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REVIEW

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# Pharmaceutical Waste a Global Challenge to Ecosystem

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The authors declare that the manuscript was formulated in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Authors Contribution**

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

## Abstract

The pharmaceutical industry is one of the biggest industries, having a significant share of the world's economy. At the same time, with the high production of pharmaceutical products, this industry is becoming a significant threat to the environment by producing vast amounts of pharmaceutical waste, which imparts specific hazardous, debilitating effects on the environment. Waste products made by the pharmaceutical industry, mainly drugs that contain active pharmacological ingredients (APIs), cause hazardous effects on the environment. Primarily, Improper disposal of expired pharmaceuticals, ampules, or vials containing amounts of drugs, unused capsules, and pills in nearby water resources is the primary reason for the pharmaceuticals to come in contact with ecosystems. Secondly, the excretions by the personnel consuming drugs also contain some or some other active metabolite of pharmaceutical agents. Certain pharmaceuticals that remain persistent in their original form or as metabolites after exposure to environmental degradation and impart harmful effects on the ecosystem in which they are present are called 'Environmentally Persistent Pharmacological Products' (EPPPs). The toxic effects of these EPPPs are directly imparted on birds, animals, and humans, and it is an essential concern from a public health point of view as well. Certain important case studies are also included in the article.

## KEYWORDS

Pharmaceutical waste, environmental contamination, pollution, ecotoxicological waste, environmentally persistent pharmaceuticals, ecosystem, antibiotics,

## INTRODUCTION

One of the biggest sectors in the world, the pharmaceutical business, is in charge of medication discovery, research, manufacturing, and distribution. Fortunately, both the average lifespan and quality of life for humans are increasing due to the ongoing advancements in medical research. However, the rapid advancements in the pharmaceutical and medical industries are producing a significant volume of pharmaceutical waste. In 2022, the pharmaceutical industry generated around 1.48 trillion US dollars in sales globally, with an estimated average annual growth rate of 4%, which is highly concerning, just India is producing over 62 million tons of pharmaceutical waste (including both recyclable and nonrecyclable garbage), out of which almost 10-15 million tons of the garbage is of biomedical and pharmaceutical origin (Bhattacharya et al., 2021). Because of growth in pharmaceutical industry, research and manufacturing of new drugs newer and advance drugs are arriving. Thank goodness that medical science is constantly advancing and improving human longevity and quality of life.

Pharmaceutical wastes including used needles, syringes, bandages, plastic bottles, tubes, empty vials or ampules of vaccines, antibiotics, and other xenobiotics, as well as wastes generated from personal care products. The majority of individuals dispose of medications, vials, ampules, and unused or expired drugs at open landfill sites, dumping grounds, and other places because they are unaware of the possible risks and repercussions associated with improper disposal of pharmaceutical wastes. When these medications are disposed of improperly, the surrounding ecosystems get contaminated, which has dangerous consequences for those biological systems. With their high rates of population expansion, nations like India will face more issues as the amount of pharmaceutical compounds contaminating the ecosystem rises and their possible negative effects on biological systems become more of an international issue. There is proof that the introduction of pharmaceuticals into ecosystems and living things jeopardizes species variety, genetic diversity, and community diversity (Nestor et al.,2017).

From the perspective of public health, the environmental effects of pharmaceutical waste are quite significant. Pharmaceutical goods guarantee the drug's effectiveness and safety up to the indicated expiration date on the medication container. There is no guarantee that a medication will lose all of its efficacy or become ineffective after its expiration date (Vishwas, 2022). Research on the proper disposal of currently unused and expired medications is emerging, and it directly affects humans and other ecological life forms.

