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ANTI-DIABETIC AND ANTI-CANCER PHARMACEUTICALS AS EMERGING ENVIRONMENTAL CONTAMINANTS

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ABSTRACT

The category of pharmaceuticals is significant in terms of emerging pollutants since there is the continual release of these chemicals to the environment due to their increasing use throughout the world. Anticancer and antidiabetic pharmaceuticals are particularly challenging in this context as a result of their widespread application, persistence in the environment, and considerable biological activity. Large-scale discharges of antidiabetics such as metformin, for instance, have the ability to impact the community structure of microbial populations, as well as affect nitrification process and metabolic processes in soil and aquatic systems. Even at environmentally relevant ng/L–µg/L concentrations, cytostatics used in the treatment of cancer-pharmaceuticals intended to be cytotoxic and genotoxic – may cause DNA damage, inhibit microbial growth, and interfere with cell division. Due to the stress response associated with sub-lethal exposures that leads to upregulation of multi-drug efflux pumps, these two categories of pharmaceuticals can also facilitate the emergence of AMR in bacteria.

Keywords: *Pharmaceutical Pollutants, Ecotoxicology, Metformin, Cytostatic Drugs, Microbial Ecology, Antimicrobial Resistance (AMR), Wastewater Treatment, Environmental Contamination.*

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1. INTRODUCTION

Antidiabetic drugs significantly affect microbial populations in humans and the environment. In humans, metformin alters gut microbiota, promoting short-chain fatty acid-producing and mucin-degrading bacteria, and affecting the Firmicutes to Bacteroidetes ratio [1]. Environmental contamination due to pharmaceutical disposal is a serious issue, with metformin causing harmful effects on fish microbiomes [2], including changes in Firmicutes and elimination of beneficial Planococcaceae in brown trout larvae, even at low exposure levels [3]. Additionally, metformin exposure increases virulence gene expression in fish pathogens, impacting long-term fish health and development [4].

2. CLASSES OF ANTI-DIABETIC DRUGS DISCUSSED:

2.1. Insulin and insulin analogues

Micropollutants are very soluble in water, have poor biodegradability characteristics, and bioaccumulate in food chains, causing imbalances in ecosystems [5]. They occur in low quantities (µg/L) and adversely affect the aquatic and soil microorganisms, change biofilm properties, and represent potential hazards to humans [6]. Some of these microorganisms, such as the species Rhodococcus, are capable of aiding the natural degradation of pharmaceuticals [7].

2.2. Biguanides

Metformin, an emerging pollutant in wastewaters and surface water bodies, degrades to guanylurea, accumulating in the environment. In this research, strain NyZ550 of the genus Aminobacter is isolated with the ability to utilise metformin as the sole carbon, nitrogen, and energy source under aerobic conditions. Moreover, strain NyZ550 can degrade various nitrogen-containing compounds, such as dimethylamine, while simultaneously degrading metformin. Metformin degradation leads to the accumulation of guanylurea and dimethylamine as byproducts, detected by ion chromatography, gas

chromatography-mass spectrometry, and transcriptome analysis [8].
A microbial consortium was created consisting of strain NyZ550 and genetically modified Pseudomonas putida PaW340 for the elimination of metformin and guanylurea, its degradation product. The obtained results give insight into metformin biodegradation and can help solve the problem of its accumulation in the environment.

2.3. Sulfonylureas

Glibenclamide (glyburide) is a diabetes drug taken orally in patients with type 2 diabetes. The consumption and presence of such drugs in high concentrations and unmetabolized form in sewage is a potential environmental hazard. Their presence in untreated form as well as in their active metabolites raises an environmental hazard. One of the methods of eliminating them is biodegradation, which is an effective technique in wastewater treatment. This research focuses on the biodegradation of acarbose, glibenclamide, gliclazide, glimepiride, metformin, and its metabolite guanylurea. Tandem Mass Spectrometry with Liquid Chromatography was employed in this research.Metformin was found to degrade into the dead-end product guanylurea, with a minor pathway leading to complete mineralisation. Acarbose, glibenclamide, and glimepiride underwent complete degradation, while gliclazide showed resistance. These findings highlight the need for monitoring programs to evaluate the environmental persistence of these important drugs [10].

