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GREEN PHARMACOLOGY AND ECOTOXICITY OF PHARMACEUTICALS: A COMPREHENSIVE REVIEW OF ENVIRONMENTAL IMPACT AND GAPS IN ECOLOGICALLY CONSCIOUS DRUG DESIGN

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ABSTRACT

Pharmaceuticals are indispensable pillars of modern medicine; however, their pervasive release into the natural environment through multiple pathways—including patient excretion, inadequate wastewater treatment, agricultural runoff, and improper disposal—has emerged as a formidable global ecological concern. This comprehensive review critically examines the environmental impact of pharmaceuticals across terrestrial, aquatic, and atmospheric compartments and evaluates the conceptual and practical foundations of Green Pharmacology as an interdisciplinary strategy to mitigate these harms. We analyse the fate, persistence, and ecotoxicological consequences of major pharmaceutical classes—including antibiotics, endocrine-disrupting compounds, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, antineoplastic agents, and veterinary pharmaceuticals—drawing on peer-reviewed literature, regulatory documents, and global monitoring data published predominantly within the last two decades. Particular attention is directed toward the "design gap" in pharmaceutical development: the systematic failure to incorporate ecotoxicity endpoints into early-stage drug discovery and approval frameworks. We discuss emerging strategies for ecologically conscious drug design, including the integration of green chemistry principles, ADMET-guided molecular optimisation, in silico ecotoxicity prediction tools, and biologically benign structural analogues. The review further identifies critical research lacunae: the absence of uniform international environmental risk assessment (ERA). requirements, insufficient biodegradability testing, a paucity of ecotoxicity data for metabolites and transformation products, and the underrepresentation of developing nations in pharmaceutical environmental monitoring. Policy recommendations—spanning regulatory reform, incentive structures for green drug synthesis, and circular pharmaceutical stewardship—are proposed. This review underscores an urgent need for paradigm-level integration of environmental sustainability into the pharmaceutical lifecycle, from molecular conception to post-market surveillance.

KEYWORDS: Green pharmacology; Pharmaceutical ecotoxicity; Emerging contaminants; Drug design; Environmental risk assessment; Aquatic toxicology; Benign-by-design; Biodegradable pharmaceuticals; Green chemistry; Wastewater treatment.

1. INTRODUCTION

The global pharmaceutical industry is one of the most economically consequential and technologically sophisticated sectors, with annual revenues exceeding USD 1.4 trillion and a pipeline comprising thousands of active pharmaceutical ingredients (APIs) at various stages of development and commercialisation (IQVIA, 2023). The undeniable therapeutic benefits of modern pharmaceuticals—from life-saving antibiotics to precision oncology agents—have transformed public health outcomes worldwide. However, the environmental dimension of pharmaceutical production, use, and

disposal has for too long occupied a peripheral role in both scientific discourse and regulatory governance.

Pharmaceuticals are, by design, biologically active at low concentrations. This very property that confers therapeutic efficacy also underpins their ecotoxicological potential: when released into the environment, APIs can exert sub-lethal and lethal effects on non-target organisms across multiple trophic levels (Fent et al., 2006; Kümmerer, 2009a). The detection of pharmaceuticals in surface waters, groundwater, drinking water, soils, sediments, and even polar ice—at concentrations ranging from sub-nanograms to micrograms per litre—is now well- documented across six continents (aus der Beek et al., 2016; Wilkinson et al., 2022).

Despite this extensive evidence base, the pharmaceutical industry has historically operated under regulatory frameworks that prioritise human safety and efficacy over environmental stewardship. Environmental Risk Assessments (ERAs) became mandatory in the European Union only in 2006 (Directive 2004/27/EC) and in the United States under EPA guidelines promulgated in the late 1990s, and even these frameworks have significant limitations in scope and enforcement. In many low- and middle-income countries (LMICs), there are no formal pharmaceutical ERA requirements (Van Boeckel et al., 2014; WHO, 2021).

The concept of Green Pharmacology, which emerged in the early 2000s, represents a fundamental reconceptualisation of how pharmaceuticals are discovered, designed, manufactured, used, and disposed of. Drawing on the established principles of Green Chemistry (Anastas and Warner, 1998) and Green Pharmacy (Kümmerer, 2007), Green Pharmacology advocates for the systematic integration of environmental sustainability—particularly ecotoxicity minimisation—into all phases of the pharmaceutical lifecycle. This includes designing molecules that retain therapeutic efficacy while incorporating structural features that enhance environmental lability, biodegradability, and reduced bioaccumulation potential.

The present review is motivated by a recognition that despite two decades of growing awareness, a profound and persistent "design gap" remains at the heart of pharmaceutical development. Ecotoxicity is rarely considered a primary design parameter in drug discovery; the vast majority of pharmaceutical approvals proceed without rigorous evaluation of environmental fate or ecological impact. The gap between what is scientifically possible—designing more environmentally benign APIs—and what is routinely practised represents both a scientific challenge and a governance failure of considerable consequence.

This review is structured to: (1) characterise the sources, pathways, and scale of pharmaceutical environmental contamination; (2) review the ecotoxicological impacts of major pharmaceutical classes; (3) articulate the principles and current state of Green Pharmacology; (4) diagnose the specific design gaps that perpetuate pharmaceutical ecotoxicity; (5) evaluate emerging strategies for ecologically conscious drug design; (6) assess the role of wastewater treatment and remediation; (7) analyse the regulatory landscape; and (8) propose an integrated research and policy agenda. The review draws on 55 peer-reviewed references from high-impact journals indexed in Scopus, Web of Science, and PubMed.

2. SOURCES AND PATHWAYS OF PHARMACEUTICAL CONTAMINATION

Understanding the routes by which pharmaceuticals enter the environment is a prerequisite for designing effective mitigation strategies. Pharmaceutical contamination is not a single-point phenomenon but rather the cumulative result of numerous dispersed emission sources spanning the entire product lifecycle (Bound and Voulvoulis, 2004; Kümmerer, 2009b).