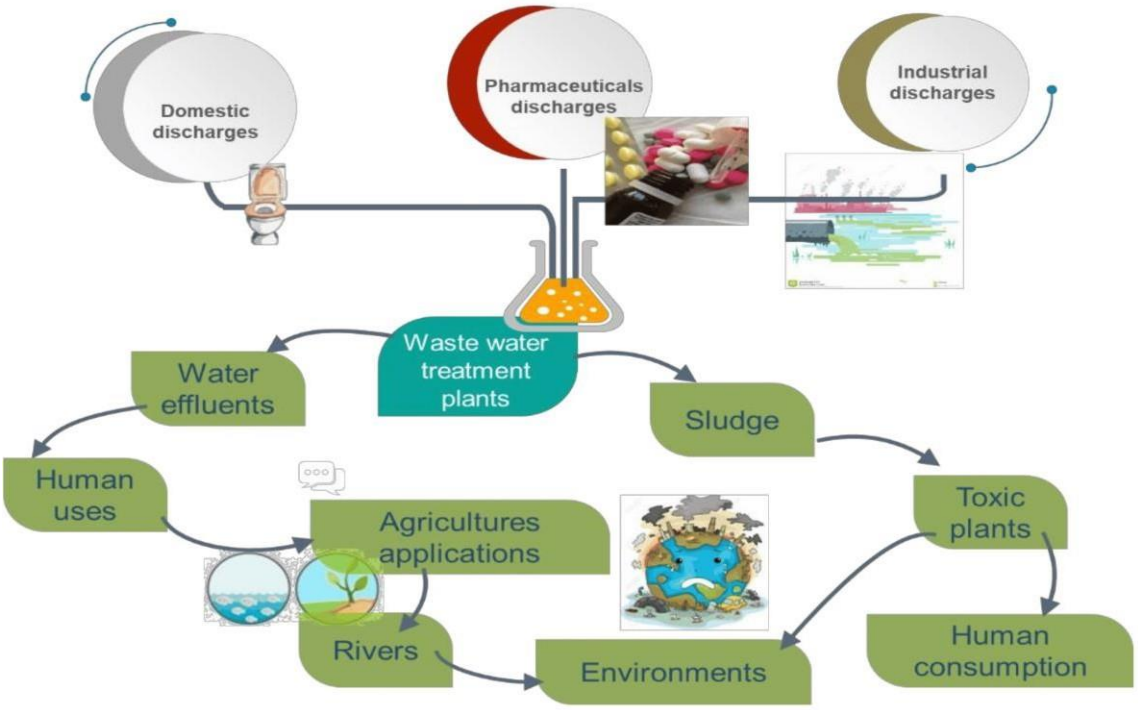


Figure 1- Sources pf pharmaceutical wastes to enter in the environment (Mansouri et al., 2021)

## ENVIRONMENTALLY PERSISTANT PHARMACEUTICAL PRODUCTS (EPPPs):

Consumers, medical professionals, chemists, druggists, and the pharmaceutical industry all excrete pharmaceuticals, which come out in the environment together via sewage and unused or expired medications, typically in close proximity to water bodies. Microbes found in surroundings go through a process of environmental deterioration with these products. However, certain compounds do not change at all, even after the breakdown process. Environmentally insistent pharmacological pollutants are pharmaceuticals that are tenacious in the environment and can pass in the non-target species, such as marine biodiversity and wildlife, and cause long-term bad impacts on these ecosystems, affecting their reproductive abilities and life expectancy and thus causing a decrease in the population of such non-target species. Environmentally persistent pharmaceutical pollutants slowly accumulate to manifest themselves into a final irreversible condition, which is frequently only noticed several generations later, affecting the sustainability of aquatic organisms' populations (Santos et al.,2010)

Human and animal pharmaceutical products, together with the metabolites (degradation products) that are associated with them, wind up in (Stahl-Timmins et al., 2013). The main way that drugs have been detected in these areas is through medical and veterinary procedures (Fick et al.,2009). Second, when drugs are consumed and subsequently dumped in open landfills, beneath sinks, or in restrooms (Bound et al., 2005). Afterward, the component of the drug is liberated and eventually contaminates the aquatic ecosystem since most individuals fail to dispose of their unwanted and expired prescriptions on the open land or in sewage (Gaw et al., 2014).

