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Spread of Pharmaceutical products in environment

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Abstract: Nowadays, the scientific community has focused and prioritized research on "emerging pollutants", including pharmaceuticals and their metabolites or residues, are continuously introduced into various environments which this contamination can occur all along their life cycle. It's recognized to be environmental micropollutants owing to their ubiquitous occurrence in water bodies at concentrations ranging from ng to µg/L. The continuous emissions to the environment and despite their degradation to a certain extent, pharmaceuticals of all categories have been detected in the environment**.** In first place the wastewater treatments contribute to discharge of pharmaceuticals in the environment, or; they have been detected in aquatic environments, mainly in surface water. These concentrations have been present in the water and their levels have been quantified and acknowledged as a potential ecological risk and human health. Indeed, analytical methods can detect traces of compounds with high sensitivity. Tandem mass spectrometry-based methods (GC/MS or LC/MS/MS) provide further insight into the possible structure of detected compound increasing selectivity.

1. Introduction

Human activities release high levels of toxic pollutants from multiple sources around the globe, were contaminated the Earth (Raghunandan *et al.,* 2018). Thus, rapid industrialization are responsible for 3.4 million deaths worldwide yearly because of Waterborne diseases (Javed *et al*., 2022; Muhammad *et al.,* 2022; Raza *et al*., 2022). One of these emerging pollutants; Pharmaceutical products, which they have not been thoroughly evaluated in terms of their environmental impact and are largely unregulated in environmental health (Akerman-Sanchez and Rojas-Jimenez, 2021; Razzaq *et al*., 2021; Syed *et al*., 2021, 2022; Shakir *et al*., 2022). Different environments are daily exposed to these emerging pollutants, and their residues, from various sources; hospital and municipal wastewater, disposal and discharges from pharmaceutical production, or consumer use (Ebele *et al*., 2017) through feces and urine following metabolized fraction will eventually end up in sewage (Zeidman *et al.,* 2020). These products are added to the list of priority substances by the Water Framework Directive of the European Union Decision 2015/495 as an emergence contaminant (Li *et al*., 2019), approximately 3000 pharmaceutical substances (Grzesiuk *et al*. 2023). They are very reactive contaminants due to their exhibit affinity to both organic and inorganic surfaces (Thiebault *et al*., 2016a, 2016b) and they considered as ecotoxic compounds which can elicit health-related problems (Xiong *et al.,*2017).

Now, Pharmaceutical contaminants (PhACs) appear broadly in the geosphere (Verlicchi *et al*., 2015) and biosphere (Christou *et al,* 2017). they have been detected in many aquatic bodies systems including drinking water supplies, groundwater and surface water (Blair *et al*., 2015; Zhao *et al*., 2015), rivers (Lin *et al*., 2018), lakes (Xie *et al*., 2015), wastewater (Liu *et al.,* 2015), effluent and influents, and sludge (Halling-Sørensen *et al*., 2019); also, soils and sediments (Ma *et al*., 2016) are contaminated by them. Recently, some research has been found that a few pharmaceutical compounds contaminated food chain and hence their concentration is increased (Lagesson *et al*., 2016).

The wastewater treatment plant (WWTPs) outlets are the primary point sources of these bioactive compounds because these substances are used as prescription or non-prescription medicines excreted from the human body in urine and feces in their unchanged forms either as intact substances or metabolites and often end up in the sewer system (Naghdi *et al.,* 2017). But WWTPs are not able to remove pharmaceuticals because they are generally designed to handle easily and moderately degradable organics at trace levels (ng/L-µg/L) in water bodies (Wang *et al*., 2018). Further, the reuse of wastewater effluent contaminated by these pollutants cans lesd in soil and water matrices (Medrano-Rodríguez *et al.,* 2020).

Hence, UNESCO (2017) announced that an adequate treatment of wastewater is released directly to the environment at 80 percent. Intel now, wastewater treatment plants (WWTPs) can not completely remove these type of micropollutants which persist in the environment because of high water solubility and poor biodegradability (Candido *et al.,* 2017). Especially in areas whereby are poor or no sanitation processes like as, in many African communities (Segura *et al.,* 2015). The percentage removal of pharmaceutical in Sewage Treatment Plants (STPs) can be highly variable, to depend on the physical-chemical properties of pharmaceuticals and the specific technology implemented, and reactors conditions (Caracciolo *et al*., 2015) ; For instance, the removal efficiency for ketoprofen reported in South Africa was in the range of 88- 90% (Zunngu *et al.,* 2016), whereas -83% was observed for the same compound in Algeria (Kermia *et al*., 2016).