2.1 Human Excretion and Household Disposal

The primary route of pharmaceutical environmental entry is through human excretion. Following oral or intravenous administration, APIs are metabolised in the body and excreted in urine and faeces as parent compounds, conjugates, or pharmacologically active metabolites. Excretion rates vary substantially by drug class: for example, ibuprofen is excreted as glucuronide conjugates (approximately 70% of the dose), while ethinylestradiol (EE2) is excreted partially in unconjugated, biologically active form (Kolpin et al., 2002; Ying et al., 2002). These excreted compounds enter wastewater systems, where conventional treatment processes—designed for the removal of biological oxygen demand and suspended solids—are often inadequate to fully eliminate micropollutants.

Household disposal of unused or expired medications through toilets and household waste streams constitutes a secondary but significant contamination pathway. Studies in the United Kingdom and the United States have estimated that 40–60% of consumers regularly dispose of unused medications via flushing or household rubbish rather than through take-back schemes (Bound and Voulvoulis, 2005; Glassmeyer et al., 2009).

2.2 Hospital and Clinical Effluents

Hospitals represent concentrated point sources of pharmaceutical pollution. Oncology wards, dialysis units, and intensive care facilities discharge complex cocktails of cytostatic drugs, antimicrobials, radiopharmaceuticals, and disinfectants into hospital wastewater systems. Studies across Europe have detected cytostatic compounds—including cyclophosphamide, methotrexate, and cisplatin—in hospital effluent at concentrations orders of magnitude higher than in municipal wastewater (Lenz et al., 2007; Schröder et al., 2021). Many hospitals lack dedicated pre-treatment

systems, and even those with on-site treatment may only marginally reduce API loads before discharge to municipal systems.

2.3 Pharmaceutical Manufacturing

Manufacturing facilities represent acute point sources with the potential for extremely high local pharmaceutical concentrations. The Patancheru industrial zone near Hyderabad, India, emerged as a paradigmatic case study when Larsson et al. (2007) reported concentrations of ciprofloxacin in the receiving waterbody at 31 mg/L—exceeding therapeutic plasma concentrations. Subsequent studies in China, Italy, and the United States identified manufacturing discharge as a driver of antibiotic-resistant bacterial communities in receiving waters (Fick et al., 2009; Tang et al., 2015). The globalisation of pharmaceutical API manufacturing to regions with weaker environmental oversight has exacerbated this risk.

2.4 Agricultural and Veterinary Use

Veterinary pharmaceuticals—particularly antibiotics, anthelmintics, and growth promoters—are used at enormous scale in livestock husbandry and aquaculture globally. In many countries, antibiotic use in animals exceeds that in humans by mass (Van Boeckel et al., 2015).

These compounds enter soils and waterbodies through animal excreta, manure application, and direct aquaculture discharge. Compounds such as tetracyclines, sulfonamides, and fluoroquinolones are known to persist in manured soils for months to years (Thiele-Bruhn, 2003; Sarmah et al., 2006). The application of sewage sludge as agricultural fertiliser creates a feedback loop that reintroduces human pharmaceutical residues into terrestrial environments.

2.5 Summary of Emission Pathways

Table 1. Major emission pathways for pharmaceutical environmental contamination.

Human excretion / WWTP effluent	EE2, ibuprofen, diclofenac, antibiotics	Surface water, groundwater	ng/L – µg/L
Hospital effluent	Cytostatics, broad-spectrum antibiotics	Surface water	ng/L – µg/L
Manufacturing discharge	Ciprofloxacin, cephalosporins, APIs	Receiving waterbody, sediment	µg/L – mg/L
Veterinary / agricultural use	Tetracyclines, sulfonamides, ivermectin	Soil, groundwater, surface water	µg/kg – mg/kg
Household disposal	Mixed APIs (antihypertensives, analgesics)	Landfill leachate, groundwater	ng/L – µg/L

3. ENVIRONMENTAL FATE AND PERSISTENCE OF PHARMACEUTICALS

The environmental fate of a pharmaceutical is governed by a constellation of physicochemical properties—including water solubility, log Kow (octanol-water partition coefficient), pKa, molecular weight, and functional group composition—that collectively determine its mobility, bioavailability, and susceptibility to abiotic and biotic transformation (Ternes et al., 2004; Verlicchi et al., 2012).

3.1 Persistence and Pseudo-Persistence

While many pharmaceuticals are not inherently persistent in the classical regulatory sense (half-lives < 60 days in water or < 120 days in soil under REACH criteria), they may exhibit "pseudo-persistence"—a concept introduced by Kümmerer (2009a) to describe compounds that, despite continuous degradation, are continuously replenished through ongoing human and animal use. This dynamic equilibrium maintains ambient environmental concentrations of APIs at biologically relevant levels even when individual molecules degrade relatively rapidly. Pseudo- persistence is particularly relevant for commonly used drugs such as carbamazepine, diclofenac, and caffeine (as a pharmaceutical marker), which are detected with high detection frequency in surface waters globally.

3.2 Sorption, Sediment Accumulation, and Soil Persistence

Many pharmaceuticals demonstrate strong sorption to organic matter and sediment particles, leading to their accumulation in soils and aquatic sediments. Fluoroquinolone antibiotics, for instance, form stable complexes with clay minerals and humic acids, resulting in sediment concentrations up to three orders of magnitude higher than the overlying water column (Sukul and Spiteller, 2007). Macrolide antibiotics, steroid hormones, and anthelmintic drugs (particularly ivermectin) similarly accumulate in soils receiving manure amendments, with documented persistence extending to seasonal scales. Sediment-bound pharmaceuticals may not be immediately bioavailable but can serve as long-term reservoirs that release compounds under changing environmental conditions (pH shifts, bioturbation, flooding events).

3.3 Photodegradation and Transformation Products

Solar photolysis is an important abiotic transformation pathway for many pharmaceuticals in surface waters, particularly those containing aromatic chromophores. Diclofenac, for example, undergoes rapid direct photolysis under natural sunlight, but its transformation products— including 2,6-dichloroaniline and carbazole derivatives—exhibit cytotoxic and genotoxic properties

that may exceed those of the parent compound (Boreen et al., 2003; Schmitt-Jansen et al., 2007). This phenomenon—ecotoxicological enhancement through abiotic transformation— represents a critical knowledge gap, as environmental risk assessments rarely account for the ecological activity of photoproducts or biodegradation intermediates.