Recent studies have revealed that drugs can be seen in surface water, groundwater, municipal wastewater, as well as in potable water in low amounts. The effects and associated risks of long-term

exposure to low amounts of these pharmaceuticals in marine creatures are little understood (Sayadi et al., 2010). Pharmaceutical contaminants that are persistent in the environment have a considerable impact on aquatic bodies and water resources. The reason behind the improper eradication of EPPPs from municipal wastewater is the high cost and large investment required for these treatment techniques. This has become the most convenient way for EPPPs to enter the environment, and its seepage can directly contaminate groundwater supplies, having negative impacts on the population that depends solely on these resources for their regular water needs. Possible dangers of Encounter low quantities of pharmaceuticals can have the harmful effects mentioned below-

- Pharmacological action (interference of the immune system and hormones),
- Ecotoxicological effects (acute and chronic toxicity, genotoxicity, and carcinogenicity),
- The orientation of conventional toxicological research—individual compounds are experienced on a particular species—presents a substantial challenge in evaluating the ecotoxicological effects of persistent pharmaceuticals at the environmental level. Some of the first medications discovered in sewage were hormones, especially estrogen compounds, which have been detected in sizable amounts. (Shore et al., 1993).

Antibiotics are observed to be present in surface and ground waters, which is of concern because antibiotics in the environment lead to the formation of drug-resistant strains of bacteria. Exposure of bacteria to low doses of antibiotics causes the development of tolerance from the side of bacteria towards specific antibiotic drugs. When this antibiotic-resistant bacterium subsequently infects humans, regular doses and composition of therapeutic antibiotics remain ineffective against resistant bacteria. Antibiotic resistance is becoming the reason for almost 14,000 deaths annually, making an issue alarming for society (Reckhow et al., 2007).

Chemicals used in pharmaceutical production and manufacturing, persistent organic pollutants like polychlorinated biphenyls, perfluoroalkyl substances, and polybrominated diphenyl ethers (PBDEs), are a significant source of concern due to their toxic implications. There's a chance that these drugs will have pharmacological activity in creatures that aren't targeted since their molecular targets have evolved to be conserved in that species. (Ebele et al., 2016).

**Table 1- some important pharmaceuticals and their rate of removal from sewage treatment plant (source: e-bulletin "Panacea" by department of pharmacology AIIMS Rajkot)**

| Drugs | Removal rate |
|---|---|
| Clarithromycin, Erythromycin, Estrone, Lincomycin, Apramycin, Carbamazepine | 0% |
| Atenolol, Bezafibrate, Clofibric acid, Furosemide, Diazepam | 10-30% |
| Amoxicillin, ciprofloxacin, Enalapril, Ibuprofen, Ofloxacin | 30-60% |
| Hydrochlorothiazide, ranitidine, sulfamethoxazole | Variable |

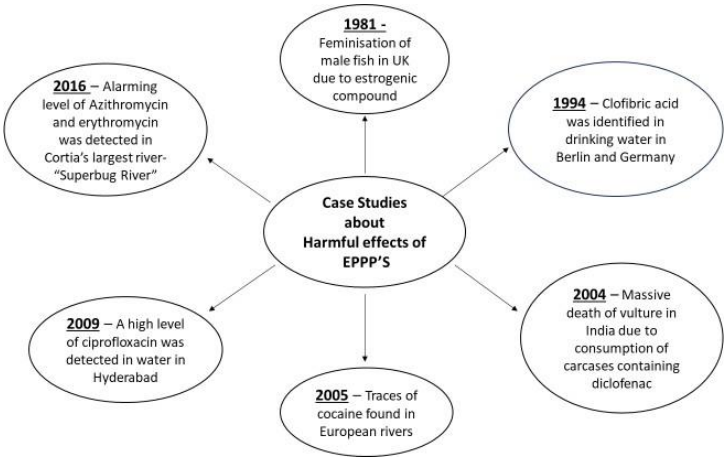


**Figure 2- Some important case studies showing harmful effects of EPPPs on environments [source: e-bulletin "Panacea" by department of pharmacology AIIMS Rajkot]**

Multiple drugs found in drinking water in Berlin, Germany.