Studies of Rivera-Utrilla (2013) guess that pharmaceuticals persist in the environment for more than one year such as cyclophosphamide, erythromycin, naproxen, and sulfamethoxazole while others, can persist for several years and also have the capacity to bioaccumulate such as clofibric acid or some compounds reorganize or transform their structure in sewers (Jelic *et al.* 2015), during wastewater treatment (Evgenidou *et al*., 2015) and in the environment (Pico *et al*. 2015) by a variety of biotic degradation(by bacteria and fungi) and abiotic processes (hydrolysis and photolysis) occurring in such systems. Moreover, conventional treatment processes, chlorination usually result in the formation of highly toxic intermediates (Cao *et al.* 2016). For instance, Su (2016) showed that the degradation of the antibiotic sulfamethoxazole can be back-transformed to the parent compound via transformation products by sediment-based bacteria.

Many treatment technologies to removal pharmaceutical substances have been studied, including physical, chemical and biological processes; adsorption (Zhang *et al*., 2016a), coagulation (Saitoh *et al.,* 2017), membrane separation (Dolar *et al.,* 2012), advanced oxidation processes (Tang *et al*.,2018), aerobic and anaerobic degradation (Feng *et al*., 2017), and compost (Liu *et al.*,2018a;2018b). Insight of the inefficiency of WWTPs for removal of pharmaceutical contaminants, new technologies have been developed: anaerobic membrane bioreactors, up flow layer anaerobic reactors, and mobile bed biofilm reactors (Shi *et al* ., 2017). Also, conventional surface drinking water treatment utilizes coagulation, flocculation, sedimentation, filtration and disinfection as basic methods (Behira *et al*., 2015).

Biological treatment processes are promising for PhACs degradation due to reduced cost and energy use, increased operational efficiency and sustainability, and ability to treat a wide range of compounds compared to physico-chemical treatments (Domaradzka *et al*., 2015), On the other hand, biological treatment is the key driving process of wastewater treatment, relying on microbial communities to remove and stabilize contaminants. It was shown that PhACs could be removed or transformed in Conventional activated sludge CAS systems by biological degradation, sorption, and volatilization (Blair *et al*., 2015). However, the most widely and commonly studied type of Wastewater Treatment Plant (WWTP) around the world is activated sludge (Yan *et al.,* 2014). Although bioremediation processes are the most attractive and successful clean-up technologies, they are characterized by some disadvantages. This efficacy technique used for remediation of the polluted site over other biological and conventional methods (Zhang *et al.,* 2018). Additionally, microorganisms have the ability to increasing concentrations of contaminations, which may extend the bioremediation procedure due to their adaptation (Singh and Kumar, 2016). But It must be carried to the removal of primary pharmaceutical contaminants that do not necessarily eliminate the toxicity in the environment (Petrie, 2015).

So, it is important to understand the transformation pathways in the environment and during wastewater treatment since pharmaceuticals are released in environment. To date, little or no information available on the occurrence and fate of PhACs in the environment from regions such as Russia, southern Asia, Africa, the Middle East, South America, and Eastern Europe have been done in high income countries than in North America, Europe and parts of Asia (Beek *et al.,* 2016). For instance, in the African continent, just 10 countries have published data on occurrence of PhACs in the environment because of the high prevalence of infectious diseases, over prescription, the availability cheap over-the-counter drugs as well as inadequate environmental barriers (Madikizela *et al.,* 2017). **(Figure 1).**