2.4.DPP-4 inhibitors

In leaky-gut mice, microbial DPP4 suppresses glucose metabolism by lowering active GLP-1, and it is not affected by human DPP4 inhibitors like sitagliptin. A new selective microbial DPP4 inhibitor, daurisoline-d4 (Dau-d4), enhances glucose tolerance in diabetic mice [11].
The role of gut microbiota in regulating human metabolism and food behaviour is largely unclear. We explored whether bacterial DPP4-like homologs mimic human DPP4, crucial for metabolism. Our findings identified new DPP4 homologs in several gut bacteria and linked DPP4-like genes in Parabacteroides and Porphyromonas to type 2 diabetes (T2D). The DPP4-like enzyme from Parabacteroides merdae replicated the proteolytic action. of the human enzyme on hormones such as peptide YY, neuropeptide Y, GIP, and GLP-1. In experiments with lipopolysaccharide-treated mice, overexpressing this enzyme reduced active GIP and GLP-1 levels. Additionally, this enzyme was variably inhibited by antidiabetic drugs linagliptin, saxagliptin, sitagliptin, and vildagliptin. Our results suggest that gut-derived proteolytic enzymes might contribute to glucose metabolic dysregulation in T2D, pointing to potential new diabetic medications. Moreover, SGLT2 inhibitors, like empagliflozin and dapagliflozin, have shown significant effectiveness in reducing glucose levels through increased urinary excretion [12]. Reduce the HbA1c by 0.6–0.8%.

- Lead to weight reduction
- Improve lipid profiles and blood pressure
- Reduce the risk of cardiovascular and renal events Significant results have been obtained from cardiovascular outcome trials, including thousands of patients [13]. The EMPA-REG OUTCOME study, for instance, showed a decreased incidence of mortality due to any cause, heart failure admission, and cardiovascular death.It can be deduced from these findings that SGLT2 inhibitors offer an effective and holistic therapeutic modality for type 2 diabetes mellitus [14].

2.6. Thiazolidinediones

Thiazolidinediones are antidiabetic medications for type 2 diabetes mellitus [15]. They work by acting as agonists of PPARγ, thus lowering insulin resistance [16].The antineoplastic (ANP) drugs utilised in chemotherapy attract a lot of concern over their potential environmental pollution via hospital waste and excreta of outpatients. This paper discusses the existing approaches in mitigating the ANP waste in terms of their toxicity and transformation products, and their biodegradation through bacteria and fungi found in sewage plants. The review stresses the need for the adoption of a holistic treatment technique of ANP waste degradation using multiple processes [17]. Some of the major anticancer and antidiabetic drugs, as well as their effects on the environment and microbes, are summarised in Table 01.

Table 01: Environmental occurrence and microbial impacts of antidiabetic and anticancer drugs

Drug Class	Example Drugs	Main Environmental Source	Environmental persistence	Major Effects on Microbial Communities	Ecotoxicological Consequences
Biguanides	Metformin	Domestic sewage, WWTP effluent	High	Inhibits nitrification, alters biofilms	Eutrophication
Sulfonylureas	Glimepiride, Glibenclamide	Wastewater discharge	Moderate	Microbial stress	Persistence in aquatic systems
DPP-4 Inhibitors	Sitagliptin	Hospital wastewater	Moderate	Alters microbial enzyme activity	Metabolic dysregulation

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SGLT2 Inhibitors	Empagliflozin	Human excretion	Limited data	Shifts microbial populations	Unknown long-term effects
Anticancer Drugs	Cyclophosphamide, 5-Fluorouracil	Oncology effluent	High	DNA damage and cytotoxicity	Reduced biodiversity
Transformation Products	Guanylurea	Metformin degradation	Very high	Persistent microbial inhibition	Long-term toxicity

