Microbial Cell Factories For the Management of Pharmaceutical Micropollutants

Article *in* International Journal of Ecology and Environmental Sciences · January 2023

DOI: 10.55863/ijees.2023.2676

3 authors, including:

Meghmala Waghmode
P.D.E.A'S Annasaheb magar mahavidyalayA

Ashok Bankar
MES-AGC, Savirtibai Phule Pune University

International Journal of Ecology and Environmental Sciences 49: 5-16, 2023
ISSN: 2320-5199 (Online); https://doi.org/10.55863/ijees.2023.2676

Review

Microbial Cell Factories for the Management of Pharmaceutical Micropollutants

MEGHMALA S. WAGHMODE[1]*, NEHA N. PATIL[1] AND ASHOK V. BANKAR[2]

[1]*Department of Microbiology, PDEA's Annasaheb Magar Mahavidyalaya, Hadapsar, Pune-411028 Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India.*

[2]*Department of Microbiology, MES Abasaheb Garware College, Pune- 411004 Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India.*

E-mail: meghmicro@gmail.com, nehanitinpatil@gmail.com, awb.agc@mespune.in

***Corresponding author**

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 µg 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) *Labrys* sp. SMX-W1-SC11 (62.2%) and *Gordonia* sp. SMX-W2-SCD14 (51.4%) 5 mg/L, 288 Hr.	3-amino-5-methylisoxazole, 4-aminophenol and hydroquinone	Mulla et al. (2018)
	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.

Author's Contribution: Manuscript is made by Meghmala Waghmode under the supervision of Dr. Ashok Bankar and Prof. Neha Patil.

Conflict of interest: The authors declare that they have no conflict of interest.

REFERENCES

Abdalla, K.Z. and Hammam, G. 2014. Correlation between biochemical oxygen demand and chemical oxygen demand for various wastewater treatment plants in Egypt to obtain the biodegradability indices. International Journal of Sciences: Basic and Applied Research, 13(1), 42-48.

Aissaoui, S., Ouled-Haddar, H., Sifour, M., Harrouche, K. and Sghaier, H. 2017. Metabolic and co-metabolic transformation of diclofenac by *Enterobacter hormaechei* D15 isolated from activated sludge. Current Microbiology, 74(3), 381-388.

Amorim, C.L., Moreira, I.S., Maia, A.S., Tiritan, M.E. and Castro, P.M. 2014. Biodegradation of ofloxacin, norfloxacin, and ciprofloxacin as single and mixed substrates by *Labrys portucalensis* F11. Applied Microbiology and Biotechnology, 98(7), 3181-3190.

Andersson, D.I. and Hughes, D. 2014. Microbiological effects of sublethal levels of antibiotics. Nature Reviews Microbiology, 12(7), 465-478.

Aracagök, Y.D., Göker, H. and Cihangir, N. 2017. Biodegradation of micropollutant naproxen with a selected fungal strain and identification of metabolites. Zeitschrift für Naturforschung C, 72(5-6), 173-179.

Asimakopoulos, A.G. and Kannan, K. 2016. Neuropsychiatric pharmaceuticals and illicit drugs in wastewater treatment plants: a review. Environmental Chemistry, 13(4), 541-576.

Bessa, V.S., Moreira, I.S., Tiritan, M.E., Castro, P.M.L. 2017. Enrichment of bacterial strains for the biodegradation of diclofenac and carbamazepine from activated sludge. International Biodeterioration Biodegradation, 120, 135–142. https://doi.org/10.1016/j.ibiod.2017.02.008.

Bhattacharyya, P.N., Sonowal, S., Bhattacharyya, L.H., Prasad, R. and Sarma, H. 2022. Bioremediation of cytostatic pharmaceutical and personal care products and emerging technologies. Emerging Contaminants in the Environment, pp.579-601.

