IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2021 Vol.:21, Issue:3

Ecopharmacology - Is It a Necessity for Human Survival?

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An official Publication of Human Journals
ISSN 2349-7203
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Submitted: 22 May 2021
Accepted: 29 May 2021
Published: 30 June 2021

Keywords: Ecopharmacology, Active pharmaceutical ingredients (API), Ecotoxicity, Ecoshadow, Green chemistry, Ecopharmacovigilance

ABSTRACT

Over the years there has been an increasing global concern on the potential impact of pharmaceuticals on the environment. Ecopharmacology is a new branch of science concerned with the entry and the potential ecotoxic effects of the active pharmaceutical ingredients (API) on the environment. Pharmaceuticals from various therapeutic classes enters into the environment either through excretion after human use, agriculture, and veterinary use, through the disposal of expired medicine, and as residues from manufacturing units. The non-targeted population is at the receiving end of the consequences of these pollutants, with direct onslaught for years together. Varying concentrations of pollutants found in water sources can harm aquatic life and human health. Antibiotics in sub-therapeutic doses used as 'growth promoters in poultry have resulted in Multidrug resistant (MDR) strains of human pathogens. Precautionary measures should be undertaken to attenuate these adverse effects of pharmaceuticals on the environment. Green Pharmacy is one among them which aims at zero pharmaceutical waste in our environment. Ecopharmacology is thus an important science to be considered as it is still in its infant stage in almost all parts of the world. It could therefore be a part of the regulatory requirement former to the launch of any new drug.

INTRODUCTION

Pharmaceuticals have been really helpful to mankind although accompanied by many known and unanticipated hazards to consumers, either directly or not [1]. If they are bliss to humanity, they are also causing diseases. But, what about human medicines when they have a sequel on the environment?[2] There has been growing concern among scientists and environmentalists about the vast amount of drugs that end up in the environment one way or another. Impacts of drugs on ecology have long been regarded as an under-explored arena of the investigation but are in fact, a potential research hotspot [3].

Ecopharmacology as a novel branch of science was uprooted to ensure that consequential environmental problems associated with pharmaceuticals are pointed out in a timely way and maneuvered accordingly. Developed parts of the world have expeditiously adapted to the concept, however, developing countries are still on the verge of acceptance [4]. With only limited data available on the topic, its extension on to a wider sector and evaluating its impact therein has become the major concern for environmentalists, ecologists and pharmacologists alike. This review targets to collate published data on the effects of pharmaceuticals on our environment and various strategies to productively tackle the issue.

Definitions

Following is the list of definitions on the various branches of science which deals with the ecological role of pharmaceuticals.

Ecopharmacology- Ecopharmacology describes the entry of chemicals or drugs into the environment through any route and at any concentration disturbing the balance of ecology (ecosystem), as a consequence [5].
Ecopharmacovigilance - Holm *et al* defined it as "the science and activities associated with the detection, evaluation, understanding, and prevention of adverse effects of pharmaceuticals in the environment" [6].
Environmental pharmacology- is defined as "the effect of pharmaceuticals and house care products on the environment and ecosystem" [7].

Pharmacoenvironmentology- The term environmental pharmacology was coined by Halling Sorensen in 1998. It seeks to deal with "the environmental impact of drugs given to humans and animals at therapeutic doses"[8].

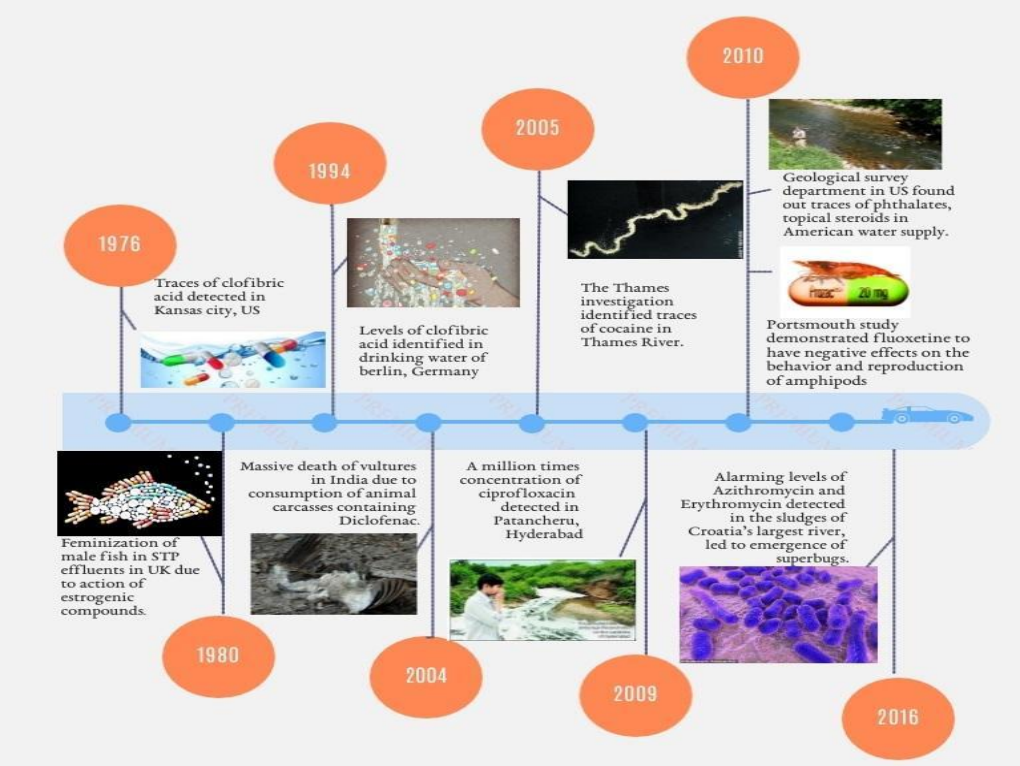

Figure No. 1: Historical background - A chronological sequence of events for organizing a screening system on the ecological impacts of pharmaceuticals [4, 8-12].