3. SOURCES, FATE, AND OCCURRENCE IN THE ENVIRONMENT

The primary route by which anti-cancerous and antidiabetic medications enter the environment is through patient excretion into the sewage system [18]. For example, the complete Metformin medication is excreted unmetabolized via the urinary bladder. Some cytostatics, including cyclophosphamide, are excreted with parent compound as well as active metabolites [19]. Contamination of sewage occurs from hospital effluents and improper disposal of unused medication as well as emissions from production processes. The result is localized contamination of relatively high levels [20].

Conventional wastewater treatment plants (WWTPs) using activated sludge are ineffective at the removal of highly polar and water-soluble medications such as Metformin. Low elimination rates range from 0% to 70%. In most cases, the compound cannot be removed efficiently, and it is released to the environment [21]. Cytostatics contain a complicated structure and are found in very low concentrations, which are incompatible with a microbial population in activated sludge [22]. Research shows removal rates are lower than 50% in some cases and nearly 0%. For cyclophosphamide, 5-fluorouracil, and platinum compounds, effluent from WWTPs is the major source [23].

The environmental pathway of pharmaceutical contaminants from human use to ecosystem exposure is illustrated in Figure 01.

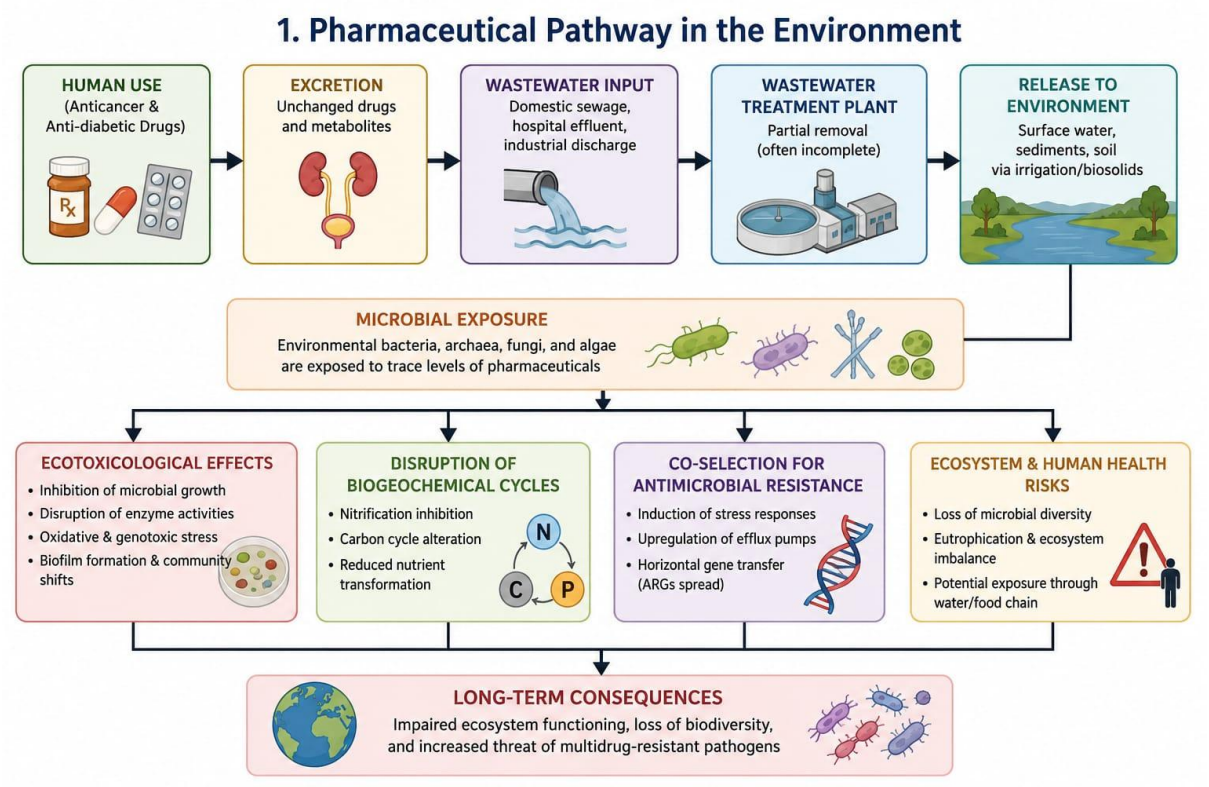

Figure 01: Environmental pathway of antidiabetic and anticancer drugs from human use to microbial ecosystem exposure.