Bilal, M., Adeel, M., Rasheed, T., Zhao, Y. and Iqbal, H.M., 2019. Emerging contaminants of high concern and their enzyme-assisted biodegradation–a review. Environment International, 124, 336-353.

Bouju, H., Nastold, P., Beck, B., Hollender, J., Corvini, P.F.X. and Wintgens, T. 2016. Elucidation of biotransformation of diclofenac and 42 hydroxydiclofenac during biological wastewater treatment. Journal of Hazardous Materials, 301, 443-452.

Brausch, J.M. and Rand, G.M. 2011. A review of personal care products in the aquatic environment: environmental concentrations and toxicity. Chemosphere, 82(11), 1518-1532.

Buchicchio, A., Bianco, G., Sofo, A., Masi, S. and Caniani, D., 2016. Biodegradation of carbamazepine and clarithromycin by *Trichoderma harzianum* and *Pleurotus ostreatus* investigated by liquid chromatography–high-resolution tandem mass spectrometry (FTICR MS-IRMPD). Science of the Total Environment, 557, 733-739.

Chen, H., Yao, J., Wang, F., Choi, M.M., Bramanti, E. and Zaray, G. 2009. Study on the toxic effects of diphenol compounds on soil microbial activity by a combination of methods. Journal of hazardous materials, 167(1-3), 846-851.

Chen, R., Liu, X. and Ma, Y. 2022. Isolation and identification of acetaminophen degrading strain Shinella sp. HZA2. Journal of Environmental Science and Health, Part B, 1-6.

Chojnacka, K., Skrzypczak, D., Izydorczyk, G., Mikula, K., Szopa, D., Moustakas, K. and Witek-Krowiak, A. 2022. Biodegradation of pharmaceuticals in photobioreactors–a systematic literature review. Bioengineered, 13(2), 4537-4556.

Chopra, S. and Kumar, D. 2020. Biodegradation and kinetic analysis of acetaminophen with co-culture of bacterial strains isolated from sewage wastewater. Current microbiology, 77(10), 3147-3157.

Cleuvers, M. 2004. Mixture toxicity of the anti-inflammatory drugs diclofenac, ibuprofen, naproxen, and acetylsalicylic acid. Ecotoxicology and Environmental Safety, 59(3), 309-315.

Cuthbert, R.J., Dave, R., Chakraborty, S.S., Kumar, S., Prakash, S., Ranade, S.P. and Prakash, V. 2011. Assessing the ongoing threat from veterinary non-steroidal anti-inflammatory drugs to Critically Endangered Gyps vultures in India. Oryx, 45(3), 420-426.

da Silva, C.K.H., Polidoro, A.S., Ruschel, P.M.C., Thue, P.S., Jacques, R.A., Lima, É.C., Bussamara, R. and Fernandes, A.N. 2022. Laccase covalently immobilized on avocado seed biochar: A high-performance biocatalyst for acetaminophen sorption and biotransformation. Journal of Environmental Chemical Engineering, 10(3), 107731.

Das, D., Cuthbert, R.J., Jakati, R.D. and Prakash, V. 2011. Diclofenac is toxic to the Himalayan Vulture Gyps himalayensis. Bird Conservation International, 21(1), 72-75.

de Campos, E.A.R., Ten Caten, C.S. and de Paula, I.C. 2021. End-of-use and end-of-life medicines—Insights from pharmaceutical care process into waste medicines management. Environmental Science and Pollution Research, 28(41), 58170-58188.

De Gusseme, B., Vanhaecke, L., Verstraete, W. and Boon, N. 2011. Degradation of acetaminophen by Delftia tsuruhatensis and Pseudomonas aeruginosa in a membrane bioreactor. Water research, 45(4), 1829-1837.

de Wilt, A., Butkovskyi, A., Tuantet, K., Leal, L.H., Fernandes, T.V., Langenhoff, A. and Zeeman, G. 2016. Micropollutant removal in an algal treatment system fed with source separated wastewater streams. Journal of hazardous materials, 304, 84-92.