PHARMACEUTICALS IN THE ENVIRONMENT: SOURCES AND ITS ENTRY

Pharmaceutical Products (PPs) and other key ingredients are emitted during the processes of production, consumption and discarding of medicinal products which are used for both human and non-human purposes [13].

Human sources

Pharmaceutical products are qualitatively, quantitatively, spatially and temporally shared out into the environment by different routes due to enormous humanization and the consumption of drugs in private households or hospitals and other places [14]. The entry of these compounds from the human body to the environment is:

- When a drug is given to the patient, it may be metabolized to a greater or lesser extent and released into the environment as the parent drug or its metabolites, or as a combination. For example, 80-90% of the Amoxicillin is released in the parent form, while only 3% of Carbamazepine excreted in unchanged form[15].

- The pharmaceutical ingredients can be released into the environment consequently from the washing of medicine applied skin and remnants excreted from the skin via sweat [16]. It has been reported that transdermal patches containing fentanyl retain 28-84% of the loaded drug after removal from the skin [17].

- The unused or expired drugs are usually thrown directly in toilets or end up in land fill or disposed of into sewer networks. These substances are subjected to biological and chemical degradation processes, but some may still spread on land and even leach into surrounding groundwater and rivers[18].

Hospital

The practice of modern medicine demands the production of large amounts of pharmaceuticals and personal care products globally. The dispensing and utilization of drugs in the hospital setting are increasing with time. Two major factors of drug accumulation are patient non-compliance and dispensing of purportedly excessively large quantities [19].

Estimates from Denmark reveal that hospitals are the source of 24% of the total antibiotic load in the Capital Region[20]. For specific pharmaceuticals such as cytostatics, hormonal preparations or radiocontrast agents, it is seen that hospitals are the predominant contributors (70-90%) while for analgesics or antihypertensives they contribute less [15]. It is determined that antibiotic discharge volume into wastewater by European hospitals approximates 86 tonnes annually. Furthermore, large scale uses of disinfectants in hospitals for various purposes also lead to their build-up in wastewaters [21].

Household

Two main routes for the entry of pharmaceuticals into the surroundings from private households are:

- One is the effluent from WWTPs after being eliminated from the body. Effluents are contaminated by the drug residues released from human or animal sources after its administration. Depending on the drug characteristics, a significant quantity are excreted

unchanged and reaches sewage sludge via toilet or sink which flows to the surface water [16]. For instance, Nadolol, an adrenergic antagonist, is eliminated unchanged from the body [22]. In contrast, only 4% of the parent form of the analgesic paracetamol is excreted in the urine unchanged; the remaining may be excreted as glucuronides, sulphate, cysteine and mercapturic acid metabolites through urine [23].

Table No. 1: Excretion rates of unchanged parent form of selected pharmaceuticals in urine. [22-24]

Pharmaceutical product	Pharmacological class	Parent compound excreted (%)
Ibuprofen	NSAIDs	10
Paracetamol	Analgesic	4
Amoxicillin	Antibiotic	60
Erythromycin	Antibiotic	25
Sulfamethoxazole	Antibiotic	15
Atenolol	Antihypertensive	90
Metoprolol	Antihypertensive	10
Carbamazepine	Antiepileptic	3
Felbamate	Antiepileptic	40-50
Cetirizine	Antihistamine	50
Benzafibrate	Hypolipidemic	50

- The other route is the discarding of expiry products or unused medicines which are dumped via sink/toilet or in domestic waste taken to the disposal areas [25]. Improper disposal of a single blister of EE2 (Ethinyl estradiol) pills for one menstrual cycle in a dose of 30 mg has the potential to pollute 24 million litres of water, which approximates contaminated water generated daily by a city of 10,0000 inhabitants" [26].

Industrial sources

Recent researches have shown direct emissions from drug manufacturing sites causing heavy environmental discharges that exceed toxic threshold concentrations substantially in some

cases. Generally, the effluents produced are non-biodegradable and enter into water bodies and soil [22]. Because production is concentrated in specific sites, the risks are not associated with mode of use. Therefore, the environmental hazards associated with manufacture include a distinct, broader range of pharmaceuticals relative to those associated with the risks of excretion [27].

The first a series of papers published in 2007 reported at Patancheru, near Hyderabad, India showing high emission of pharmaceuticals from drug manufacturers. The concentration of ciprofloxacin, a broad-spectrum antibiotic, was elevated to 31 mg/l, approximately 1 million times more than that present regularly in processed municipal sewage effluents and noxious to a wide variety of organisms. The combined total 1-day release of ciprofloxacin was 44 kg, that is equal to the total intake of ciprofloxacin in Sweden over 5 days, or in other words, adequate to treat everybody in a city with 44000 inhabitants.

Corresponding to these findings in India, a Chinese factory, mg^{-1} levels of oxytetracycline were detected in final processed effluent and in dwelling surface water, whereas large concentrations of penicillin metabolites were reported in another factory. These findings attracted widespread attention from media, which led to increased scientific and societal interest in this route of exposure [28].

Veterinary sources

The third most often listed emission source for pharmaceuticals is veterinary. The application of pharmaceuticals in food-producing livestock has serious health implications to people as the drug remnants are seen in meat, eggs, milk and honey [29]. In many instances, about 90% of the antibiotic administered orally may excrete unchanged in animals. When eliminated from animals through urine and manure, they can reach the surface and/or groundwater by the means of a non-point source pollution through manure-applied grounds [30]. The literature reveals that most of the expelled antibiotics are not easily degraded and are actively adsorbed in soils. All other antibiotics except erythromycin and few sulpha drugs can persist in surface waters even in minute quantities. However, in most of the cases, quantities observed are in parts per billion ranges; 100 to 1000 folds beneath minimum inhibitory concentration [31].