The ineffectiveness of the removal process has led to the environmental pollution of several drugs, such as metformin [24]. It is common in WWTP effluents and surface waters, where it can occur at high ng/L up to low mg/L concentrations. Levels exceeding 100 µg/L have been recorded in heavily polluted river water bodies, thus making it one of the most highly concentrated pharmaceutical drugs [25].

The concentration levels of anticancer drugs in the environment are much lower, occurring in low ng/L and high µg/L. A study found that the maximum level of cyclophosphamide in hospital effluents was 176 µg/L, while its concentration

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in surface water was only 1 µg/L [26]. Although the concentration of anticancer drugs is much lower compared to that of metformin, the former still has ecotoxicological importance [27].

4. EFFECTS OF ANTI-DIABETIC DRUGS ON MICROBIAL COMMUNITIES USING ECOTOXICOLOGY

The environmental effects of anti-diabetic drugs have been studied extensively with regard to metformin due to the high consumption levels and abundance in the environment [28]. Metformin interferes with mitochondrial complex I in human mitochondria; similarly, it inhibits bacterial NADH dehydrogenase, an enzyme in their electron transport system [29]. This helps to establish the biochemical action of metformin against environmental microbes [30, 31]. The way that metformin affects the environmental microbial community is illustrated in Figure 02**.**