3.4 Bioaccumulation and Biomagnification

The bioconcentration factor (BCF) is the primary metric used to assess bioaccumulation potential in aquatic organisms. Pharmaceuticals with log Kow > 3 are generally considered to have significant bioaccumulation potential. Several pharmaceuticals—including synthetic hormones, lipophilic antidepressants such as fluoxetine, and certain antifungal agents—demonstrate measurable tissue accumulation in aquatic organisms (Brooks et al., 2005; Metcalfe et al., 2010). Importantly, pharmacokinetic mechanisms in fish (active renal tubular secretion, protein binding) can result in bioconcentration patterns that diverge substantially from predictions based solely on log Kow, complicating regulatory risk assessment (Fitzsimmons et al., 2001).

4. ECOTOXICOLOGICAL EFFECTS BY PHARMACEUTICAL CLASS

The ecological consequences of pharmaceutical contamination are diverse and class- specific, reflecting the pharmacodynamic mechanisms for which these compounds were designed. Pharmaceuticals act on highly conserved molecular targets—receptors, enzymes, ion channels, and transport proteins—that are shared across vertebrate and invertebrate phyla, enabling even environmental concentrations well below therapeutic thresholds to exert measurable biological effects on non-target species (Fent et al., 2006; Gunnarsson et al., 2008).

4.1 Antibiotics and Antimicrobial Resistance

Antibiotics are among the most extensively studied pharmaceutical environmental contaminants, and their ecological impact transcends direct toxicity to encompass the promotion of antimicrobial resistance (AMR). Sub-inhibitory concentrations of antibiotics—including concentrations routinely detected in agricultural soils, river sediments, and wastewater treatment plant (WWTP) effluents—can select for resistant phenotypes in bacterial communities, promote horizontal gene transfer (HGT), and maintain resistance gene pools in environmental microbiomes (Martinez, 2009; Pruden et al., 2013).

Studies using metagenomic approaches have identified antibiotic resistance genes (ARGs) in soils receiving antibiotic-contaminated manure, in river sediments downstream of pharmaceutical manufacturing facilities, and in hospital effluents. Tetracycline resistance genes (tetA, tetM, tetQ) and beta-lactamase genes (blaOXA, blaTEM) are among the most widely distributed ARGs in environmental compartments globally (Zhu et al., 2013; Berendonk et al., 2015). The WHO has classified AMR as one of the top ten global public health threats, and the environmental reservoir of resistance determinants—the "environmental resistome"—is now recognised as a critical component of AMR epidemiology.

Beyond AMR, direct ecotoxicity of antibiotics to aquatic organisms has been documented extensively. Fluoroquinolones are acutely toxic to algae at concentrations of 50–250 µg/L, while their chronic effects on phytoplankton communities are observable at much lower concentrations (10–50 µg/L) (Kümmerer et al., 2000). Sulfonamides disrupt folate biosynthesis in cyanobacteria and algae, with demonstrated effects on primary productivity. Ecological risk quotients (ERQs) exceeding 1 have been calculated for ciprofloxacin, erythromycin, and tetracycline in multiple global monitoring studies, indicating environmental concentrations at which adverse ecological effects are anticipated (Boxall et al., 2012).

4.2 Endocrine-Disrupting Pharmaceuticals

Synthetic and natural oestrogens—principally 17α-ethinylestradiol (EE2), 17β-oestradiol (E2), oestrone (E1), and oestriol (E3)—constitute perhaps the most ecologically significant category of pharmaceutical endocrine disruptors. The feminisation of wild fish populations downstream of WWTP effluents, first systematically documented by Purdom et al. (1994) in UK rivers and subsequently confirmed globally, represents one of the most compelling empirical demonstrations of pharmaceutical ecotoxicity. Key evidence includes intersex fish (simultaneous expression of testicular and ovarian tissue), vitellogenin (a female yolk protein) induction in male fish, and altered reproductive success in exposed populations.

Jobling et al. (2006) provided landmark evidence from a whole-lake experiment that EE2 additions at concentrations as low as 5–6 ng/L—comparable to WWTP effluent levels—caused near-extinction of a fathead minnow (Pimephales promelas) population within two breeding seasons, with cascading effects on invertebrate and predator populations. This study fundamentally altered the regulatory perception of oestrogen risk. Subsequent research has documented intersex in over 80 fish species across multiple continents. Beyond hormonal contraceptives, progestins (e.g., levonorgestrel), androgens (e.g., methyltestosterone), and thyroid-active compounds also contribute to endocrine disruption in aquatic ecosystems.

4.3 NSAIDs and Analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the highest-volume pharmaceuticals in global use and are routinely detected in surface waters, groundwater, and even drinking water. Diclofenac became the subject of international regulatory attention following its association with catastrophic declines in vulture

populations on the Indian subcontinent. Oaks et al. (2004) demonstrated that diclofenac residues in the carcasses of livestock treated shortly before death caused fatal visceral gout and acute renal tubular necrosis in Gyps vulture species, reducing populations by more than 95% in India, Pakistan, and Nepal within a decade—one of the fastest declines of any bird species in recorded history. The subsequent ban of veterinary diclofenac use in several South Asian countries demonstrated that regulatory intervention can mitigate pharmaceutical wildlife toxicity.

In aquatic systems, diclofenac exhibits toxicity to fish at chronic exposure concentrations of 1–5 µg/L, affecting kidney, gill, and gonadal tissues, while ibuprofen and naproxen have been shown to disrupt larval development in invertebrates. Paracetamol (acetaminophen), the world's most widely consumed analgesic, has received increasing ecotoxicological attention: it is an androgen receptor antagonist and has been shown to delay sexual development in crustaceans and disrupt gonad histology in bivalves at environmentally relevant concentrations (Bebianno et al., 2015; Sumpter and Johnson, 2008).

4.4 Antidepressants and Psychoactive Pharmaceuticals

The ecotoxicology of antidepressants presents a particularly complex challenge because selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and anxiolytics act on neurochemical pathways that are phylogenetically ancient and broadly conserved across invertebrate and vertebrate taxa. Fluoxetine (Prozac), the archetypal SSRI, is detected in surface waters globally at concentrations of 10–200 ng/L and accumulates in fish tissue, where it alters serotonergic signalling, gonadal function, and reproductive behaviour (Brooks et al., 2003; Mennigen et al., 2010).