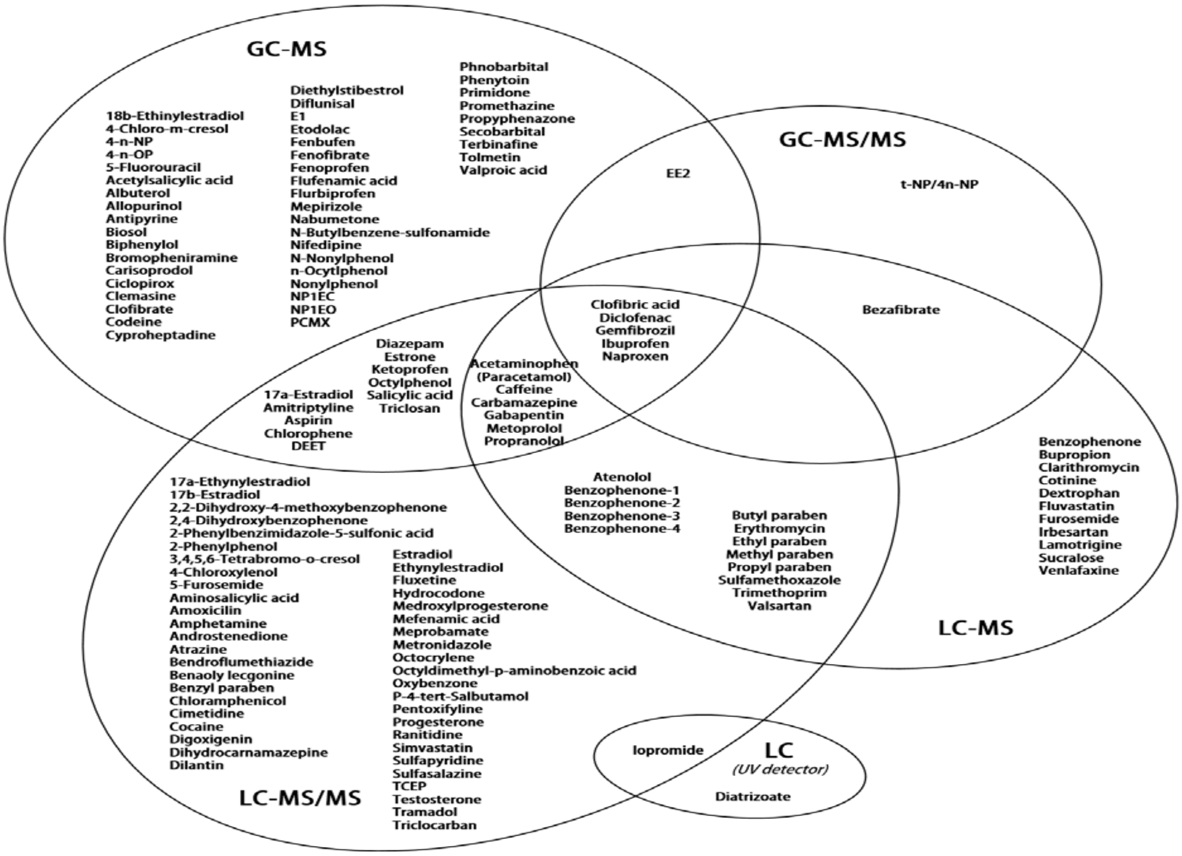

Figure 1: Methods used for detection of PhACs in environmental samples

The rapid detection of a large number of substances, which were previously undetectable, in the aquatic environment has made possible by the rapid development of automated analytical instrumentation. Multi-class pharmaceuticals have focused by recent analytical methods (Kivrak *et al.,* 2016). In light of their selectivity and sensitivity, both analyses are commonly coupled to mass spectrometry (MS) or tandem mass spectrometry (MS/MS) for qualitative and quantitative analysis, or liquid chromatography coupled with mass spectrometry or tandem mass spectrometry (LC-MS, LC-MS/MS)(Simazaki *et al*.2015). Currently, pharmaceutical residues in a growing number of different bodies are detected by techniques GC and LC (Sadkowska *et al*. 2017). Therefore, these advanced analytical techniques should be applied to detect pharmaceutical occurrence in drinking water (Wiest *et al*. 2018).

Source of pharmaceuticals residues

Pharmaceuticals residues are introduced into the environment by a diverse range of pathways and from different sources as the domestic wastewater, hospital effluents, industrial wastewater from pharmaceuticals production, run-off from aquacultures and concentrated animals feeding operations, and fish farming as well as a rural run-off and manure (Wiest *et al*., 2018) but the discharge of sewage effluents was identified as a main route of surface waters contamination, since the wide range of pharmaceuticals and personal care products (PPCPs) are ubiquitously detected in treated wastewater (Arpin-Pont *et al.,* 2016) , therefore, the recalcitrant molecules released and survived in the environment (Rana *et al*., 2017; Moghaddam *et al*., 2022; Yazdanian *et al*., 2022) **(Figure 2).**