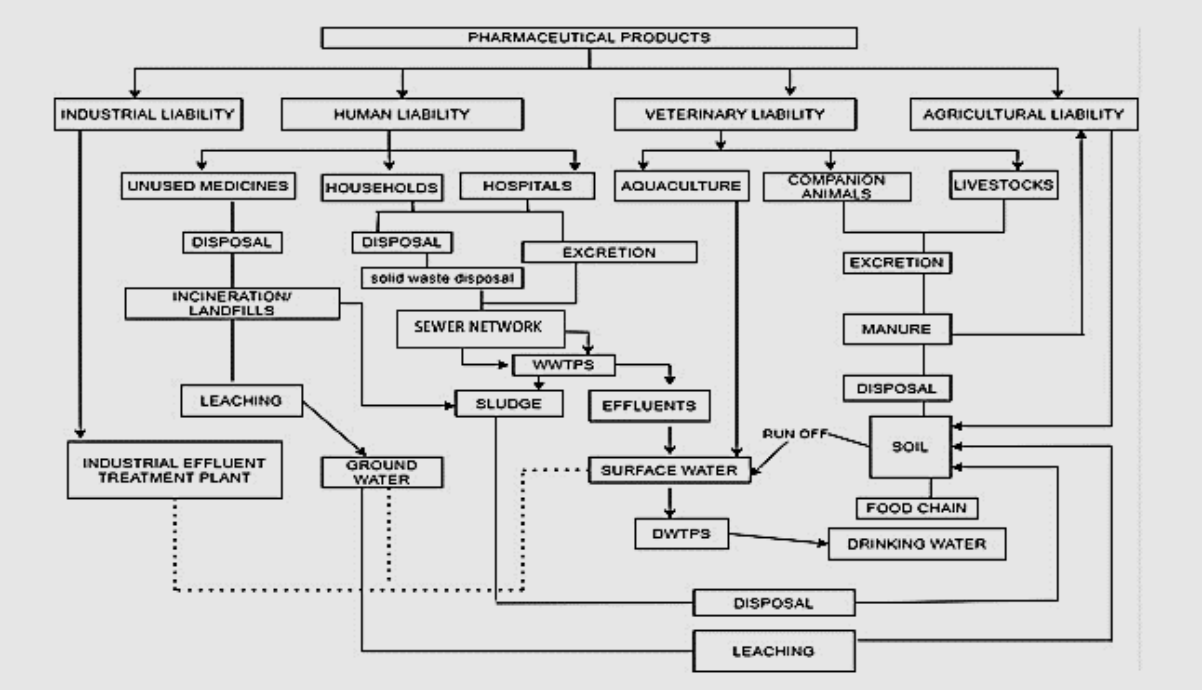

Figure No. 2: Pathway of pharmaceuticals in the environment from different sources [32-34]

PHARMACEUTICALS WITH POTENTIAL ECOTOXIC EFFECTS

Pharmaceuticals freed into the environment can be considered under different categories and definitions.

- **Pharmaceutical active compounds (PhAC)** may enter the environment by one route or other as a parent compound or pharmacologically active metabolites. Once PhACs enters the environment, they undergo biodegradation.

Table No. 2: Most commonly observed PhAC[7]

DRUG CLASSES WITH EXAMPLES
Beta-blockers: Metoprolol, propranolol, betaxolol, bisoprolol, nadolol.
Steroid and hormonal preparations: 17 alpha Ethinyl estradiol, 19-norethisterone, mestranol.
Antibiotics: Macrolides, sulfonamides, fluoroquinolones, chloramphenicol, trimethoprim, lincomycin.
Anticonvulsants: Carbamazepine, primidone.
Antidepressant: Fluoxetine.
NSAIDs: Acetyl salicylic acid, codeine, diclofenac, ibuprofen, paracetamol, Ketoprofen, naproxen.
Miscellaneous veterinary drugs
Household products
Pesticides and insecticides
Radiocontrast agents Barium salts

- **Pharmaceutical and personal care products(PPCPs)** refers to any product used by individuals for personal health or cosmetic reasons. It comprises all human and veterinary drugs, diagnostic agents, "nutraceuticals" and other consumer chemicals such as cosmetics, fragrances and sun-screens, "excipients", biopharmaceuticals, dyes, pesticides and many others [5, 35].
- **Environmentally persistent pharmaceutical pollutants (EPPP)** are defined as compounds that resist biodegradation by microbes and persist in the environment in the active form. EPPPs are found in water and contribute to the extinction of species and the imbalance of the ecosystem; causing developmental, genetic, immunological and hormonal health effects in humans and other species or the development of resistant microbes. External half-lives of these agents though dependent on the environment (water, air, soil, and sludge) are generally long and maybe more than one year for various compounds. For instance, a study revealed that although clofibrate has not been in use for a great deal of time its metabolite clofibric acid was found very recently in surface and well-water [36].

FATE OF PHARMACEUTICALS IN THE ENVIRONMENT

- Once PhACs enters into the environment, they suffer one of three following fates which include: a) Biodegradation into carbon dioxide and water, e.g. aspirin b) Undergo some other forms of degradation to form metabolites c) Remain in the environment unvaried and end up in the receiving waters [37].

- Different processes such as aerobic-anaerobic biodegradation and abiotic transformation in particular sediment sorption, hydrolysis and degradation of UV-light are used for controlling the dissipation of pharmaceuticals in the aquatic nature. The process is selected based on the physicochemical properties of the pharmaceuticals and the particularities of the targeted environment.

- According to recent reports, the most momentous methods for the removal of pharmaceuticals from the dissolved state are aerobic and anaerobic biodegradation. The expulsion of drugs from the system depends upon the age of the sludge and hydraulic retention time [38]. In accordance to previous researches, the bio-degradation of Diclofenac occurs when the sludge retention time was at least a minimum of 8 days [39].