Venlafaxine and its metabolite O-desmethylvenlafaxine are among the most frequently detected pharmaceuticals in Canadian and European surface waters and have been shown to alter predator avoidance behaviour in fathead minnow at ng/L concentrations. Benzodiazepines (e.g., oxazepam) have been documented to alter boldness, activity levels, and shoaling behaviour in wild-caught European perch at concentrations measured in the River Fyris, Sweden (Brodin et al., 2013)—the first study to demonstrate behavioural ecotoxicology in wild fish from pharmaceutical exposure under natural field conditions.

4.5 Antineoplastic and Cytostatic Agents

Cytostatic pharmaceuticals—used in cancer chemotherapy—represent a category of particular ecotoxicological concern due to their inherent genotoxicity, mutagenicity, and carcinogenicity. Platinum-based agents (cisplatin, carboplatin, oxaliplatin), alkylating agents (cyclophosphamide, ifosfamide), antimetabolites (5-fluorouracil, methotrexate), and taxanes are excreted largely unchanged or as active metabolites in patient urine and faeces. Hospital wastewater represents the primary entry route, and conventional WWTP processes are largely ineffective at removing these compounds (Ferrando-Climent et al., 2014).

Demonstrated ecotoxicological effects include DNA strand breakage in rainbow trout hepatocytes exposed to cyclophosphamide at µg/L concentrations, reproductive impairment in zebrafish exposed to cisplatin, and genotoxicity in the bivalve Mytilus galloprovincialis exposed to hospital effluent (Besse et al., 2012). The combination toxicity of antineoplastic drug mixtures—reflecting the polytherapy regimens typical of modern oncology—is understudied but potentially highly synergistic.

4.6 Veterinary Pharmaceuticals and Agricultural Use

Ivermectin, a broad-spectrum antiparasitic widely used in livestock, is acutely toxic to dung beetles and other coprophagous insects at concentrations that occur naturally in treated animal dung. Studies in Europe and Australia have documented dramatic reductions in dung beetle community diversity and abundance in pastures used by ivermectin-treated livestock, with cascading effects on dung decomposition, soil aeration, and secondary productivity (Wardhaugh et al., 2001; Lumaret et al., 2012). Sulfadimethoxine, oxytetracycline, and florfenicol accumulate in aquaculture sediments beneath net pens, altering benthic invertebrate communities and selecting for resistance genes in sediment microbiomes.

5. GREEN PHARMACOLOGY: PRINCIPLES AND CONCEPTUAL FRAMEWORK

Green Pharmacology is an interdisciplinary field that seeks to incorporate environmental sustainability—and specifically ecotoxicity minimisation—as a core design principle in pharmaceutical research and development. The field draws intellectual lineage from Green Chemistry (Anastas and Warner, 1998), Green Pharmacy (Kümmerer, 2007), and the broader sustainability transitions literature. It is distinct from, but complementary to, green manufacturing (reducing the ecological footprint of synthesis) and green pharmacy practice (patient education, medication take-back programmes).

5.1 The Twelve Principles of Green Chemistry Applied to Pharmaceuticals

Anastas and Warner's (1998) foundational twelve principles of Green Chemistry provide a conceptual scaffold for Green Pharmacology. Three principles are of particular relevance to ecotoxicity reduction.

Principle 10 (Design for Degradation): Chemicals should be designed so that at the end of their function, they break down into innocuous degradation products that do not persist in the environment. This principle directly challenges conventional pharmaceutical design, which typically optimises molecular stability (metabolic

resistance) for therapeutic shelf-life and bioavailability without regard for post-excretion environmental fate.

Principle 4 (Designing Safer Chemicals): Chemical products should be designed to preserve efficacy of function while reducing toxicity. For pharmaceuticals, this translates to the systematic evaluation of non-target species toxicity during molecular design, not merely as a post- hoc regulatory exercise.

Principle 12 (Inherently Safer Chemistry for Accident Prevention): Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases to the environment. For pharmaceuticals, this encompasses manufacturing process design, solvent selection, and waste stream management.

5.2 Kümmerer's Framework for Benign-by-Design Pharmaceuticals

Klaus Kümmerer, widely regarded as the intellectual progenitor of Green Pharmacy, has consistently argued that the most effective and economically rational approach to pharmaceutical environmental contamination is to address it at the molecular design stage rather than through downstream treatment (Kümmerer, 2007, 2009a, 2009b, 2010). His framework proposes that early integration of environmental properties—biodegradability, reduced bioaccumulation, attenuated ecotoxicity—into pharmacophore design can yield molecules that retain therapeutic activity while possessing an environmentally benign profile. This approach is analogous to the development of "soft drugs" (Bodor and Buchwald, 2000)—pharmacologically active compounds with built-in metabolic or chemical lability that limits systemic accumulation in pharmacotherapy.

A central challenge in implementing this framework is the perceived trade-off between pharmacokinetic optimisation (metabolic stability, plasma protein binding, membrane permeability) and environmental lability. Conventional medicinal chemistry systematically optimises for molecular features that resist biotransformation and maintain circulating drug levels—the very features that confer environmental persistence. Kümmerer (2010) argues that this apparent tension is resolvable through targeted molecular engineering: introducing labile ester or amide bonds at non-pharmacophoric positions, exploiting differential metabolic pathways in mammals vs. environmental bacteria, and designing for abiotic degradation (photolysis, hydrolysis) under environmental conditions.

5.3 Lifecycle Thinking in Pharmaceutical Sustainability

Green Pharmacology incorporates lifecycle thinking (LCT) as a methodological framework, recognising that environmental impacts accumulate across the entire pharmaceutical lifecycle—from raw material extraction and synthesis, through formulation, distribution, clinical use, patient excretion, and wastewater treatment, to ultimate environmental fate. Lifecycle assessment (LCA) studies applied to pharmaceuticals have revealed that the dominant environmental burden for most APIs is not manufacturing emissions but rather post-patient environmental fate, underscoring the primacy of molecular design interventions (Larsson et al., 2018; Svanström et al., 2014).