Demirjian, A., Sanchez, G.V., Finkelstein, J.A., Ling, S.M., Srinivasan, A., Pollack, L.A., Hicks, L.A. and Iskander, J.K. 2015. CDC grand rounds: getting smart about antibiotics. Morbidity and Mortality Weekly Report, 64(32), 871.

Fick, J., Lindberg, R.H., Tysklind, M., Haemig, P.D., Waldenström, J., Wallensten, A. and Olsen, B. 2007. Antiviral oseltamivir is not removed or degraded in normal sewage water treatment: implications for development of resistance by influenza A virus. PLoS One, 2(10), e986.

Gadkari, J., Bhattacharya, S. and Shrivastav, A. 2022. Importance and applications of biofilm in microbe-assisted bioremediation. pp. 153-173, In: Development in Wastewater Treatment Research and Processes, Elsevier.

Gagnon, C., Lajeunesse, A., Cejka, P., Gagne, F. and Hausler, R. 2008. Degradation of selected acidic and neutral pharmaceutical products in a primary-treated wastewater by disinfection processes. Ozone: Science and Engineering, 30(5), 387-392.

Galani, A., Alygizakis, N., Aalizadeh, R., Kastritis, E., Dimopoulos, M.A. and Thomaidis, N.S. 2021. Patterns of pharmaceuticals use during the first wave of COVID-19 pandemic in Athens, Greece as revealed by wastewater-based epidemiology. Science of The Total Environment, 798, 149014.

Ghlichloo, I. and Gerriets, V. 2021. Nonsteroidal anti-inflammatory drugs (NSAIDs).

Grover CR, Bhavadesan M 2016. Antibiotic residues in milk: a public health concern. In: National Conference on Food Safety and Environmental Toxins. Centre for Science and Environment, New Delhi. 47 pages.

Gwenzi, W., Selvasembian, R., Offiong, N. O., Mahmoud, A., Sanganyado, E. and Mal, J. 2022. COVID-19 drugs in aquatic systems: a review. Environmental Chemistry Letters, 1–20. Advance online publication. https://doi.org/10.1007/s10311-021-01356-y

Hebbal, M.A., Latha, C., Vrinda Menon, K. and Deepa, J. 2020. Occurrence of oxytetracycline residues in milk samples from Palakkad, Kerala, India, Veterinary World, 13(6), 1056-1064.

Hernandez-Cardenas, C., Thirion-Romero, I., Rodríguez-Llamazares, S., Rivera-Martinez, N.E., Meza-Meneses, P., Remigio-Luna, A. and Perez-Padilla, R. 2021. Hydroxychloroquine for the treatment of severe respiratory infection by COVID-19: A randomized controlled trial. PLoS ONE, 16(9), e0257238. https://doi.org/10.1371/journal.pone.0257238.

Islas-Espinoza, M., Reid, B.J., Wexler, M. and Bond, P.L. 2012. Soil bacterial consortia and previous exposure enhance the biodegradation of sulfonamides from pig manure. Microbial Ecology, 64(1), 140-151.

Ivshina, I.B., Rychkova, M.I., Vikhareva, E.V., Chekryshkina, L.A. and Mishenina, I. 2006. Catalysis of the biodegradation of unusable medicines by alkanotrophic rhodococci. Applied Biochemistry and Microbiology, 42, 392–395.

Ivshina, I.B., Tyumina, E.A., Kuzmina, M.V. and Vikhareva, E.V., 2019. Features of diclofenac biodegradation by *Rhodococcus ruber* IEGM 346. Scientific Reports, 9(1), 1-13.

Jelic, A., Gros, M., Ginebreda, A., Cespedes-Sànchez, R., Ventura, F., Petrovic, M. and Barcelo, D. 2011. Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment. Water Research, 45(3), 1165-1176.