- Oftentimes drugs are excreted in the form of conjugated and non-conjugated polar metabolites. However, cleavage of the conjugates in sewage treatment plants (STP) may result in the liberation of API as known for the steroid hormone and estradiol in the contraceptive pills, 17- ethinylestradiol[40,41].

Table No. 3: Removal rates of various drugs in the STPs [36,42]

Drugs	**Removal rate**
Carbamazepine, Clarithromycin, Erythromycin, Estrone, Lincomycin, Spiramycin	0%
Atenolol, Benzafibrate, Clofibric Acid, Furosemide, Diazepam	10-30%
Amoxicillin, Ciprofloxacin, Enalapril, Ibuprofen, Ofloxacin	30-60%
Hydrochlorothiazide, Ranitidine, Sulfamethoxazole	variable

- As drug compounds are often resistant to hydrolysis, this reaction can be characterized as negligible for most human drugs. Direct and indirect photolysis, on the contrary, is a primary route of abiotic transformation of pharmaceuticals in surface waters (sulfamethoxazole,

ofloxacin and propranolol) [42]. Pharmaceuticals such as clofibric acid and carbamazepine in organic-free and salt-water undergoes slow photodegradation within an estimated half-lives in the span of 100 days at latitudes of 50°N in winter. Apart from substance properties, the efficacy of photodegradation depends upon the strength of the solar irradiation thereby on latitude and season [38].

- Another important phase for elimination is the sorption of pharmaceuticals which later on may have an implication on the distribute and bioavailability of pharmaceutical compounds in the environment, and their removal upon wastewater treatment [43]. Laboratory studies detected the sorption behaviour of pharmaceuticals such as NSAIDS and benzodiazepines (diclofenac, ibuprofen and carbamazepine) in sandy sediments and showed that sorption coefficients were relatively low. For instance, some antibiotics, e.g. tetracyclines, are known to bind to soil or to form complexes with ions that are present [42,44].

HARMFUL EFFECTS OF PHARMACEUTICALS IN ENVIRONMENT

Negative consequences to the aquatic and wildlife

- **Feminization of fishes**

Sewage water in many locations are reported to have high estrogenic content such as synthetic estrogen – 17 α ethynylestradiol (EE2) which are used in oral contraceptive pills or estrogen mimics like nonylphenol. These substances harm the reproductive health of fishes. This effect was first reported in the United Kingdom. The male fishes showed feminization by abnormally producing Vitellogenin (VTG), a protein that female fishes synthesize during the production of eggs, in testes. In France, a very high ratio of intersex Gudgeon fishes were reported in Dore River, near steroid drugs production sites [7,40].

- **The disappearance of dung beetles**

Avermectins are the widely used class of veterinary medicinal product (VMP) and pose a serious environmental risk. The drug residue being an insecticide kills a large variety of insects that feed on dung. Moreover, it also inhibits the growth of eggs and larvae of flies. This deleterious effect has ended up in the disappearance of the dung beetle and thus negatively affects the food chain by reducing the food source for birds [45].

- **Developmental delay in amphibians**

Antidepressants such as Fluoxetine (SSRI) are found in water sources. As most of these chemicals are non-degradable or take more time, they find their way up the food chain. This result in developmental complication in the aquatic organism such as delayed development of tadpoles in untreated sewage water and behavioural changes in other aquatic species [46,12]. Swimming activity of shellfish has been altered by fluoxetine and if this has happened by a decline in serotonin level is yet to find out [47].

- **Drug contaminants in biofilms**

Biofilms are extracellular polymeric matrices composed of polysaccharides, lipids and DNA produced by microorganisms which encapsulates them and makes them bind to each other and surfaces. Bacterial biofilms reduce the antibacterial efficiency of topical agents in healing infections and may impair wound healing. Sub-therapeutic levels of antibiotics such as B-lactams resulting from improper disposal of unused drugs or used as growth promoters in agriculture, induce biofilm formation in *S. aureus*. Anti-diabetics and antihistamine medications can cause serious disruption to the biofilm. Propranolol and fluoxetine have deleterious effects on zooplankton and benthic organisms [48].

- **Toxic effect of anti-parasites in fish farming**

Anti-parasites such as Emamectin benzoate are used in fish farming for the treatment of sea lice. This is very poisonous to marine crustaceans. For example, dying Nephritis (Norway Lobster) was reported in Loch Shell, Scotland after sea lice treatment at fish farms in 2010 [49].

Impact on human population

Although there are no systemic studies to show the definite hazards or toxic manifestations in human species from the pharmaceuticals distributed in ecology through the skin and oral exposure, effects on various animal species have been demonstrated. The ineluctable interplay between the different ecological compartments renders humans to be the direct or indirect victim of drug pollution. Even though humans are at greater risk to be threatened with such pharmaceutical agents, further investigations are needed to establish the extent of the same [2].

- **Auto-immune disorders and endocrine abnormalities**

Some of the available current data support the role of the environmental exposure of pharmaceuticals and the development of specific autoimmune disorders. Crystalline silica exposure is associated with the development of systemic sclerosis (SSc), systematic lupus erythematosus (SLE), rheumatoid arthritis (RA) and anti-neutrophil cytoplasmic antibody (ANCA) related vasculitis. It can be thought of as an indirect effect of Xenobiotics on autoimmune disorder induction. The mechanisms by which environmental factors alter basic biological processes to induce autoimmune diseases continue to be examined but remain largely unknown [50].

The endocrine-disruptor hypothesis was initially devised for xenoestrogens. EDCs (endocrine disrupting chemicals) are natural or manmade compounds including pharmaceuticals that mimic or interfere with the action of hormones. EDCs act via receptors of the steroid receptor superfamily and can affect many organs of the body. Environmental toxins can also affect the components in different cellular regulatory systems including the steroid and thyroid hormone receptor families. The functions of the brain, the cardiovascular, the urogenital system and the skeletal are regulated by these hormones and can therefore be affected by EDCs [51].