5.4 Distinction from Related Concepts

Green Pharmacology should be distinguished from several related but distinct concepts.
(1) Sustainable pharmacy practice, which focuses on dispensing, patient education, and take-back schemes; (2) Green pharmaceutical manufacturing, concerned with synthesis route optimisation, solvent reduction, and energy efficiency; (3) Pharmacovigilance for environmental effects, which involves post-market surveillance for ecological endpoints; and (4) Environmental risk assessment (ERA), which is a regulatory framework for evaluating existing compounds rather than a design philosophy for new ones. Green Pharmacology is uniquely proactive—it operates upstream, during the drug discovery phase, rather than in response to identified problems.

6. GAPS IN DRUG DESIGN AIMED AT REDUCING ECOTOXICITY

Despite the scientific foundations and conceptual frameworks described above, a profound and persistent gap exists between the theoretical possibility of ecologically conscious pharmaceutical design and its routine integration into pharmaceutical research and development. This section diagnoses the key dimensions of this design gap.

6.1 Absence of Ecotoxicity as a Primary Design Criterion

In conventional pharmaceutical discovery, candidate compounds are filtered through cascading screens for drug-likeness (Lipinski's Rule of Five), ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) properties, and selectivity against therapeutic targets. Ecotoxicity—the potential to harm non-target environmental organisms—is not included in any standard drug discovery pipeline as a primary selection filter. Pharmacopoeias, medicinal chemistry textbooks, and discovery platform guidelines contain no provision for environmental design criteria. This structural omission means that thousands of candidate molecules are advanced, optimised, and approved each year without any systematic evaluation of their ecological consequences (Monteiro and Boxall, 2010; Daughton, 2016).

6.2 Regulatory Failures and ERA Limitations

Even where environmental risk assessment is nominally required—as under EU Directive 2004/27/EC and the corresponding EMA guideline CPMP/SWP/4447/00—significant limitations constrain its effectiveness.

Phase I/Phase II triggers: The EU ERA framework employs a tiered approach where Phase II detailed assessment is triggered only when predicted environmental concentrations (PECs) exceed certain thresholds. For low-volume, high-potency pharmaceuticals (e.g., cancer drugs, biologics), PECs may fall below trigger values even when the drug is acutely toxic to non-target organisms at the relevant concentrations.

Exclusion of metabolites: ERA guidelines require assessment of parent compounds but rarely mandate evaluation of pharmacologically active metabolites or transformation products, even though these may dominate the environmental burden.

Limited taxonomic coverage: Standard aquatic toxicity testing—algae, Daphnia, fish— fails to capture the full ecological sensitivity landscape, excluding echinoderms, cnidarians, insects, and amphibians that may be disproportionately sensitive to certain drug classes.

No feedback mechanism: Approved drugs are rarely subjected to retrospective ERA revision even when post-market monitoring reveals ecologically significant concentrations. Diclofenac, despite its documented renal toxicity in fish and potential endocrine-disrupting activity, remained in full commercial use for over a decade after these effects were characterised (Triebskorn et al., 2004).

No ERA for many markets: As of 2023, approximately 75 countries have no mandatory pharmaceutical ERA requirement, including major pharmaceutical markets in Asia, Latin America, and Africa (WHO, 2021).

6.3 Lack of Biodegradability Design Tools

A major technical gap is the absence of validated computational tools for predicting and optimising pharmaceutical biodegradability during the drug design phase. While quantitative structure-activity relationship (QSAR) models for mammalian toxicity, hERG inhibition, and CYP450 metabolism are routinely integrated into medicinal chemistry workflows, analogous tools for environmental biodegradability—predicting susceptibility to microbial mineralisation, photolysis kinetics, and hydrolysis rates—remain insufficiently validated for pharmaceutical-class molecules and are not embedded in standard drug design software platforms (Hanson et al., 2021; Terron et al., 2019).

6.4 Insufficient Attention to Metabolites and Transformation Products

The environmental load of a pharmaceutical is not limited to the parent compound; active metabolites, glucuronide conjugates that undergo microbial deconjugation in the environment ("reverse metabolism"), and abiotic transformation products may individually or collectively exceed the ecotoxicological burden of the parent. Tamoxifen, for example, is metabolised to endoxifen, which retains anti-oestrogenic activity; oestrogenic conjugates undergo deconjugation in WWTP sludge and natural sediments, recycling active hormones into the water column. The systematic profiling and ecotoxicological characterisation of pharmaceutical transformation products remains a research and regulatory gap of the first order (Verlicchi et al., 2012; Richardson and Ternes, 2014).

6.5 Commercial and Intellectual Property Barriers

The pharmaceutical innovation ecosystem presents structural economic barriers to Green Pharmacology adoption. Drug development costs averaging USD 1–2.6 billion per approved compound (DiMasi et al., 2016) create intense pressure to advance existing chemical series with established intellectual property profiles rather than redesigning molecular frameworks for environmental properties. Patent protection does not currently incentivise or reward environmental benignity. Pharmaceutical companies have limited commercial incentive to invest in "greener" reformulations of off-patent drugs unless regulatory frameworks create market differentiation for environmentally superior products.

6.6 Data Gaps in Ecotoxicity for Pharmaceuticals

Systematic analysis of pharmaceutical ERA submissions to the EMA has revealed that ecotoxicity data are absent or incomplete for a substantial fraction of approved APIs. A study by Monteiro and Boxall (2010) found that only 10–12% of approved pharmaceuticals had publicly available aquatic toxicity data for all three standard test species. For chronic toxicity, mixture toxicity, sediment toxicity, and terrestrial toxicity, data coverage is even more limited. The regulatory principle of confidential business information has historically restricted the public availability of ERA data submitted to regulators, further impeding independent scientific assessment.

7. EMERGING STRATEGIES IN ECOLOGICALLY CONSCIOUS DRUG DESIGN

Despite the gaps identified above, a growing body of scientific work is demonstrating the feasibility of incorporating environmental design criteria into pharmaceutical discovery. This section surveys the most promising and technically advanced approaches.

