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Review Article

Pharmaceuticals and their transformation products in environment and plants

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Abstract

Antibacterial drugs, analgesics, anti-infective, contrast media, antiepileptics, anti-inflammatory drugs, beta-blockers, and hormones are transferred to the environment from hospital and agricultural effluents, pharmaceutical industrial waste, human and animal excrements from households and sewers. Residues of pharmaceuticals in water and soil cause damage to the ecosystem. Their transformation products could be equally or more toxic and persistent than parent compounds. Some metabolites save biological activity in the environmental objects, including antibacterial activity. The objective of this review is to describe the environmental occurrence, transformation, eco-toxicity, analytical practices, degradation, and removal strategies used to control and prevent environmental contamination by pharmaceuticals (antibiotics, coccidiostatic agents, nonsteroidal anti-inflammatory drugs, beta-adrenomimetics, anthelmintics, hormones). Their determination in routine analysis through simple on-site devices and approaches is of great interest. Instrumental analysis is making progress in the advancement of qualitative and quantitative methods. Gas and liquid chromatography, capillary electrophoresis, and mass spectrometry are commonly used because of their high specificity, simultaneous multicomponent determination opportunities, and low detection limits. Highly sensitive methods generally with accurate mass spectrometric detection are required. High-performance liquid chromatography coupled with high-resolution mass spectrometry is an effective method. The use of green chemistry principles is preferred for both on-site and instrumental analysis, because fewer toxic reagents and solvents are required. The most promising approach for water treatment and manure detoxification is to merge chemical and biological strategies. Persistent pharmaceuticals will be most effectively eliminated by a combination of different treatment technologies.

Keywords: Pharmaceuticals, Water and soil contamination, Veterinary drugs, Manure Determination, Detoxification

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Introduction

Pharmaceuticals contamination sources and environmental pathways

Pharmaceuticals (PHs) have been recognized as ubiquitous water contaminants (Khan et al., 2020a; Samal et al., 2022; Saxena et al., 2021). Anti-bacterial, analgesics, anti-infective, contrast media, anti-epileptics, anti-inflammatories, beta-blockers, and hormones are among the most used PHs. Hospital effluents, pharmaceutical industries, agricultural runoffs, and human and animal excrements from households and sewers are responsible for transferring pollutants into the environment, which can damage the ecosystem. Pharmaceuticals enter aquatic and soil cultures, as well as wastewater treatment plants, primarily through hospital effluents (Khan et al., 2020b; Samal et al., 2022). The wastewater discharge from wastewater treatment plants (WWTPs) is mixed with surface and groundwater (Tavengwa and Dalu, 2022).

Differences in the application of pharmaceuticals for human and farm animals define their environmental pathways. Antibiotics, coccidiostatic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), beta-adrenomimetics, anthelmintics, thyrostatics, etc. are widely used in veterinary medicine. VDs are metabolized in animals, partially excreted unmodified, and transported into the environment either directly through excrement or indirectly through manure using. Control of the veterinary drug residues and their metabolites in environmental objects (water, soil, and plants) is necessary for the health of future generations and environmental safety.

Several thousand tons of antimicrobials and their transformation products (TPs) get into the environment annually (Krzeminski et al., 2019; Osińska et al., 2020). The level of contamination of water and soil by antibiotics is in line with the level of contamination by pesticides (Mejías et al., 2021). Their content in wastewater varies from several $ng·L^{-1}$ to $mg·L^{-1}$, and in soil from $mg·kg^{-1}$ to $mg·kg^{-1}$ (Samal et al., 2022; Yang et al., 2021). The transfer of veterinary antibiotics (VAs) occurs primarily with manure rather than direct excretion. Despite that antibacterial drugs are metabolized in animals, partially they are excreted unmodified. According to Al-Wabel et al. (2021) and Tasho and Cho (2016), the unmodified form percentage for certain tetracyclines is about 70% and for macrolides it is up to 90%. Non-compliance in drug use, wastewater treatment, and the use of manure as fertilizer can lead to contamination of plant raw materials for feed. Plant raw materials can contain significant levels of antibiotic residues (Ben et al., 2022).

In-depth studies on the fate and toxicity of PHs require monitoring data. At the same time, Maximum Residue Levels (MRLs) for antimicrobial residues in plants are not yet established and monitoring is not currently being done (Makarov et al., 2023). Therefore, water and feed could be additional sources of drugs and their transformation product residues in animals.