Table No. 4: Specific effects of EDCs on human population [51]

Categories:	Specific effects of EDCS
Males	• Poor semen quality • Testicular cancer /prostate disorders • Malformed reproductive tissue
Females	• Breast and reproductive tissue cancer • PCOD • Endometriosis/uterine fibroids
Children	• Impaired behaviour, mental, immune and thyroid functions • Precocious puberty and obesity, osteoporosis

- **Effects of cytotoxic agents**

While looking at the chemotherapeutic agents, the health effects on total lifetime consumption of natural resources contaminated with their ultra-low concentrations are way

lower to induce any pharmacological or toxicological manifestations. For instance, a normal chemotherapeutic dose administered for Bleomycin is 20–30 mg/m^2, while its concentration found in portable water samples was 1.3 × 10^{-5} mg/l [52]. Nevertheless, there is a need for serious investigation on the occurrence of drugs in running water, their variability in space and time and the associated uncertainty factors. Human studies have detected 1% of the total dose of cyclophosphamide being excreted in the urine in unchanged form when 1 mg of the drug is topically applied [16]. Furthermore, researches on drug compounds intended to evaluate their collective effectsare scanty and necessary in the short future[53].

- **Impact of Epigenetic Changes**

The term 'Epigenetics' refers to heritable changes in gene expression without the accompanying alterations in the DNA sequence. Commonly used pharmaceutical drugs can cause persistent epigenetic changes by altering epigenetic homeostasis. Epigenetic mechanisms can be restructured leading to profound diseases like cancer.

- Drugs that affect chromatin architecture or DNA methylation can cause direct effects. E.g.: Hydrazine inhibits DNA methylation while isotretinoin has transcription factor activity.
- Diseases such as 'tardive dyskinesia' have also been implicated to having epigenetic effects.
- May be involved in the aetiology of cancer, heart disease, neurological and cognitive disorders, diabetes, obesity, infertility and sexual dysfunction.
- Drug-induced SLE may be epigenetic.

A study in New York City reported that children were more likely to get serious breathing problems like asthma when exposed to higher levels of polycyclic aromatic hydrocarbons (PAH) in the womb than those not exposed [7,54].

Antimicrobial pollution and emergence of resistance

Antibiotics on a large scale have resulted in antibiotic pollution furthermore leading to a major threat to public health i. e. antibiotic resistance. On the other hand, it is also argued that antibiotics present in the environment are at very low concentration thereby negligible risks to mankind [37].

However, antibiotics present in the environment even at lower concentration may build up in inhabitants through continuous exposure to the polluted environment. For example,

antibiotics such as macrolides and quinolones have been previously identified in chlorinated drinking water[55]. Triclosan, an antimicrobial compound has been detected greatly in various water bodies around the world and, more recently, in urine, human serum and breast milk of individuals not currently using antimicrobial, with health effects ranging from reproductive problems to muscle weaknesses [56].

The term **Ecoshadow** has been introduced to describe the environmental impact of antibiotics. Broad-spectrum antibiotics that are stable will have a larger impact on the bacterial flora (a long eco-shadow) than those with a narrow antibacterial spectrum which dissociates more rapidly (a short eco-shadow) [43].

a) Antimicrobial resistance from hospitals

Hospitals use wide range of antibiotics over longer duration, causing *de novo* resistance to evolve. Antibiotic-resistant pathogens including the resistant opportunistic pathogen *Pseudomonas aeruginosa*, *Escherichia Coli* carrying ESBL and Vancomycin-resistant enterococci (VRE) are enhanced within hospital effluents. Despite the fact that hospitals are subject to a great deal of scrutiny, they provide reasonably controlled environments for antibiotic use, and resistance evolution is relatively easy to monitor [57]. Antibiotic use by the general public, on the other hand, is widely unauthorized. Likewise, even when correctly used, approximately 70% of antibiotics pass the human digestive system unaltered and are excreted via urine [58]. Whereas in municipal sewages, these antibiotics are mixed with ARBs (antibiotic-resistant bacteria) and ARGs (antibiotic-resistant genes) [57].

b) Sewage plants as a potential reservoir for resistance

Sewage from hospitals and the general public is combined and transported to WWTPs, where it is biodegraded using a variety of biological and physicochemical processes. Sewage is a highly nutrient-rich habitat that supports wide range of bacteria and has been constantly supplemented with new ARBs, ARGs, and antibiotics themselves. Although ARB and ARG abundances in sewage water are greatly reduced, WWTP treatment has a much lower success rate in reducing the abundance of resistance genes in biosolids. Prolonged treatment of antibiotics within broader spectrum can thus lead to resistance evolution between the ecosystem and the general populace. Antibiotic use in the general population is difficult to regulate, hence WWTPs may be a key point of intervention in preventing resistance evolution and transmission[37,44].

c) The mechanism involving fish and aquaculture

Antibiotics are directly applied through pens in open-water aquaculture to support growth and prevent disease, resulting in the evolution and widespread dispersion of ARBs and ARGs in open waters. On the other hand, closed systems, in which human or animal waste is fed to fish in aquaculture, are of significant importance because they may aid in the transfer of multi-resistant genes between systems [57].