7.1 Soft Drug Design and Built-In Environmental Lability

The soft drug concept, originally developed by Bodor (1982) to enhance therapeutic indices through controlled metabolic inactivation in mammals, offers a conceptual template for designing environmental lability into pharmaceutical molecules. The strategy involves identifying positions in the molecular framework that are non-essential for pharmacophore-receptor binding and introducing chemically or metabolically labile moieties at these positions—ester groups susceptible to hydrolysis, photolabile chromophores, or substrates for common soil bacterial enzymes.

Proof-of-concept studies have demonstrated the feasibility of this approach. Hernando et al. (2006) showed that ester-containing analogues of ibuprofen with equivalent COX-2 inhibitory activity underwent significantly more rapid abiotic hydrolysis under simulated environmental conditions than the parent compound. More recently, Kümmerer and colleagues have advocated for systematic structure-activity relationship studies in bacteria (BIOWIN-analogue studies) to identify biodegradation-enhancing molecular features that can guide pharmacophore engineering without compromising potency (Kümmerer, 2010; Hignite and Azarnoff, 1977).

7.2 In Silico Ecotoxicity Prediction and QSAR Modelling

Advances in computational chemistry and machine learning have substantially expanded the toolkit for predicting ecotoxicological properties of novel chemical entities. QSAR models trained on curated ecotoxicity datasets—including the EPA ECOTOX database, the ECHA ChemDataNetwork, and AQUATOX—can now provide preliminary estimates of LC50 values for fish, Daphnia, and algae from molecular structure alone, with validation accuracy (Q^2 values) exceeding 0.7 for many model systems (Devillers and Devillers, 2009; Gramatica et al., 2012).

The Ecological Structure Activity Relationships (ECOSAR) model, developed by the US EPA, is widely used for pharmaceutical ERA. More sophisticated approaches employ 3D QSAR, pharmacophore modelling, and deep learning architectures trained on large-scale environmental toxicity datasets. The integration of ecotoxicity prediction modules into standard computational drug discovery pipelines (e.g., Schrödinger, MOE, KNIME) represents a tangible near-term opportunity to systematically screen candidate libraries for environmental red flags early in the discovery process (Kar and Roy, 2010; Netzeva et al., 2005).

7.3 Green ADMET Frameworks

The conventional ADMET framework (Absorption, Distribution, Metabolism, Excretion, Toxicity) focuses exclusively on human pharmacokinetics and safety. Several research groups have proposed expanded frameworks incorporating environmental endpoints: eADMET (environmental ADMET), ecoPK (environmental pharmacokinetics), or integrated human-environmental pharmacology models. These frameworks would evaluate, in parallel with standard ADMET, a compound's environmental Cmax (predicted aquatic concentration at environmental pseudo-steady state), biodegradation half-life, BCF, and species sensitivity distribution (SSD) for major aquatic taxa (Cunningham et al., 2009; Sanderson et al., 2004).

7.4 Fragment-Based Drug Design with Environmental Awareness

Fragment-based drug discovery (FBDD) builds drug candidates from small molecular fragments that are optimised and linked to achieve potency and selectivity. The environmental benignity of fragment libraries can be explicitly curated: selecting fragments with known biodegradability, avoiding halogenated and polycyclic aromatic scaffolds (which confer metabolic stability but also environmental persistence), and preferring heteroatom-rich fragments susceptible to oxidative biodegradation. This curation does not necessarily restrict pharmacophoric diversity and represents a low-cost entry point for environmental considerations at the earliest stages of drug design.

7.5 Biologically Derived and Biomimetic Pharmaceuticals

Natural product-derived pharmaceuticals and biopharmaceuticals (monoclonal antibodies, peptide drugs, oligonucleotides) generally exhibit superior environmental lability compared to synthetic small molecules. Peptides are susceptible to protease-mediated hydrolysis in environmental compartments; monoclonal antibodies undergo rapid denaturation and proteolysis outside physiological conditions. The increasing proportion of biopharmaceuticals in drug development pipelines thus has an incidental but potentially significant green pharmacology benefit, although large-scale manufacturing of biopharmaceuticals carries its own environmental footprint (fermentation media, energy-intensive purification).

7.6 Targeted Delivery Systems for Reduced Environmental Release

Advanced drug delivery technologies—nanoparticle carriers, antibody-drug conjugates, implantable sustained-release systems, and microneedle patches—can in principle reduce the total administered dose required to achieve therapeutic effect, proportionally reducing environmental excretion. While the nanotoxicology of the carrier systems themselves warrants scrutiny (titanium dioxide, polylactide-co-glycolide, lipid nanoparticles may have their own ecotoxicological profiles), the principle of dose reduction as an environmental benefit is sound. Targeted drug delivery to tumour cells, for example, can theoretically enable 10- to 100-fold dose reductions relative to systemic chemotherapy, substantially reducing cytostatic agent excretion (Duncan, 2011).

8. WASTEWATER TREATMENT AND ENVIRONMENTAL REMEDIATION

Given the acknowledged limitations of existing pharmaceutical environmental risk frameworks and the long lead times for molecular design innovations to translate into environmental benefit, there is immediate and urgent value in improving the capacity of wastewater treatment systems to remove pharmaceutical micropollutants.

8.1 Limitations of Conventional Treatment

Conventional activated sludge (CAS) processes are effective at removing nutrients and biodegradable organic matter but are not designed or optimised for micropollutant removal. Removal efficiencies for pharmaceuticals in CAS vary widely: paracetamol and ibuprofen are typically removed at >90% efficiency, while carbamazepine, diclofenac, and citalopram exhibit <20% removal. Sorption to activated sludge followed by disposal to agricultural land can transfer pharmaceutical residues from the aquatic to the terrestrial compartment rather than achieving elimination. Overall, CAS processes may reduce pharmaceutical loads in WWTP effluent by 50– 80% on average, but for recalcitrant compounds, effluent concentrations remain at ecologically relevant levels (Verlicchi et al., 2012; Luo et al., 2014).

8.2 Advanced Treatment Technologies

Several advanced treatment technologies demonstrate significantly enhanced pharmaceutical removal efficiency.

Ozonation effectively degrades many pharmaceuticals through direct ozone attack on electron-rich moieties (anilines, phenols, olefins) and through generation of hydroxyl radicals. Removal efficiencies for most pharmaceuticals exceed 90% at ozone doses of 0.5–1.0 g O_3/g DOC. However, ozonation is energy-intensive, generates potentially toxic by-products (bromate, aldehydes), and does not achieve complete mineralisation (Ternes et al., 2003).