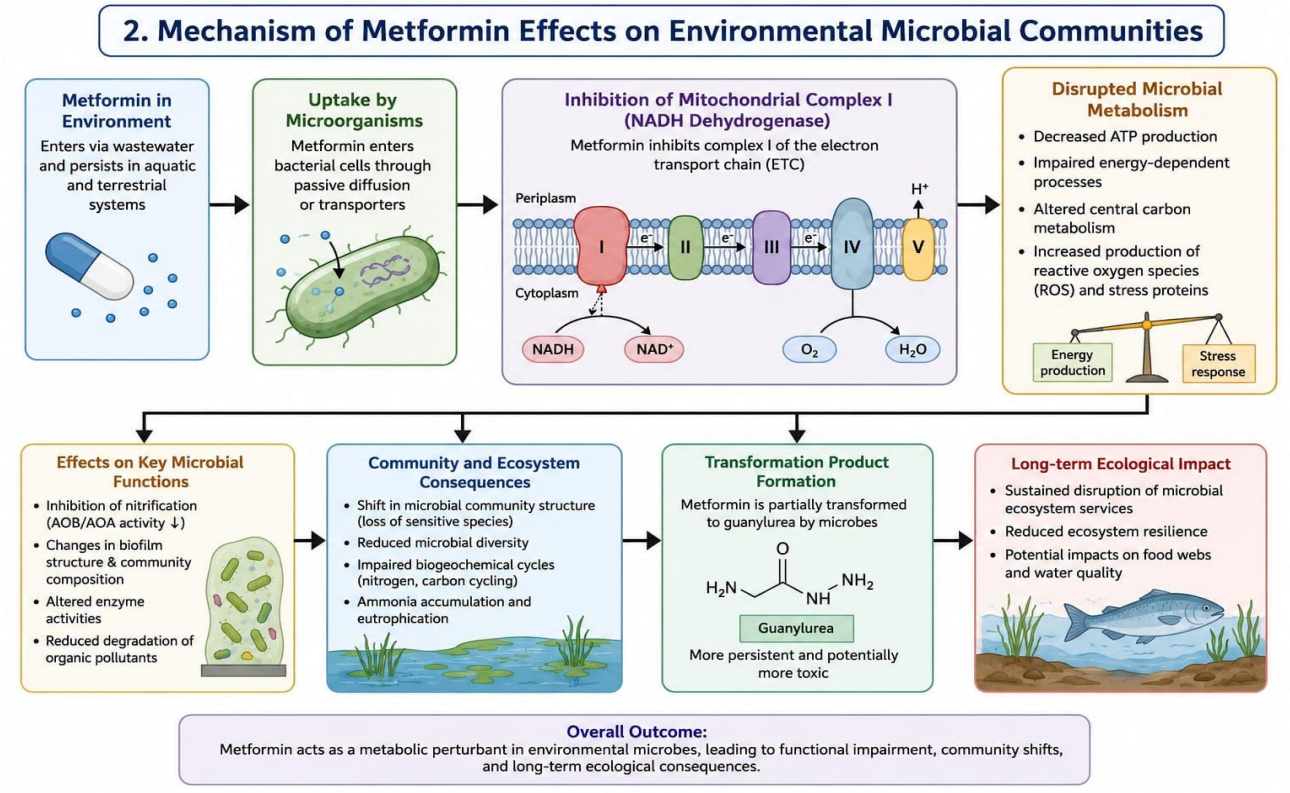

Figure 02: Mode of action of metformin on the disruption of microbial metabolism within environments

Experimental evidence suggests that environmentally relevant levels of metformin cause significant disruptions within microbial ecosystems [32]. This includes biofilm reconfiguration whereby some bacterial groups are favoured over others while nitrification activities, conducted by ammonia-oxidising bacteria (AOB) and archaea (AOA), is hindered. Studies suggest that metformin at µg/L concentrations can lead to inhibition of AOB within the sediments of freshwater systems [33], which may consequently cause ammonia accumulation and eutrophication of the ecosystem. In addition, studies have demonstrated that metformin induces changes in the metabolic activity of microbes, causing stress and xenobiotic degradation, but reduces carbon metabolism [34].

Role of Biotransformation and Transformation Products. In spite of the high stability of metformin, biodegradation by microorganisms does occur, leading to the main transformation product of metformin, which is guanylurea. Unfortunately, guanylurea is also a stable compound that, in some cases, proves to be more harmful than metformin [35]. Guanylurea was found to act as an inhibitor of microorganisms' activities, making it possibly even more environmentally dangerous than metformin. As can be seen from the above, when assessing ecotoxicity, the focus should be on both APIs and their environmental transformation products [36].

5. ECOTOXICOLOGICAL EFFECTS OF ANTICANCER DRUGS ON MICROBIAL COMMUNITIES

Anticancer medicines work against dividing cells, whether human cancer cells or prokaryotes. Genotoxic actions like DNA alkylation (cyclophosphamide) and inhibition of DNA synthesis (5-fluorouracil) make researchers concerned about the negative effect of anticancer medicines on DNA structure. Various experiments, like the Ames test, reveal the ability of these medicines to affect DNA structure in environmental microorganisms. Thus, a mixture of cytostatics in hospital waste triggered significant genotoxic effects in Vibrio fischeri, which

may accelerate the increase in mutations' frequency and enhance microbial evolution, damaging cells [37].

Anticancer medicines, for instance, 5-fluorouracil, have an inhibiting effect on the functioning of various microorganisms. Experiments revealed the considerable inhibition of respiration and nitrification processes in activated sludge microorganisms as well as cyanobacteria photosynthesis inhibition at low concentrations. Consequently, the function of cyanobacteria, the primary producers, will be compromised in aquatic ecosystems [38].