Sub-inhibitory levels of macrolides, for example, were shown to cause abnormalities in zebrafish, such as yolk sac swelling and non-inflated swim bladder, as well as affecting the spontaneous movement in embryos[58]. Experimental fish models exposed to antibiotics such as quinolone, sulphonamide and tetracycline also showed similar results. Furthermore, quinolones and their metabolites can remain in the body for a long time, causing bioaccumulation and chronic toxicity [57]. Antibiotic pollution has also been shown to be harmful to amphibians, with tetracycline causing pericardial oedema, shortened body length and other malformations in Xenopus tropicalis, despite being studied less frequently[59].

d) The role of the livestock production environment

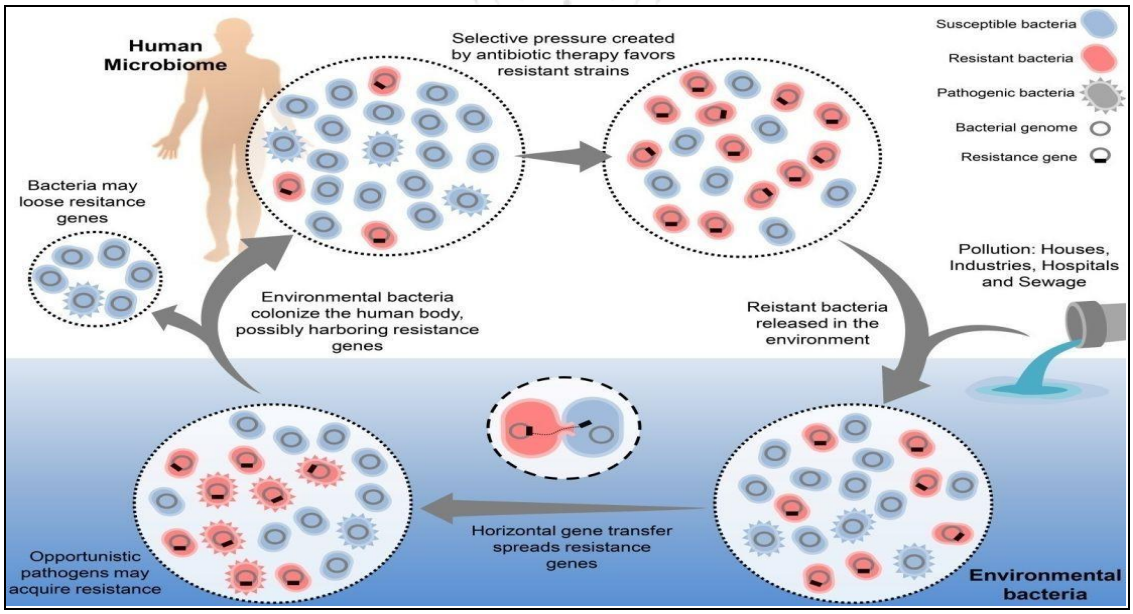

Figure No. 3: Schematic representation of the interactions between pollution, resistant bacteria and aquatic environments [63].

Veterinary antibiotics account for about 80% of antibiotics sold in the United States, and in Canada, the amount of antibiotics used by biomass in animals is two-fold than used by

humans [57,60]. Antibiotics in AFOs are not only used to treat acute infections but also pre-emptively on the herd level and to promote growth leading to intensive selection of microbiomes associated with farm animals and resulting in manure and wastewater contaminated with ARBs [61,62]. Manure from AFOs is often collected in waste lagoons where it degrades. Consequently, manure is often used as fertiliser on surrounding crop fields, releasing ARGs and surviving ARBs to the soil microbiome. ARGs and ARBs from manure can thus enter both surface and groundwater via run-off [37].

MITIGATIVE STRATEGIES

The initial step should be to reduce the proportion or quantity of pharmaceutical waste produced at its source rather than dealing with it after the formation of waste or recycle the material for some other productive use. However, reduction and recycling are desirable options. They are not considered as the final remedy to the problem of pharmaceutical waste disposal. A lot of practices are implemented by the industries to reduce waste generation and material losses. Some of them are discussed below [64].

Developing an eco-friendly manufacturing process

It is very desirable to develop manufacturing procedures with less hazardous solvents. Highly toxic solvents such as benzene, chloroform, and trichloroethylene are minor to ethyl acetate, alcohols, and acetone. Some compounds should be avoided wherever possible due to their ecotoxicity, physical properties, or environmental persistence (e.g. methylene chloride, heavy metals). In bulk chemical processing, substituting aqueous washes for solvents during filtrations decreases liquid waste and vapour emissions. In addition, using aqueous solutions instead of solvent-based solutions while coating tablets lowers concern on health, environmental and safety issues. Automation of process equipment, as well as servicing, regular calibration, and preventive maintenance, both help to reduce pollution. Organic synthesis reaction optimization improves product yields while reducing waste generation. Inadequate chemical reactions causes' improper strain, temperature and material control systems, resulting in additional solid, gaseous and liquid wastes.

Initially, a small quantity of medication should be prescribed -

- Do not provide sample medication to patients.
- Educate consumers about safe disposal methods for unused and expired medication.

- Provide academic modules for health practitioners.
- Establish centralized procurement and distribution of medication in hospitals.
- Return excess pharmaceuticals to manufacturer.
- Establish and publicize take-back programs of unused medication.
- Include environment criteria in GMP.
- Use of hazardous materials should be minimal and waste materials obtained from select products should be recovered, controlled and recycled.
- Advanced systems should be developed for recycling intermediates, raw materials (e.g., solvents), utility materials (e.g., lubricants, cooling water, steam condensate, heat transfer liquids) and wastes.
- The efficiency of chemical reactions can be optimized by examining solvents, reactants and catalysts.
- Equipments used for processing should be modified to minimize pollution and wastes.
- Processes should be maximized to improve the yield of the product and desired properties, limiting additional processing (e.g. drying and milling, re-crystallization).
- The efficiency of processes can be maximized using appropriate instruments, computer programs and automated control systems for minimal waste production.[65].