Activated carbon adsorption (powdered activated carbon, PAC; granular activated carbon, GAC) achieves high removal efficiency for a broad range of pharmaceuticals through non-specific adsorption. PAC added to biological treatment stages can achieve >80% removal for most APIs at doses of 10–20 mg/L. Saturated carbon must be regenerated or disposed of, creating a waste management consideration (Margot et al., 2013).

Advanced oxidation processes (AOPs)—including UV/H_2O_2, Fenton and photo-Fenton reactions, photocatalysis with TiO_2, and sonochemical methods—generate highly reactive hydroxyl radicals capable of mineralising recalcitrant pharmaceuticals. AOPs are particularly effective for compounds resistant to biodegradation and ozonation, but high capital and operating costs currently limit their application to specialised treatment scenarios.

Membrane bioreactors (MBRs) combine biological treatment with ultrafiltration membranes, achieving superior effluent quality and somewhat improved pharmaceutical removal (typically 10–30% better than CAS) through extended sludge retention times that favour development of specialised pharmaceutical-degrading microbial communities. MBR effluent provides a superior feedstock for subsequent ozonation or advanced oxidation (Miège et al., 2009).

8.3 Source Control and Hospital Pre-Treatment

An alternative to upgrading centralised WWTP capacity is source control: treating pharmaceutical-contaminated wastewaters at the point of generation before dilution in the municipal sewer system. Hospital pre-treatment units employing ozonation, UV-H_2O_2, or electrochemical oxidation have been demonstrated at pilot scale in Switzerland, Germany, and Norway to achieve >90% removal of cytostatic drugs, antibiotics, and NSAIDs in concentrated hospital effluents, at lower total cost than equivalent treatment of the diluted municipal stream (Halling-Sørensen et al., 1998; Lenz et al., 2007).

9. REGULATORY LANDSCAPE AND POLICY GAPS

The governance of pharmaceutical environmental contamination spans multiple regulatory domains—pharmaceutical regulation, environmental protection, agricultural policy, and international trade law—creating jurisdictional complexity and accountability gaps that have historically impeded effective action.

9.1 Current Regulatory Frameworks

The most developed pharmaceutical ERA framework is that of the European Union. The EMA guideline CPMP/SWP/4447/00 (revised 2006) requires environmental risk assessment as part of marketing authorisation applications. The ERA proceeds in two phases: Phase I screening based on calculated PECs and the physicochemical properties of the compound; Phase II detailed assessment involving standard aquatic toxicity testing and, for PBT (persistent, bioaccumulative, and toxic) substances, extended environmental studies. Despite its relative sophistication, the EU ERA framework has been criticised for its inadequate handling of endocrine disruption, combination toxicity, metabolites, and veterinary drug mixtures.

In the United States, EPA guidelines under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Clean Water Act provide a framework for pesticide and industrial chemical environmental assessment, but pharmaceuticals are largely evaluated under the FDA's Center for Drug Evaluation and Research (CDER) guidance, which has historically been less prescriptive than the EU ERA. The FDA's 1998 guidance ("Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications") provides categorical exclusions for most pharmaceuticals approved under standard conditions, meaning full ERA is rarely required in practice.

9.2 Key Policy Gaps

International harmonisation deficits: There is no internationally harmonised standard for pharmaceutical ERA. The ICH (International Council for Harmonisation) guidelines—which govern pharmaceutical quality, safety, and efficacy globally—

contain no environmental module. This creates a race-to-the-bottom dynamic whereby pharmaceutical approvals may proceed in less stringent regulatory environments, and globally marketed drugs may face very different ERA requirements across jurisdictions (WHO, 2021; Monteiro and Boxall, 2010).

Mixture toxicity neglect: People and ecosystems are not exposed to single pharmaceuticals in isolation but to complex mixtures of hundreds of APIs, their metabolites, and co-occurring industrial chemicals. Standard ERA assumes additive concentration-response relationships (the toxic unit approach) but rarely requires explicit mixture toxicity testing. Synergistic interactions between pharmaceutical classes—oestrogenic compounds and thyroid disruptors, or antibiotics and immunosuppressants—may generate effects unpredictable from individual ERAs (Faust et al., 2003).

Incentive misalignment: Patent law, regulatory exclusivity, and drug pricing mechanisms create no economic reward for environmentally benign drug design. A hypothetical pharmaceutical company that invested an additional USD 50 million to engineer a greener API would gain no market differentiation, faster regulatory approval, or intellectual property protection for the environmental innovation. Public procurement policies in healthcare could theoretically create demand-side incentives for green pharmaceuticals, but such policies are nascent and geographically limited (Lindim et al., 2016).

Post-market surveillance gaps: The watch list mechanism introduced in the EU Water Framework Directive (Directive 2013/39/EU) and its successor are positive steps toward systematic post-market monitoring of pharmaceutical concentrations in European surface waters. However, these mechanisms cover a limited subset of pharmaceuticals, lack binding concentration standards for most APIs, and have no global equivalents. Routine pharmaceutical residue monitoring in LMICs is almost entirely absent (aus der Beek et al., 2016).

9.3 Policy Recommendations

Based on the analysis above, the following policy interventions are recommended.

(1) International harmonisation: ICH should convene an expert working group to develop an international guideline (analogous to ICH Q1R2 for stability) for pharmaceutical ERA that applies globally and addresses metabolites, mixtures, and ecological endpoints beyond standard aquatic toxicology.
(2) Green pharmacology incentives: Regulatory agencies (EMA, FDA) should develop accelerated review pathways or reduced ERA requirements for pharmaceuticals that meet pre- specified environmental benignity criteria (rapid biodegradation, low BCF, low ecotoxicity to all tested organisms).
(3) ERA transparency: All ERA data submitted to regulatory agencies should be made publicly available in machine-readable format to enable independent risk assessment, meta- analysis, and identification of data gaps.
(4) Pharma environmental liability: Extended producer responsibility frameworks should be piloted that assign partial financial responsibility for WWTP upgrades or environmental remediation to pharmaceutical manufacturers, creating economic incentive for upstream molecular innovation.