Jindal, P., Bedi, J., Singh, R., Aulakh, R. and Gill, J.P. 2021.Epidemiological assessment of antibiotic residues in dairy farm milk and farm waste and water in northern India. Environmental Science and Pollution Research, 28, 29455–29466. https://doi.org/10.1007/s11356-020-12057-4.

Kuroda, K., Li, C., Dhangar, K. and Kumar, M. 2021. Predicted occurrence, ecotoxicological risk and environmentally acquired resistance of antiviral drugs associated with COVID-19 in environmental waters. Science of the Total Environment, 776, 145740.

Larcher, S. and Yargeau, V. 2011. Biodegradation of sulfamethoxazole by individual and mixed bacteria. Applied Microbiology and Biotechnology, 91(1), 211-218.

Larsson, D.J. and Fick, J. 2009. Transparency throughout the production chain—a way to reduce pollution from the manufacturing of pharmaceuticals? Regulatory Toxicology and Pharmacology, 53(3), 161-163.

Lassouane, F., Aït-Amar, H. and Rodriguez-Couto, S. 2022. High BPA removal by immobilized crude laccase in a batch fluidized bed bioreactor. Biochemical Engineering Journal, 184, 108489.

Lenz, K., Mahnik, S. N., Weissenbacher, N., Mader, R. M., Krenn, P., Hann, S., Koellensperger, G., Uhl, M., Knasmuller, S., Ferk, F., Bursch, W. and Fuerhacker, M. 2007. Monitoring, removal and risk assessment of cytostatic drugs in hospital wastewater. Water Science and Technology, 56(12), 141-149.

Liu, S., Liu, Y. and Zhang, J. 2021. Proteomic mechanisms for the regulation of growth, photosynthetic activity and nitrogen fixation in *Nostoc* sp. PCC 7120 exposed to three antibiotic contaminants, Ecotoxicology and Environmental Safety, 225, 112753. https://doi.org/10.1016/j.ecoenv.2021.112753.

Liu, W., Chen, Q., He, N., Sun, K., Sun, D., Wu, X. and Duan, S. 2018. Removal and biodegradation of 17α-estradiol and diethylstilbestrol by the freshwater microalgae *Raphidocelis subcapitata*. International Journal of Environmental Research and Public Health, 15(3), 452. https://doi.org/10.3390/ijerph15030452.

Liu, Y., Chang, H., Li, Z., Feng, Y., Cheng, D. and Xue, J. 2017. Biodegradation of gentamicin by bacterial consortia AMQD4 in synthetic medium and raw gentamicin sewage. Scientific Reports, 7, 11004. https://doi.org/10.1038/s41598-017-11529-x.

Liu, Y., Chang, H., Li, Z., Zhang, C., Feng, Y. and Cheng, D. 2016. Gentamicin removal in submerged fermentation using the novel fungal strain *Aspergillus terreus* FZC3. Scientific Reports, 6, 35856, doi:10.1038/srep40279.

Llorca, M., Castellet-Rovira, F., Farré, M. J., Jaén-Gil, A., Martínez-Alonso, M., Rodríguez-Mozaz, S., Sarra, M. and Barceló, D. 2019. Fungal biodegradation of the N-nitrosodimethylamine precursors venlafaxine and O-desmethylvenlafaxine in water. Environmental Pollution, 246, 346-356.

MacDougall, C. and Polk, R.E. 2005. Antimicrobial stewardship programs in health care systems. Clinical Microbiology Reviews, 18(4), 638-656.

Marco-Urrea, E., Pérez-Trujillo, M., Blánquez, P., Vicent, T. and Caminal, G. 2010. Biodegradation of the analgesic naproxen by *Trametes versicolor* and identification of intermediates using HPLC-DAD-MS and NMR. Bioresource Technology, 101, 2159–66.

Migliore, L., Fiori, M., Spadoni, A. and Galli, E. 2012. Biodegradation of oxytetracycline by *Pleurotusostreatus mycelium*: A mycoremediation technique. Journal of Hazardous Materials, 215–216, 227–232 .