Selected classes of PhACs

Different classes of pharmaceuticals are detected in the environment including Different classes of pharmaceuticals are recognized in the environment including anti-nflammatories, analgesic, blood lipid regulators , psychiatric medications, diuretics, and hormones (Grenni ,2013; Durairaj et al. 2021; Ahmed *et al.*, 2022; Gopalakrishnan *et al*., 2022; Heboyan *et al.,* 2022a, 2022b). Some of the relative percentages of mentioned drugs are available in **Figure 3.**

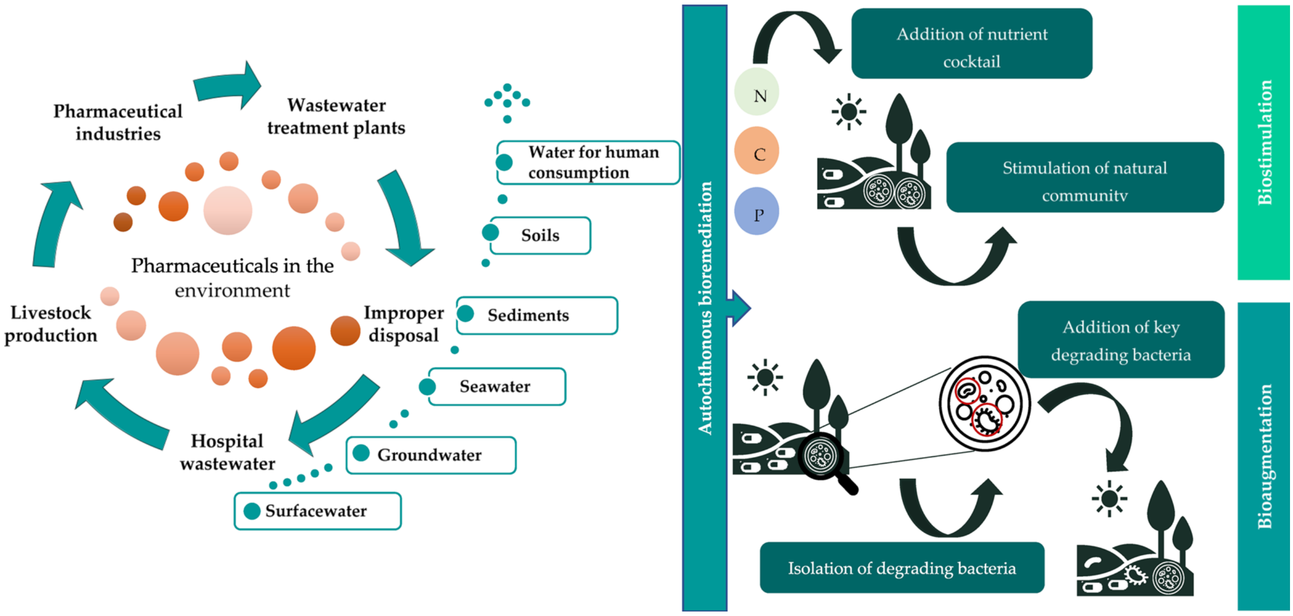

Figure 2: Environmental fate of pharmaceutical products in environments (Fernandes *et al*., 2021)

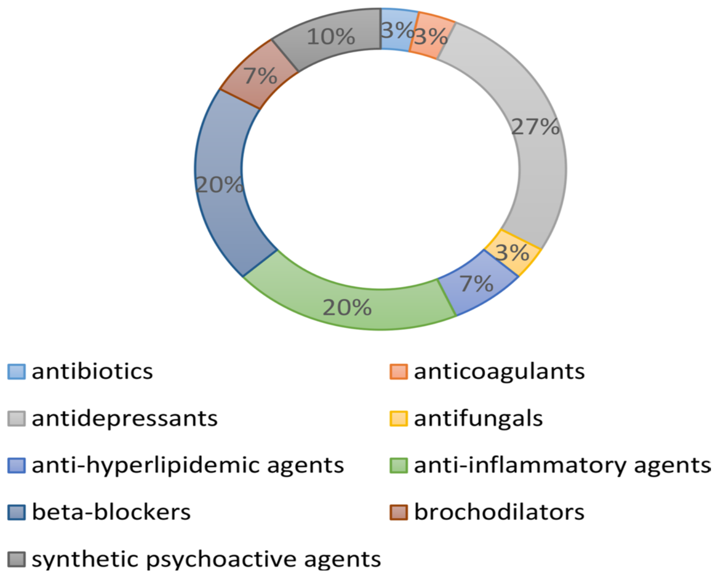

Figure 3: Pharmaceutical products classes relative percentages in the biodegradation examination (Maia *et al.,* 2017)