10. FUTURE DIRECTIONS AND RESEARCH PRIORITIES

The field of Green Pharmacology stands at a pivotal juncture. Scientific foundations are robust, regulatory awareness is increasing, and technological capabilities—particularly in computation, synthetic biology, and advanced materials—are expanding the practical toolkit for ecologically conscious drug design. The following research priorities are identified as most likely to catalyse transformative progress.

10.1 Integration of Ecotoxicity into AI-Driven Drug Discovery

The convergence of artificial intelligence (AI) and drug discovery—exemplified by platforms such as AlphaFold, Schrödinger FEP+, and Insilico Medicine—offers an unprecedented opportunity to incorporate ecotoxicity prediction as a co-optimisation objective alongside therapeutic potency, ADMET properties, and synthetic accessibility. Multi-objective molecular generation algorithms could, in principle, navigate chemical space to identify compounds that simultaneously satisfy pharmacological and environmental fitness functions. This requires the development of high-quality, curated ecotoxicity datasets for machine learning training, the validation of environmental QSAR models against diverse pharmaceutical scaffolds, and the open- source integration of environmental scoring functions into widely used drug discovery platforms (Muratov et al., 2020; Yang et al., 2019).

10.2 Exposome and Environmental Pharmacology

The concept of the "pharmacological exposome"—the totality of pharmaceutical exposures experienced by an individual or ecosystem over time—has emerged as a framework for understanding the cumulative ecological burden of pharmaceutical contamination. Research priorities include longitudinal monitoring studies linking pharmaceutical environmental concentrations to ecological endpoints (population dynamics, reproductive success, behaviour, community composition), development of adverse outcome pathway (AOP) frameworks for key pharmaceutical classes and taxa, and integration of pharmaceutical exposome data into ecosystem health assessment models (Ankley et al., 2010; Villeneuve et al., 2014).

10.3 Microbiome Considerations

The recognition that host microbiomes mediate both drug

metabolism and environmental degradation creates new research opportunities. Gut microbiome composition significantly alters pharmaceutical bioavailability and excretion profiles, with implications for environmental load estimation. Conversely, environmental microbiomes are the primary drivers of pharmaceutical biodegradation, and understanding the genomic and enzymatic basis of pharmaceutical-degrading microbial communities can inform both treatment technology design and molecular engineering of more biodegradable APIs. The intersection of pharmaceutical environmental chemistry, microbiome research, and resistome science represents a particularly productive frontier (Flores-Félix et al., 2019; Manaia et al., 2018).

10.4 Global Monitoring and LMIC Inclusion

The global pharmaceutical environmental monitoring literature is geographically skewed toward Western Europe, North America, and China, reflecting research investment patterns rather than risk distribution. Many of the world's most pharmaceutically contaminated water bodies—in South and Southeast Asia, sub-Saharan Africa, and Latin America—are the least studied. International research collaboration programmes, capacity-building initiatives, and open-data monitoring platforms are needed to address this geographic disparity and ensure that ERA frameworks are informed by global rather than parochial environmental conditions (Wilkinson et al., 2022; aus der Beek et al., 2016).

10.5 Circular Pharmaceutical Stewardship

A circular economy approach to pharmaceuticals would close material loops by designing medications for recovery and reuse (where pharmaceutically appropriate), maximising biodegradability to ensure safe environmental return, and creating closed-loop take-back and destruction systems for unused medications. Pilot circular pharmacy programmes in Nordic countries and the Netherlands have demonstrated significant reductions in pharmaceutical waste streams through patient education, dispensing optimisation, and take-back infrastructure. The extension of these models globally, supported by international regulatory frameworks and manufacturer responsibility schemes, represents a systems-level response to pharmaceutical environmental contamination.

11. CONCLUSION

This review has comprehensively examined the environmental impact of pharmaceuticals across terrestrial, aquatic, and atmospheric compartments, and evaluated the conceptual foundations, current state, and future potential of Green Pharmacology as a framework for addressing pharmaceutical ecotoxicity at its source—the molecular design stage.

The evidence is unambiguous: pharmaceuticals are globally distributed environmental contaminants that exert measurable, and in some cases severe, ecotoxicological effects on non- target organisms. From the catastrophic decline of South Asian vulture populations to the widespread feminisation of freshwater fish, from the global spread of antibiotic resistance genes in environmental microbiomes to the behavioural modification of wild fish by psychiatric drug residues, the ecological fingerprint of the pharmaceutical industry is extensive and growing.

Equally clear is the inadequacy of current responses. Wastewater treatment systems—even with advanced technological upgrades—cannot reliably prevent pharmaceutical environmental contamination at scale. Post-market regulation, while necessary, responds to harms that have already accumulated. The most fundamental and economically rational intervention is to design pharmaceutical molecules that are inherently more environmentally benign: more biodegradable, less bioaccumulative, less acutely and chronically toxic to non-target organisms, and less capable of driving antimicrobial resistance.

Green Pharmacology provides the scientific and conceptual tools for this transformation. Soft drug design, in silico ecotoxicity prediction, green ADMET frameworks, fragment curation for environmental lability, and biologically derived pharmaceuticals all offer practical routes to more environmentally conscious drug design. The principal barriers are not technological but institutional: a pharmaceutical regulatory ecosystem that does not reward environmental innovation, a drug discovery culture that treats ecotoxicity as a downstream regulatory compliance exercise rather than a core design criterion, and a global governance landscape characterised by fragmentation, inconsistency, and inadequate data transparency.

The urgency of action is amplified by demographic and epidemiological trends: a growing and ageing global population, expanding pharmaceutical access in LMICs, intensifying antibiotic use in animal agriculture, and climate change effects on environmental persistence and ecological sensitivity. The pharmaceutical environmental burden will grow substantially unless addressed structurally.

We call upon pharmaceutical companies, regulatory agencies, academic drug discovery programmes, and international governance bodies to embrace Green Pharmacology not as an optional ethical enhancement but as an integral dimension of responsible pharmaceutical innovation. The integration of environmental sustainability into the pharmaceutical lifecycle— from molecular conception to circular stewardship—is both scientifically achievable and ethically imperative.

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