Moghiseh, Z. and Rezaee, A. 2021. Removal of aspirin from aqueous solution using electroactive bacteria induced by alternating current. Environmental Science and Pollution Research, 28(20), 25327-25338.

Montesdeoca-Esponda, S., Checchini, L., Del Bubba, M., Sosa-Ferrera, Z. and Santana-Rodriguez, J.J. 2018. Analytical approaches for the determination of personal care products and evaluation of their occurrence in marine organisms. Science of the Total Environment, 633, 405-425.

Mulla, S.I., Hu, A., Sun, Q., Li, J., Suanon, F., Ashfaq, M. and Yu, C.P. 2018. Biodegradation of sulfamethoxazole in bacteria from three different origins. Journal of Environmental Management, 206, 93–102. https://doi.org/10.1016/j.jenvman.2017.10.029.

Murshid, S. and Dhakshinamoorthy, G.P. 2019. Biodegradation of sodium diclofenac and mefenamic acid: kinetic studies, identification of metabolites and analysis of enzyme activity. International Biodeterioration & Biodegradation, 144, 104756.

Nambirajan, K., Muralidharan, S., Roy, A.A. and Manonmani, S. 2018. Residues of diclofenac in tissues of vultures in India: A post-ban scenario. Archives of Environmental Contamination and Toxicology, 74(2), 292-297. doi: 10.1007/s00244-017-0480-z.

Neuwoehner, J., Reineke, A.K., Hollender, J. and Eisentraeger, A. 2009. Ecotoxicity of quinoline and hydroxylated derivatives and their occurrence in groundwater of a tar-contaminated field site. Ecotoxicology and Environmental Safety, 72(3), 819-827. https://doi.org/10.1016/j.ecoenv.2008.04.012.

Nippes, R.P., Macruz, P.D., da Silva, G.N. and Scaliante, M.H.N.O. 2021. A critical review on environmental presence of pharmaceutical drugs tested for the covid-19 treatment. Process Safety and Environmental Protection, Part B, 152, 568–582. https://doi.org/10.1016/j.psep.2021.06.040

Osorio-Lozada, A., Surapaneni, S., Skiles, G.L. and Subramanian, R. 2008. Biosynthesis of drug metabolites using microbes in hollow fiber cartridge reactors: case study of diclofenac metabolism by *Actinoplanes* species. Drug Metabolism and Disposition, 36, 234–240. doi: 10.1124/dmd.107.019323.

Palma, T.L., Donaldben, M.N, Costa, M.C. and Carlier, J.D. 2018. Putative Role of *Flavobacterium, Dokdonella* and *Methylophilus* strains in paracetamol biodegradation. Water, Air, and Soil Pollution, 229(6), art 200.

Palma, T.L., Magno, G. and Costa, M.C. 2021. Biodegradation of Paracetamol by Some Gram-Positive Bacterial Isolates. Current Microbiology, 78, 2774–2786 https://doi.org/10.1007/s00284-021-02543-4.

Pan, L-J., Li, J., Li, C-X., Tang, X-D., Yu, G-W. and Wang, Y. 2017. Study of ciprofloxacin biodegradation by a *Thermus* sp. isolated from pharmaceutical sludge, Journal of Hazardous Materials, 343(5), 59-67. http://dx.doi.org/10.1016/j.jhazmat.2017.09.009.

Parshikov I.A., Heinze, T.M., Moody, J.D., Freeman, J.P., Williams, A.J. and Sutherland, J.B. 2001 The fungus *Pestalotiopsis guepini* as a model for biotransformation of ciprofloxacin and norfloxacin, Applied Microbiology and Biotechnology, 56 :474-477.

Patel, M., Kumar, R., Kishor, K., Mlsna, T., Pittman, C.U. and Mohan, D. 2019. Pharmaceuticals of emerging concern in aquatic systems: Chemistry, occurrence, effects, and removal methods. Chemical Reviews, 119(6), 3510-3673. doi:10.1021/acs.chemrev.8b00299.