- **Non-steroidal anti-inflammatory drugs (NSAID)**

Represent the major class of detected pharmaceuticals (Hester, 2015) in seawater, surface water and sewage (Lolic *et al.,* 2015). Naproxen detected in the environment with diclofenac (DCF), ibuprofen (IBP) (Kermia, 2016). They are detected in seawater, surface water and sewage (Mainero Rocca *et al.,* 2015). Frequently, in worldwide along high concentrations between 0.02 ng/L to 20.00 µg/L of DCF are found in ground water (Yang *et al.,* 2017), surface (including marine) (Alygizakis, 2017), sewage (Dasenaki, 2015) and even drinking water (Khaneta *al.,* 2015).

- **Anti-epileptic**

In the African environment that includes wastewater, drinking water and bio-solids has detected as a common antiepileptic drug (K'oreje *et al.,* 2016). Generally, Carbamazepine is detected in wastewater and in the environment, therefore it is widely studied globally (Fernandez- Lopez *et al.,* 2016).

- **Antibiotics**

Van Boeckel (2015) study demonstrated that antibiotics are present in the surface ground- and waste-water in many parts of the world, much greater than for humans because of the uncontrolled use of antibiotics in livestock breeding which use is. Antibiotics (Sulfamethoxazole, Ciprofloxacin, Trimethoprim, Ofloxacin, Norfloxacin) are the second most important pharmaceutical group found in effluent and influent of WWTPs (Liu *et al.,* 2020a, 2020b) with a 21 % detection frequency and concentration at 8128 ng/L (Hughes *et al.,* 2013) Although cephalosporins and penicillins are the most commonly used antibiotics, it is intriguing that β-lactam antibiotics are rarely detected in different bodies as Wastewater (Wang *et al*., 2018), sludge (Ostman *et al*., 2017), drinking water , groundwater (Yang *et al*., 2018), surface water (Ding *et al.,* 2017), sediments (Kafaei *et al*., 2018) and soil (Pan and Chu, 2018). Also, animals have been using antibiotics on a large scale to prevent or treat diseases. Like in poultry farming, antibiotics are may be administered through feed or drinking water to whole focks rather than to individuals animals (Behira *et al*; 2011). So, Residues veterinary pharmaceuticals, including a lot of non-biodegradable antibiotics, are introduced into the environment via land application of sewage sludge and animal manure.

- **Hormones**

Compounds detected in South African WWTP influent, effluent and river water were estrone, 17-b-estradiol, estriol, 17-aeethinylestradiol, progesterone and testosterone (Manickum and John, 2014).

Effect of pharmaceuticals residues in environment

PhACs found in water and the environments are biologically active to affect homeostatic mechanisms in the human body even at very low concentrations, so they are of public concern (Simazaki *et al*., 2015). At low concentrations, and long-term exposure to low doses of these compounds can cause adverse effects to ecosystems (song, 2018). Their presence on traces in drinking water for a long time, it can cause adverse effects on human health (Rudd *et al*., 2014; Hanif *et al*., 2021, 2022).

The presences of these bioactive substances in environment have been found to cause harmful effects to both aquatic organisms and human beings (Vasquez *et al*., 2014), by indirect effect, it can increase the susceptibility of organisms to pathogens, promote the prevalence of diseases in the aquatic ecosystem and cause changes at the population level (Ellis *et al*., 2011; Ali *et al*., 2021). For instance, many studies have indicated that the aquatic microorganisms such proteobacteria, algae, cyanobacteria, daphnia, and fish had a significant harm due to presence of antibiotics in water (Cheng *et al*., 2020).

Furthermore, recent studies have demonstrated that these pollutants are harmful to both invertebrates and vertebrates, at low or natural concentrations (Välitalo *et al*., 2017).Thus, the destruction of microflora and lower organism devastating to the entire ecological system, can change to the carbon recycling processes and the ecological environment, and basically will impact the health of humans (song, 2018).