The long-term impact of cytostatics leads to intensive selective pressure in microbial communities, according to 16S rRNA gene sequencing. The outcome is evident from the reduction in sensitive microorganisms, the growth of resistant species, and lower microbial diversity in general [39].

6. A CROSS-CUTTING THREAT: CO-SELECTION FOR ANTIMICROBIAL RESISTANCE (AMR)

The non-antibiotic pharmaceutical pollutants also constitute a great challenge in the fight against the AMR global pandemic because, according to the co-selection hypothesis, exposure to one stressor (for example, pharmaceutical pollutants) leads to survival of organisms that are resistant to another unrelated stressor (such as antibiotics) [40].

Two main mechanisms drive co-selection in bacteria:

1. Shared Resistance Mechanisms (Cross-Resistance): Many bacteria possess general defence mechanisms, like multi-drug efflux pumps (RND, MFS, ABC superfamilies), which expel a variety of toxic substances, including pharmaceuticals and antibiotics. The presence of these contaminants creates selective pressure, favouring bacteria that overexpress these pumps, leading to multidrug resistance [41].

Toxic compounds, including many pharmaceuticals at sub-lethal levels, can trigger a general stress response in cells. In bacteria, this leads to the SOS response, a key DNA repair mechanism that increases mutation rates and promotes horizontal gene transfer (HGT) via mobile genetic elements (MGEs) like plasmids and integrons, facilitating the spread of antibiotic resistance genes (ARGs). Genotoxic anticancer drugs are strong inducers of the SOS response, enhancing the evolution and dissemination of antimicrobial resistance (AMR).

Evidence links pharmaceutical contaminants to antimicrobial resistance (AMR). A study found that long-term exposure to metformin in soil increased the abundance and diversity of antibiotic resistance genes (ARGs), particularly those for sulfonamides and tetracyclines, by enhancing mobile genetic elements (MGEs) and facilitating horizontal gene transfer [42].

Exposure of bacterial communities to anticancer medications has been linked to a rise in genes for multidrug efflux pumps and the presence of clinical pathogens with resistance mechanisms. This suggests that environments contaminated with these medications may become reservoirs for multidrug-resistant pathogens.

Amongst the Revolutionaries of Oxygen and Nitrogen in the Medium of Anticancer Medicine, Cytotoxicity. Due to the development of drug resistance within the cancer cell, the treatment of advanced cancer is rather complicated. It is necessary to study the processes that cause drug resistance to be able to design efficient anticancer drugs. Active anticancer drugs, such as topotecan, doxorubicin, etoposide, and procarbazine, are in use at present. Hence, a lot of attention is being paid to the understanding of the way of action of the above drugs. These drugs are metabolized within the cancer cell to produce reactive oxygen species (ROS). The ROSs lead to the induction of lipid peroxidation and damage to the DNA. However, the precise role played by ROSs and RNSs in causing cytotoxicity remains unexplained to date.

7. PHARMACEUTICALS DEGRADING BY MICROBES

Usage of pharmaceuticals has caused pollution due to their incomplete breakdown when undergoing purification in the wastewater plant. Moreover, they cause health problems when they interact with humans, even at lower levels. Several ways for the breakdown of pharmaceuticals can be employed; nevertheless, the microbial breakdown is a better process since it utilises less energy and creates minimal toxicity in the environment. In this chapter, we shall discuss the microbial breakdown of several classes of medicines such as antibiotics, NSAIDs, antihypertensive drugs, antidepressants, and anticancer drugs. The bacteria, algae, and fungi break down pharmaceuticals through the process of cometabolism. They make use of pharmaceuticals as an alternative carbon source for their growth. Dehydrogenase, hydrolase, and oxidoreductase are among several enzymes that the microorganisms make use of for their breakdown. The breakdown of medicines is very similar to the one that occurs in human body via cytochrome P450 enzymes. This is a rather complex process.