Peng, F-Q., Ying, G-G., Yang, B., Liu, S., Lai, H-J., Chen, Z-F. and Zhou, G-J. 2014. Biotransformation of progesterone and norgestrel by two freshwater microalgae (*Scenedesmus obliquus* and *Chlorella pyrenoidosa*): transformation kinetics and products identification. Chemosphere, 95, 581–588.

Pérez-Estrada, L.A., Malato, S., Gernjak, W., Agüera, A., Thurman, E.M., Ferrer, I. and Fernández-Alba, A.R. 2005. Photo-fenton degradation of diclofenac: Identification of main intermediates and degradation pathway. Environmental Science & Technology, 39 (21), 8300-8306. DOI: 10.1021/es050794n.

Picó, Y., Alvarez-Ruiz, R., Alfarhan, A. H., El-Sheikh, M. A., Alshahrani, H. O., & Barceló, D. 2020. Pharmaceuticals, pesticides, personal care products and microplastics contamination assessment of Al-Hassa irrigation network (Saudi Arabia) and its shallow lakes. Science of The Total Environment, 701, 135021.

Radjenovic, J., Petrovic, M., Ventura, F. and Barcelo, D. 2008. Rejection of pharmaceuticals in nanofiltration and reverse osmosis membrane drinking water treatment. Water Research, 42 (14), 3601-3610.

Rao, M.A., Scelza, R., Scotti, R. and Gianfreda, L. 2010. Role of enzymes in the remediation of polluted environments. Journal of Soil Science and Plant Nutrition, 10(3), 333-353.

Ratna Kumari, T., Vidyavathi, M., Asha, S. and Prasad, K.V.S.R.G. 2009. Biotransformation of paracetamol by *Cunninghamella echinulata*, Journal of Pharmaceutical Research, 8(1), 1-5.

Ribeiro, A.R., Nunes, O.C., Pereira, M.F. and Silva, A.M. 2015. An overview on the advanced oxidation processes applied for the treatment of water pollutants defined in the recently launched Directive 2013/39/EU. Environment International, 75, 33-51.

Schwaiger, J., Ferling, H., Mallow, U., Wintermayr, H. and Negele, R.D. 2004. Toxic effects of the non-steroidal anti-inflammatory drug diclofenac. Part I: Histopathological alterations and bioaccumulation in rainbow trout. Aquatic Toxicology, 68(2), 141–150. doi:10.1016/j.aquatox.2004.03.014. PMID 15145224.

Selvi, A., Salam, J.A. and Das, N. 2014.Biodegradation of cefdinir by a novel yeast strain, *Ustilago* sp. SMN03 isolated from pharmaceutical wastewater. World Journal of Microbiology and Biotechnology, 30, 2839–2850. https://doi.org/10.1007/s11274-014-1710-4.

Shapiro, D.J., Hicks, L.A., Pavia, A.T. and Hersh, A.L. 2014. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. Journal of Antimicrobial Chemotherapy, 9(1), 234-40. http://www.cdc.gov/getsmart

Sharma, S., Setia, H. and Toor, A.P. 2021. Assessing the bioremediation potential of indigenously isolated *Klebsiella* sp. WAH1 for diclofenac sodium: optimization, toxicity and metabolic pathway studies. World Journal of Microbiology and Biotechnology, 37, art 33. https://doi.org/10.1007/s11274-021-02998-4.

Shiga T., Suzuki, H., Yamamoto, A., Yamamoto, H. and Yamamoto, K. 2010. Hydroquinone, a benzene metabolite, induces Th1-dependent stress response signaling and causes and- uploading *Saccharomyces cerevisiae*. Journal of Radiation Research, 51(4), 405–415.

