5-dihydronoregestrel and 6,7-dehydro noregestrel	Peng et al. (2014)
Sulfamethoxazole	Algae: *Chlorella pyrenoidosa*	4 Amino benzene sulfinic acid (4 ABSA), 3 Amino-5-methylisoxazole) 3 ASMI)	Xiong et al. (2020)
17 β–Estradiol	Freshwater algae *Raphidocelis subcapitata*	-	Liu et al. (2018)

different algal adopted strategies such as bioaccumulation, adsorption and intracellular as well as extracellular biodegradation (Jiu et al. 2018). It was observed that about 16.7 % adsorption of trimethoprim, carbamazepine, estrone, b-estradiol, ethinylestradiol, diclofenac, ibuprofen, paracetamol and metoprolol reported previously (de Wilt et al. 2016). However, algal dead biomass of *Chlorella pyrenoidosa* and *Scenedesmus obliquus* have been used for removal of progesterone and norgestrel via adsorption process (Peng et al. 2014).

This review comprises of the negative impact of pharma micropollutants on the environment and the methods used for their removal. Compared to the physico-chemical methods, there is need of biological treatment for the detoxification the persistent organic compounds. Literature survey on the detoxification of the drugs with the help of bacteria, fungi, algae as well as their consortia with their end product has been added in this review. Detoxification and removal of recalcitrant organic compounds is important, considering its occurrence and persistence in drinking water and soil. Microorganisms has the potential to reduce, detoxify and degrade such persistent pollutants from the environment. The mechanism of bioremediation of pharmaceutical micropollutants, depends on the extrachromosomal genetic material, enzymes, surfactants and biofilm forming potential. In bacterial assisted bioremediation of drugs, report is available on the 94% and 72% reduction of acetaminophen by immobilized laccase from *Lentinus polychrous* and laccase-alginate microcapsules (Chrys et al. 2022, Sotelo et al. 2022). Laccase (p-diphenol oxygen oxidoreductases, EC 1.10.3.2) has the potential to oxidize phenoloc and nonphenolic pollutants (Bilal et al. 2019). Laccase has also been reported to remove the phenolic endocrine disruptor bisphenol A (BPA) (75%, 100 mg/L) (Lassouane et al. 2022).

Enzymatic dependent drug removal mechanism in bacteria, is one of the important strategies. Hence, researchers are trying on enhancing the yield of enzymes involved in the biodegradative pathway rather than biomass. Report is available on the use of bacterial electroactive bioreactor supplied with an Alternating Current (AC) to improve laccase enzyme activity (LEA) and dehydrogenase activity (DHA) for the reduction of acetylsalicylic acid (ASA) (Zohreh and Rezaee 2021). Microbial biomass and bioproduct assisted mechanism has to be studied and implemented in WWTP for the pollutant free water and soil.

CONCLUSION

Pharmaceutical industry is one of the major sources of environmental pollution by discharging sewage water into municipal wastewater and subsequently into the environment. Municipal wastewater treatment plants primarily give focus on macro pollutants which can be removed by primary and secondary treatment. Less attention has been given to pharmaceutical drugs released into environment which has adverse effects on soil and water inhabitants. The management of pharmaceutical micropollutants is of high priority in order to prevent environmental pollution. Therefore, eco-toxicity of drugs and their adverse impact on ecosystem need to understand in depth. The microbial degradation of pharmaceutical micropollutants can be an effective biological process to detoxify the toxic compounds. Therefore, much detail study is required in this field in order to develop a green technology for management of pharmaceutical micropollutants.

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