Type 2 Diabetes Mellitus and Cancer: The Role of Pharmacotherapy

Purpose: Nowadays, T2DM is gaining momentum as a frequent health problem with elevated risks for cancers and deaths. Hence, the goal of this review paper is to investigate the relationships between T2DM and cancer, effects of antidiabetics on outcomes in the context of cancer, and influence of treatment on diabetes-related complications.

Design: The current literature review will cover information on the effects of antidiabetics on prevalence and death rates from cancer along with the effects of anticancer drugs on glucose metabolism.

It is known that T2DM increases the frequency and mortality rates of cancers. Antidiabetics such as metformin lower these indicators; therefore, many clinical trials have been conducted to learn more about

them. However, the effects of other antidiabetics cannot be discussed. Some treatment options, such as glucocorticoids and hormone therapy, increase hyperglycemia due to insulin resistance.

Further investigation is needed to enhance efficiency in managing cancer and T2DM. It is important to conduct additional trials that will enable the discovery of the influence of antidiabetics on cancer prevalence. Besides, there is a need to find out how some types of anticancer treatments can influence glucose metabolism [43].

8. CHALLENGES AND FUTURE RESEARCH DIRECTIONS

Despite progress in the last decade, challenges and knowledge gaps persist. Microbes face a mix of millions of pollutants rather than single chemicals. Research on the interactions of these mixtures is still in its early stages, but it is crucial for accurate environmental risk assessment.

Chronic, Low-Dose Exposure: The majority of ecotoxicological research is centred on acute, high-concentration impacts. of greater environmental concern is chronic low (ng/L to µg/L) concentration exposure. The evolutionary long-term effects on microbial assemblages of such pressure are unknown.

Terrestrial vs. Aquatic Systems: Most studies have centred on aquatic systems, while the fate and impact of drugs in terrestrial ecosystems, influenced by biosolids and wastewater irrigation, remain less studied but are equally important.

Bridging Lab to Field: Scaling up results from controlled laboratory studies. on aquatic systems. The fate and impact of these drugs in terrestrial ecosystems, which are affected through biosolids application and wastewater irrigation, are not as well studied but no less critical.

9. FUTURE RESEARCH COULD BE CONDUCTED IN THE FIELD OF:

a) Omics techniques such as metagenomics, metatranscriptomics, and metaproteomics in assessing the effect of pharmaceutically contaminated water in the impact of pharmaceutically contaminated water on microbial communities.

b) Non-antibiotic risk assessment related to ecology and co-selection of AMR.

c) Various technologies involved in removing pharmaceuticals from water, including ozone, advanced oxidation and activated carbon.

d) Medication disposal and green pharmacies.

10. CONCLUSION

Modern literature on science is clear that anticancer and anti-diabetic medications have an impact on ecotoxicology because these bioactive materials retain their efficacy during wastewater treatment processes and affect the microbial communities, disrupt biogeochemical cycles, and lead to the development of antibiotic resistance. For instance, metformin serves as a metabolic disruptor, whereas anticancer medications create cytotoxic and genotoxic pressure on the microbiome found in the environment. The phenomenon of AMR by non-antibiotic medicines demonstrates the connection between environmental contamination and a global public health issue. The One Health perspective should be adopted as it shows the dependency between human health and environmental sustainability. It will require a joint effort between environmentalists, toxicologists, clinicians, engineers, and decision-makers to limit the amount of hazardous substances emitted into the environment, improve removal techniques, and maintain environmental stability and efficacy of antimicrobial therapies in the future.

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13. CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

14. INFORMED CONSENT

Not applicable.

15. ETHICAL STATEMENT

Not applicable.

17. AUTHOR CONTRIBUTION

Aniket Bajaj: Data Collection, Formal Analysis, Writing – Original Draft

Rojina Khatun: Resources, Writing-Editing

Malavika Bhattacharya: Conceptualization, Supervision

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