Sholeh, M., Krutova, M., Forouzesh, M., Mironov, S., Sadeghifard, N., Molaeipour, L., Maleki, A. and Kouhsari, E. 2020. Antimicrobial resistance in *Clostridioides* (Clostridium) *difficile* derived from humans: a systematic review and meta-analysis. Antimicrobial Resistance and Infection Control, 9, 158. https://doi.org/10.1186/s13756-020-00815-5.

Simazaki, D., Kubota, R., Suzuki, T., Akiba, M. Nishimura, T. and Kunikane, S. 2015. Occurrence of selected pharmaceuticals at drinking water purification plants in Japan and implications for human health. Water Research, 76, 187–200.

Singer, A.C., Nunn, M.A., Gould, E.A. and Johnson, A.C. 2007. Potential risks associated with the proposed widespread use of Tamiflu. Environmental Health Perspectives, 115(1), 102-106.

Song, J., Hao, G., Liu, L., Zhang, H., Zhao, D., Li, X., Yang, Z., Xu, J., Ruan, Z. and Mu, Y. 2021. Biodegradation and metabolic pathway of sulfamethoxazole by *Sphingobacterium mizutaii*. Scientific Reports, 11, 23130. https://doi.org/10.1038/s41598-021-02404-x.

Sotelo, L.D., Sotelo, D.C., Ornelas-Soto, N., Cruz, J.C. and Osma, J.F. 2022. Comparison of acetaminophen degradation by laccases immobilized by two different methods via a continuous flow microreactor process scheme. Membranes, 12(3), 298.

Tyumina, E.A., Bazhutin, G.A. and Ivshina, I.B. 2022. Cell adaptations of *Rhodococci* to pharmaceutical pollutants. KnE Life Sciences, 2022, 443-455.

Ul'yanovskii, N.V., Kosyakov, D.S., Sypalov, S.A., Varsegov, I.S., Shavrina, I.S. and Lebedev, A.T. 2022. Antiviral drug umifenovir (Arbidol) in municipal wastewater during the COVID-19 pandemic: Estimated levels and transformation. Science of The Total Environment, 805, 150380. https://doi.org/10.1016/j.scitotenv.2021.150380.

Walia, K., Ohri, V. C. and Mathai, D. 2015. Antimicrobial stewardship programme (AMSP) practices in India. The Indian journal of medical research, 142(2), 130.

Wong, D. and Spellberg, B. 2017. Leveraging antimicrobial stewardship into improving rates of carbapenem-resistant Enterobacteriaceae. Virulence, 8(4), 383-390.

Xiong, J.Q., Kurade, M.B. and Jeon, B.H. 2018. Can microalgae remove pharmaceutical contaminants from water? Trends in Biotechnology, 36(1), 30-44.

Yakubu, O.H. 2017. Pharmaceutical wastewater effluent—source of contaminants of emerging concern: phytotoxicity of metronidazole to soybean (*Glycine max*). Toxics, 5(2), 10.

Yan, Z., Yang, H., Dong, H., Ma, B., Sun, H., Pan, T., Jiang, R., Zhou, R., Shen, J., Liu, J. and Lu, G. 2018. Occurrence and ecological risk assessment of organic micropollutants in the lower reaches of the Yangtze River, China: A case study of water diversion. Environmental Pollution, 239, 223-232.

Zhang, L.L., Hu, J., Zhu, R.Y., Zhou, Q.W. and Chen, J.M. 2012. Degradation of paracetamol by pure bacterial cultures and their microbial consortium. Applied Microbiology and Biotechnology, 97, 3687-3698. doi:10.1007/s00253-012-4170-5.

Zhou, R., Lu, G., Yan, Z., Jiang, R., Bao, X. and Lu, P. 2020. A review of the influences of microplastics on toxicity and transgenerational effects of pharmaceutical and personal care products in aquatic environment. Science of the Total Environment, 732, 139222.

Received:29th August 2022
Accepted:17th November 2022