In 1994, in the German municipal sewage treatment plan, certain pharmaceuticals belonging to particular classes of drugs were found, including lipid regulators, psychiatric drugs, beta-blockers, antiepileptic drugs, etc. Over 80% of drugs were found in one or the other municipal sewage treatment plant, with higher levels up to 6.3 µg, this happened because of the improper removal of drug residues from the sewage water after passage through a sewage treatment plants, leading to contamination of water bodies located nearby sewage treatment plant in which, the water was released after treatment. River and stream waters were used to measure 20 distinct medications and their related four metabolites. mostly acidic medications, such as phenazone, such as phenazone, bezafibrate, gemfibrozil, ibuprofen, diclofenac, indomethacin, naproxen, and metabolites clofibric acid and fenofibric (Thomas et al., 1998)

Feminization of male fish in United Kingdom because of presence of estrogenic EPPPs in effluents.

It was observed that in the United -kingdom and Europe, the occurrence of intersex fishes (fish present with both male and female reproductive tissues as well as feminized reproductive tracts) occurred due to the presence of certain estrogenic compounds in the effluents. These data set also implied that the amount of feminization in fish present in nearby aquatic ecosystems is directly proportional to the amount of estrogenic compound present in sewage water to which the fish is exposed. (Jobling et al. 2006).

The first assessments conducted in the United Kingdom concentrated on a small number of locations, some of which were deemed to be "hot spots" or areas with high sewage effluent concentrations (Harris et al., 1997; Tyler et al.,2008). Furthermore, within each risk category, the most severely feminized fish were found in the older year classes, thereby confirming the findings of previous investigations. In fish younger than three years of age, intersex was found to be a rare condition, thus indicating that the expression of this condition is progressive and appears at or after the onset of puberty in roaches. Occurrence and severity of the intersex condition were related more to the duration of exposure to effluent than to the year of hatching or to the predominant environmental conditions in the study rivers (Sorokin et

al., 2006). Subsequent examination of combined data sets from high-, medium-, and low-risk groups showed that increased exposure to steroid estrogens was linked with the occurrence and intensity of intersex. Additionally, Older classes from each risk group were found to be more susceptible to feminization, concluding the results of earlier studies. Intersex was shown to be an uncommon condition in fish under three years old.

**Deaths of Indian vultures due to consumption of carcass containing diclofenac**

Between 1999 and 2004, a sharp decline in vulture populations can be seen in Pakistan and the Indian subcontinent, accompanied by high vulture deaths and a notable decline in the number of vultures. Indian scientist Dr. Vibhu Prakash of the Bombay Natural History Society has been monitoring long-term vultures in Rajasthan, India's Keoladeo National Park. He recorded 353 nesting pairs of Oriental white-backed vultures (OWBVs; Gyps bengalensis) during the 1987–1988 breeding season. Just 20 nesting pairs were discovered during the 1999–2000 nest survey repetition, and neither this breeding season nor the one that followed saw any active nests (Prakash et al., 2003; Cuthbert et al., 2006a). 2- [2-(2,6-dichloro aniline) phenyl] acetic acid is the chemical name for diclofenac. In commercial formulations, it is sometimes known (and occasionally referred to) as Voltaren or Voltarol. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are a chemically various class of drugs that have parallel pharmacological actions (such as analgesic, anti-inflammatory, and antipyretic) to varied degrees. There are additional NSAIDs; however, the two most well-known in human medicine are still aspirin and ibuprofen. It is true that the discovery that diclofenac was the root cause of vulture deaths across Asia prompted serious questions regarding other veterinary NSAIDs. A survey of zoos and physicians included around 900 captive scavenger birds representing 79 species (Cuthbert et al., 2006b). A group of pathologists conducted a pathological analysis in 2001 and discovered significant renal damage following the necropsy of about fifty-five oriental white back vultures. Diclofenac's toxic effects caused significant kidney lesions that covered a large portion of the renal cortex, and they died without exhibiting any symptoms of chronic inflammation, resulting in acute renal toxicity in OWBV birds. Major indicators such as visceral gout, dehydration, and eggshell thinning were also seen, and these are the main reasons of the dramatic diminution in the population of oriental white-back vultures in Pakistan and India. These same governments removed the authorizations needed to produce veterinary diclofenac domestically in 2006. 2008 saw India pass legislation making it illegal to produce, distribute, or use diclofenac for veterinary use. The Indian government went one step further and outlawed the use of multidose vials of diclofenac, which were still available but were meant to be (Ngaio et al., 2007).