Development of Green Pharmacy and Green pill

- To reduce the negative impact on the environment, researchers have developed the concept of "green chemistry" which can be considered as an eco-friendlier approach. Green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. The use of aqueous synthesis, solvent-free synthesis and enzymes constitute various "green chemistry" techniques.
- Green Pharmacy aims at zero pharmaceutical waste in our environment. Daughton suggested the need for "green pharmacy," wherein the life cycle of pharmaceutical products are adequately evaluated, anticipated, and controlled from "cradle to grave," including processing from raw materials to disposal. The most effective and direct way to implement green chemistry into pharmaceuticals is to use eco-friendly, non-hazardous, reproducible, and

effective solvents and catalysts in the development of drug molecules and intermediates. At the same time, pharmacists should counsel patients regarding proper pharmaceutical waste disposal and organize standard procurement schemes for unused and expired medicines, to assist in developing green pharmacy for the future [66].

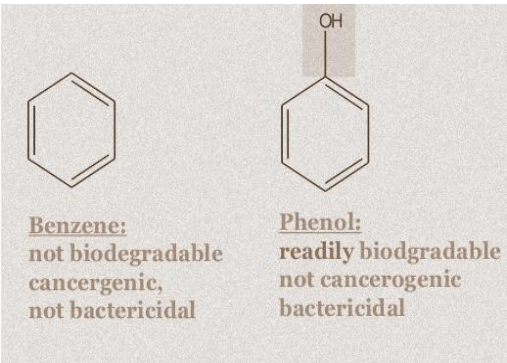

FIGURE NO. 4 [67]

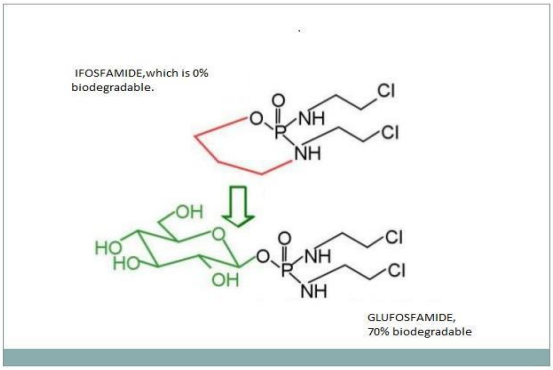

FIGURE NO. 5 [53,68]

- Another technique is the development of a "greener pill" that can have a therapeutic effect in the right dose at the right place and still can be eco-friendly. It includes processes like co-crystallization for improving bioavailability, salt formation, cyclodextrin encapsulation, or obtaining amorphous forms for enhancement of improved solubility [69,70]. Valproic acid is an example of a commonly used pharmaceutical product that can biodegrade quickly due to photo degradability during sewage treatment [71]. Carbamazepine, for example, can be biodegraded using microorganisms (Streptomyces sp.) as bioremediation agents [72].

Stakeholder Support

An organization or committee should be implemented to foster support for minimizing the number of pharmaceutical wastes. These should include government authority, pharmaceutical manufacturers, clinicians, veterinary doctors, health care professionals, environmental activists, along consumer and patient groups. An objective-oriented plan should be made for the future control of toxic waste. In a study conducted to assess the expert stakeholders view on human medicines in the surroundings, they inferred that advanced sewage treatment methods, training of healthcare experts to control over-prescription, pharmaceutical-return strategies combined with public awareness programs and requirements for all municipalities to have a minimum of secondary wastewater treatment were the most productive management techniques to abate the environmental impacts of pharmaceuticals [73].

Ecological Classification

All pharmaceuticals have to be categorized based on environmental hazard and the risk they possess. For example, ecologically categorized Pharmaceuticals by Stockholm County Council concerning the environmental hazard and environmental risk. Generally, pharmaceutical waste can be described based on its origin and composition which will aid in formulating methods for their proper disposal [74].

Table No. 5: Origin and composition of pharmaceutical waste[74]

Waste Description	Process Origin	Composition
Process liquors	Organic syntheses	Contaminated solvents
Spent fermentation broth	Fermentation processes	Contaminated water
Spent natural product raw materials	Natural product extraction processes	Leaves, tissues
Leftover raw material containers	Unloading of materials into process equipment	Sags, drums (fiber, plastic, metal), plastic bottles
Scrubber water from pollution control equipment	Dust or hazardous vapour generating processes	Contaminated water
Volatile organic compounds	Chemical storage tanks, drums	Solvents
Off-spec or out-dated products	Manufacturing operations	Miscellaneous products
Spills	Manufacturing and lab operations	Miscellaneous chemicals
Waste water	Equipment cleaning, extraction residues	Contaminated water
Spent solvents	Solvent extraction or wash practices	Contaminated solvents

Household Disposal Steps

As per National Drug Control Policy, U.S.A the following steps can be directed to consumers for household disposal of pharmaceutical products: a) Take out the prescribed medications from initial package. b) Combine the drugs with any undesired substances, like cat litter or

used coffee grounds c) The mixture is then placed into a disposable container with seal d) Remove any personal details on the empty containers with a permanent marker or duct tape, or scrape it off, including the Rx number e) The sealed container containing the drug mixture, as well as the empty drug containers, can now be discarded [75].

Minimize Use of Veterinary Drugs in Animal Husbandry and Aquaculture

Environmental studies mentioned the presence of various categories of medicinal substances in the aquatic system or soil. The use of antibiotics for prophylaxis and in animal feeders should be restricted to overcome water pollution and resistance to antibiotics. The requirement of antibiotics for veterinary purposes can be reduced with proper feeding techniques and better hygienic practices. Also, alternatives can be used to substitute antibiotics in veterinary feeds.

- In-feed enzymes (glucans, proteins and phytates)
- Competitive exclusion products
- Probiotics [76,77]

Table No. 6: Methods for disposal of various pharmaceutical dosage forms[78].