In addition, pharmaceutical and antibiotics industries lie in the development of antibiotic resistance in all organisms (Tacconelli *et al.*, 2018). And it is shown to be global (aus der *Beek et al.,* 2016). The discharge of pharmaceuticals into the environment are the responsible reason for the risk of bioaccumulation, endocrine disruption, different kinds of diseases, acquisition of antibiotic-resistance gene in bacteria and changes in microbial populations or biomagnifications have described like pharmaceutical effects (Giulivo *et al.,* 2016). However, the shift in the structure of activated sludge bacterial communities and reducing of bacterial diversity in the reactors can affect the performance of secondary biological processes in wastewater treatment plants (WWTP) (Vasiliadou, 2 018). An increasing problem and one of our greatest global health threats today is Antibiotic resistance (WHO, 2018).The target population but also influence the non-target population affected by antibiotics with high toxicity impact (Grenni *et al.,* 2018).

Worldwide, many degradation products along with their parent compounds have been detected in WwTPs effluent (irrespective of the treatment methods) and in ground and surface waters (Su *et al.,* 2016). Adverse effects of degradation products on the bioluminescence of *Vibrio fischeri* was reported for the photocatalytic by-products of metoprolol degradation (Veloutsou *et al.* 2014).

The continuous exposure to drugs can alter the diversity and taxonomic composition of microbial communities in freshwater ecosystems by selecting for organisms that can tolerate or in some cases digest the contaminant (Lee *et al.* 2016). It was also reported that pharmaceuticals can alter microbial communities by suppressing algal growth and microbial respiration in biofilms (Rosi-Marshall *et al.,* 2013). In the case of various amines derived from pharmaceutical contaminants as ascorbic acid can act by inhibiting the growth of *pseudomonas fluorescence* (Behira *et el.,*2014). Also, the presence of antibiotics in the environments since their occurrence presents one of the possible pathways of propagation of antimicrobial resistance as a greater concern (Singer *et al.* 2016). A recent meta-analysis showed that between 1973 and 2011 the sperm, count of Western men expressed as sperm concentration and total sperm count reduced by 52% and 59%, respectively (Levine *et al.,* 2017). Therefore, methods using indirect exposure, based on predicted environmental concentrations, and human pharmacology and toxicology data of pharmaceuticals have been applied to assess the toxicological effects of drinking water or fish consumption on human health.
By contrast, a number of studies still point out some human health risks related to specific routes of exposure, influenced by the local handling of secondary sludge, agricultural disposal practices, the extent of secondary sewage treatment, and local food consumption patterns. Oldenkamp et al.(2014b) showed for instance that these factors were determined for the impact of two fluoroquinolone antibiotics (ciprofloxacin and levofloxacin) on the health.

Conclusion and recommendation

The supply of clean and safe drinking water free from any substances or organisms that pose a danger to human health is a major objective of the European Union Drinking Water Directive and the World Health Organization (WHO). Ineffective removal of wastewater treatement at degrading pharmaceutical contaminants (eg : antibiotics) increase drug in water, in wastewater treatment plant effluent and surface water, drinking water sources which cause adverse effects in ecosystems and in human health even at low concentrations (µg/L or ng/L). PhACs are contaminants of growing concern because of their increasing detection in WWTPs and bodies water. Various biological treatment technologies (e.g. activated sludge process, biofiltration, soil aquifer treatment, and managed aquifer recharge system) have been investigated for PhAC removal. However, reported removal rates are variable and many compounds are poorly removed. Further, to date, the rational design of efficacious and robust biological treatment technologies has been hindered by limited knowledge of the types of microorganisms capable of PhACs biotransformation and the conditions that promote their growth and activity. This review highlights the risks associated with the inadvertent presence of PPCPs in the environment may exert detrimental impacts on aquatic life. There is a clear need for the development of advanced WWTP technologies to more efficiently remove/degrade PPCPs.

SO, to safeguard both humans and the environment from the adverse consequences of environmental pollution novel approaches must be designed. Bioremediation is one such approach. However the present review specifically addresses the integrative role of the multi-omics approaches in microbial-mediated bioremediation. Additionally, we put light on the multi-omics approaches help to comprehend and explore the structural and functional aspects of the microbial consortia in response to the different environmental pollutants in this process. And improving our knowledge of the effects of exposure of bacterial communities to pharmaceutical compounds is relevant due to their future application in technologies for the removal of emerging contaminants. Finally, future research on PPCPs should not focus only on the parent compounds but also their potential degradation products/metabolites in various matrices.

Declarations

'Not applicable' for that section.

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