**Cocaine traces found in rivers across Europe causing harmful effects on eels**

Between 2005 and 2009, cocaine consumption became an increasingly prevalent societal issue in Belgium. Investigation for cocaine and its metabolites was done from 28 rivers and 37 wastewater treatment plants in the country Belgium via solid-phase extraction and liquid chromatography coupled with mass spectrometry; benzoylecgonine (BE) and ecgonine methyl ester (EME), which are metabolites of cocaine were found, COC and BE were found in amounts ranging from less than one to 753 ng/L and less than one to 2258 ng/L, respectively, whereas EME was not detected. Due to their ongoing exposure to compounds with substantial pharmacological action, aquatic creatures may now face an emerging threat of the

presence of illegal drugs in the marine ecosystem. The overall health of the eels, the skeletal muscle's morphology, and a number of parameters indicating the skeletal muscle physiology were observed. Muscle protein profile, which is a marker of the main muscle proteins' expression levels; cytochrome oxidase activity, caspase-3, which indicates apoptosis; and alteration in the serum levels of certain enzymes like lactate dehydrogenase, creatine kinase, and aspartate aminotransferase, are markers of skeletal muscle. (Van Nuijs et al., 2009)

Eels exposed to cocaine seemed energetic, but their overall health state was the same as that of the other groups. On the other hand, their skeletal muscle displayed signs of severe damage, such as swelling and muscular breakdown, which are typical of rhabdomyolysis. Subsequent to ten days of the cocaine exposure, these alterations remained. In fact, every other parameter that was looked at exhibited changes that lasted for at least ten days after the cessation of cocaine exposure, with the exception of the expression levels of the primary muscle proteins, which did not change. This study demonstrates that the morphological and physiological structures of the silver eel's skeletal muscle are severely damaged by cocaine, even at low ambient concentrations. This confirms the detrimental effects of cocaine on the environment that may have an influence on the ecosystem. (Capaldo et al., 2018)

**Presence of antibiotics in Indian rivers:**

In scientific parlance, bacteria that can withstand a broad spectrum of drugs are referred to as multidrug-resistant bacteria. (Adegoke et al., 2016). The rise of carbapenem-producing bacteria, particularly the "superbug" NDM-1, or New Delhi Metallo-β-lactamase, is a serious health issue since it can hydrolyze a variety of β-lactam antibiotics, rendering them useless for treating severe infections. The NDM-1 gene was initially found in 2008 in Klebsiella pneumoniae isolate that was taken from an individual of Indian origin in Sweden (Yong et al., 2009). Subsequently, its presence was verified in many nations worldwide (Gottig et al., 2010). Efforts should be made to reduce the widespread and unnecessary use of antibiotics in India's general population ever since the superbug was first reported. If the bioactive substances utilized for human and veterinary needs are exposed to the environment unchecked, it will have a significant negative effect on the ecological system. It is also anticipated that the degraded versions of these chemicals would increase the extent of their environmental effect (Smit et al., 2015).

**Strategies for management of pharmaceutical wastes (Khan et al., 2021)**

Medical professionals who work in quality assurance, government administration, policy planning, recycling businesses, etc., have challenges when it comes to pharmaceutical waste management. The authorities need to use a variety of tactics and strategies to reduce disposable material. The following are some crucial tactics that may be used to manage pharmaceutical waste as efficiently as possible:

A] **Incineration:** "Thermal treatment" refers to incineration and other high-temperature waste treatment methods. Waste materials are burned by incinerators and converted into ash, gas, heat, and steam. Both small-scale and large-scale incinerators are used in the industry. The standards governing incineration must have an intricate design, such as a double chamber, and incorporate a scrubber as a means of controlling air pollution. It is necessary to disposal of the ash from these incinerators in a safe -landfills.