Category	Disposal methods	Comments
Solids	Landfill	Only about 1% of urban waste can be discarded without treatment on a routine basis.
Tablets, Capsules	In a polythene bag containing used Tea/Coffee grind, soak up to 50 tablets or capsules in about 100 ml of water and pick. Seal it and discard in a high-temperature incinerator (Temp. 850°C to 1200°C)	Big quantity-Pulverize using a heavy-duty crusher.
Semi solids	In a polythene bag, add a small portion with used tea/coffee grinds. Place them in a sealed bag and discard the containers after de-shaping them.	De-shape the container tubes and remove the label before disposal as a scrap.

Liquids	Dilute the liquid with water and drain it or transfer to ETP if the quantity is big.	Liquids with high solid contents to be disposed of in an incinerator as indicated above.
Ampoules	Injectables-ampoules/vials up to 50: Break ampoules/ vials (up to 10 ml) and collect the liquid in a polythene bag containing used Tea/Coffee grind. Seal it and discard. Powder injectables (in Vials/Ampoules) to be discarded in an incinerator as directed.	Broken glass/vials (after label removal), seals and rubber stoppers should all be thrown in the trash as waste.
Anti-infective drugs	**β-lactams**: All β-lactam antibiotics to be dissolved in small quantities by soaking in 1N Sodium Hydroxide for 30 minutes or 1 percent Hydroxylamine in Water for 10 minutes and then discard. Bigger quantity to be disposed of in an incinerator. Others: Tetracyclines- soaked in 10% of Calcium Hydroxide/any other Calcium salt in Water for 30 minutes and trash. Macrolides- (Erythromycin, Clarithromycin etc.)- Small quantity, soak in 1N Hydrochloric Acid and trash. Aminoglycosides (Gentamicin, Amikacin etc.)-Small quantity dilutes with a large volume of water and drains it.	Liquid antibiotics may be diluted with water, allowed to stand for few weeks and discharged to a sewer.
Anti-neoplastic	Return to donor or manufacturer	Not to landfill unless encapsulated
	Waste encapsulation	Not to sewer
	Waste inertization	No medium temperature incineration

	Medium and high-temperature incineration (Cement kiln incinerator)	
Steroids	-Soak in 1N Sodium Hydroxide for 30 minutes and trash.	
Hormones	-Aqueous solution to be exposed to UV for 20 minutes and trash.	Estrogens- the aqueous solution should be exposed to ultrasound at 0.6 and 2 kW in a sonicator for 60 minutes and trash.
Controlled drugs	Small quantity-Flush down the toilet to avoid misuse	Don't landfill if not enclosed.
Aerosol canisters	Landfill, Waste encapsulation	Not to be burnt, may explode.
PVC plastic, glass	Landfill	Not for burning in open containers.
Paper, cardboard	Recycle, burn, landfill	

REGULATORY FRAMEWORK- GLOBAL SCENARIO

❖ **Europe**

○ **Environment risk assessment (ERA):** It is to assess environmental risk for every new drug in the pre-approval phase. The goal of ERA is to safeguard the aquatic and terrestrial ecosystems along with groundwater and microbes in sewage treatment plants [8,79].

○ **Water framework directive (WFD):** This framework by European environmental legislation commits all its member nations to attain a better qualitative and quantitative estimation of water resources by extending the spectrum of water conservation to all specific type of water.

○ **Knowledge and new assessment on pharmaceutical products in environment waters (KNAPPE):** It focuses on advancing knowledge concerning the effects and side effects of pharmaceutical products. Besides, it also regulates the emission of pharmaceutical substances into the environment [64].

❖ **Sweden:** In 1985, the Swedish Parliament enacted the Feeding stuff Act and banned antibiotic use for growth promotion. In 2012, Sweden became the first nation to introduce environmental criteria into a national agreement with pharmaceutical marketers. Pharmaceutical firms have to adhere to the national environmental guidelines, health and safety legislation, control discharges onto land and into the water [80].

❖ **United States of America**

- **Drug enforcement administration (DEA):** DEA mandates disposal of drugs listed in CSA (controlled substances act) either by the return of the drug to the manufacturer or by destroying it with certain guidance and proper recording. Under the CSA, discarding down the drain sewer (or flushing) is a permitted method of dumping [81].

- **Resource conservation and recovery act (RCRA):** RCRA monitors appropriate safe practices in the manufacture, storage, transportation, treatment and disposal of hazardous pharmaceuticals. Health care facilities are prohibited to dispose of their dangerous pharmaceutical waste into municipal waste landfills or sewage treatment plants [82].

❖ **India:** Indian Government created the Ministry of Environment and classifies the pharmaceutical industry as 'red category' as it emits hazardous waste into the environment. The disposal of waste products from production units shall be following the regulations of the Environmental Pollution Control Board. All biomedical wastes shall be dumped as per recommendations of Bio-Medical Waste Manufacturing and Handling Rules, 1996 amended in 2018 [83].

CONCLUSION

Pharmaceutical waste disposal is a highly intricate new barrier in environmental management for health care facilities. The knowledge of proper control of pharmaceutical wastes is however deficient among medical professionals. A pragmatic approach should be there to subsume this relevant issue in the curriculum as the need of the hour. Guidance on this subject should be of utmost relevance in CMEs, conferences, and seminars. The construction of EPV is obligatory to form definite laws and governing practices in developing countries like India. We need to move from assessing the environmental risks of few medicines, towards much more extensive environmental stewardship of pharmaceuticals over their entire life cycles. All multidisciplinary stakeholders, medical professionals,

environmentalists, and the government have to join efforts to surmount this severe concern on the ecosystem and to build a promising prospect for tomorrow.

ACKNOWLEDGEMENT

We gratefully acknowledge Aneesa M. V, Ashitha Rehman and Hafees Rehman, Pharm. D Interns, Rajagiri Hospital, Kerala, India for their careful reading of the manuscript and helpful comments. The authors would also like to express their gratitude to Rajagiri Hospital, Kerala, India for providing adequate facilities and access to online resources for the literature survey conducted in order to compile comprehensive data for the review article.

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