B] **Secure landfilling**: Pharmacies are disposed of via secure land dumping at a landfill that is specifically constructed and used to handle hazardous waste. The Biomedical Waste Rules suggest that solid chemical wastes, incinerator ash, and cytotoxic pharmaceuticals be disposed of in safe landfills. Burying rubbish entails disposing of it in a landfill, and most nations still use this standard procedure. Waste materials may be disposed of in a sanitary and reasonably priced way by using a landfill that has been carefully planned and maintained. The production of liquid leachate, the attraction of rodents, and wind-blown debris are just a few of the negative environmental effects that older, poorly built, or poorly managed landfills may cause. Waste that has been deposited is often covered to keep rodents (such as mice and rats) away and compacted to improve density and stability.

C] **Waste immobilization**: Inertialization mainly involves the removal of the packaging materials, paper, cardboard, and plastic, from the pharmaceuticals. Pills are supposed to be removed from their blister packs. The waste pharmaceuticals are then processed to form a homogenous paste. Workers should take precautions by wearing protective clothing, and masks are required as the dust of these pharmaceuticals can harm them. With the help of a concrete mixture truck, a liquid paste of the pharmaceuticals is made. The paste then transformed into a solid mass. The procedure is moderately low-priced and can be carried out with unsophisticated equipment. The practice mostly involves a grinder or road roller to crush the pharmaceuticals, a concrete mixer, and supplies of cement, lime, and water. The process of encapsulation includes solidifying the medications inside a steel or plastic drum. Before being used, drums should be cleansed and free of any explosive or dangerous components.

D] **Sewer**: Certain liquid medications, such as syrups and intravenous (IV) fluids, can be flushed into sewers in over time without imparting a significant harmful impact on the environment or public health when diluted with water. Fast-moving waterways can also be utilized to flush tiny amounts of liquid antiseptics or medications that have been diluted. When sewers are in bad conditions, the consultation from hydro geologist or sanitary engineer should be done about repairing. (Sharma N et al., 2010). Avoiding direct entry of pharmaceutical waste generated either by industries or my households and hospitals in nearby water bodies can be the best possible way to avoid direct contamination of ecosystems. Proper sewage treatment plants for the treatment of IPs present in wastewater entering in nearby rivers, ponds, sea, and even landfills can be established and can be a good strategy for avoiding contamination and hazards caused by these EPPPs to the biodiversity in a particular area.

## CONCLUSION

The pharmaceutical industry has an important contribution to the world's economy. At the same time, improper disposal of the waste generated by this industry can cause hazardous effects. The consequences of improper waste management, lack of knowledge about deleterious effects of pharmaceutical wastes in the environment among healthcare workers and personnel using or consuming medications, ignorance and unawareness by municipal authorities about proper disposal and sewer treatment of pharmaceuticals cumulatively act for disturbances in locally situated ecosystems and affect the biodiversity of the particular geographical region. The pharmacologically active compounds which remain persistent in the environment, called EPPPs, can remain in the environment for a timespan of more than one year. This compound or its

active and environmentally stable forms get introduced into the environment either directly or via the excretion of the patient consuming it. By entering into locally situated water bodies or by seepage from landfills, EPPPs enter the ecosystem and impart deleterious effects on local biodiversity, like in the case of eels located in European rivers, which are affected by the presence of cocaine in waterbodies. Oriental white back vultures in the Indian subcontinent are getting affected because of consuming carcasses containing diclofenac and are subjected to bioaccumulation of diclofenac, causing acute and chronic renal damage and thinning of egg shells, causing a drastic decrease in their population, which is an alarming situation. Because of the release of antibiotic residues in rivers, the microorganisms that are resistant to advanced antibiotics are developing and are called 'superbugs,' which is a classic example of the side effects of antibiotic overuse in medical as well as veterinary practices. We developed these pharmaceuticals and drugs, which proved to be a boon for mankind and have a major role in increasing sustainability and quality of life of mankind, but at the same time, certain mistakes and small ignorance towards its disposal can become a potential threat for humans as well as biodiversity present around us. Awareness and cumulative efforts taken by people, government, and industries can change this picture and lead humanity and the biome toward a better tomorrow.

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