Contamination of plant raw materials by PHs is becoming an increasingly serious problem in food and environmental safety. Substances and their TPs can not only cause toxic effects but also increase the risk of developing antimicrobial resistance (AMR) (Khan et al., 2020a; Pires et al., 2023). It is mentioned by Gao et al. (2023) and Xiao et al. (2023) in their works that the soil-plant system is under selective pressure from antibiotic residue accumulation, which leads to antibiotic-resistance genes (ARG) emerging and spreading through horizontal gene transfer. The transfer of antimicrobial-resistant bacteria (ARB) and ARG from livestock to consumers can prevent effective disease treatment (Chen et al., 2023; Haynes et al., 2020; Tasho and Cho, 2016). The purpose of this article is to provide an overview of the environmental occurrence and transformation of the PHs, TPs eco-toxicity, the most requested analysis methods, and the degradation and removal strategies basing on the most significant works of the last decade. In the review, a separate place is given to the discussion of the transformation of pharmaceuticals the in environment, transformation product toxicity, and activity.

1. Pharmaceuticals in water: Main groups and individual representatives, occurrence, and potential risk

Pharmaceuticals are water pollutants not only due to wastewater discharge (Fig. 1). Other sources are ground runoff from livestock farms, agricultural and aquaculture facilities (Bártíková et al., 2016; Khan et al., 2020a).

Because of their toxicity to aquatic organisms, they have garnered significant attention. When exposed, PHs disrupt biological processes in non-target lower organisms (Khan et al., 2020a). Diclofenac can cause toxic effects in rainbow trout, such as gill alterations and renal lesions (Matejczyk et al., 2020a). Other examples of exposure include growth inhibition in cyanobacteria and green algae by sulfamethazine and sulfamethoxazole in combination (Xiong et al., 2019), as well as increase in gill histopathological index and oxidative DNA damage in rainbow trout and sea bream by erythromycin, and pathological index in sea bream by oxytetracycline (Khan et al., 2020a). Low-trophic level species (cyanobacteria and algae) demonstrate higher sensitivity to antibiotics than crustaceans and fish, and macrolide antibiotics are more toxic to cyanobacteria and algae compared to other groups (Yang et al., 2021).

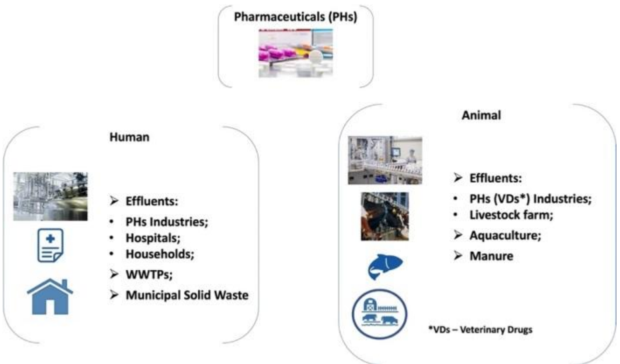

Figure-1. Sources of pharmaceuticals in water (based on Bártíková et al., 2016; Khan et al., 2020a,b; Samal et al., 2022)

The main route of environmental water pollution from VDs is the discharge into agricultural fields following the use of manure as fertilizer and non-compliance with best practices for manure decontamination and agricultural wastewater treatment. For the majority of the VDs (glucocorticoids, anthelmintics, and antibiotics), a linear dependence is found between the concentrations measured in microalgae biomass obtained from photobioreactors fed with piggery wastewaters and concentrations measured in effluent (López-Serna et al., 2022). Other routes through which VDs enter the environment may include wastewater from drug manufacturers, grazing animals, and direct use in fields and aquaculture (Khan et al., 2020b).

Anthelmintics are expelled in significant quantities into the environment as unmetabolized pharmaceuticals, or TPs. An investigation conducted in Ireland on anthelmintic residues in groundwaters and related surface waters revealed that 8 parent anthelmintics and 9 TPs were found at 22% of sites, with concentrations reaching up to 41 ng·L^{-1} (Mooney et al., 2021). Studies revealed that albendazole and its TPs were the most frequently detected substances.

The two anticoccidial veterinary drugs most frequently found in Irish groundwater were amprolium and monensin. Ionophores such as lasalocid, monensin, narasin, and salinomycin, as well as synthetic anticoccidials like amprolium, diclazuril, and nicarbazin, were found at 24% of the sites (1–386 ng·L^{-1}) (Mooney et al., 2020).

Over 250 chemical substances are authorized as antimicrobials for human and/or animal health and have global use (Rodriguez-Mozaz et al., 2020). Although they have limited effects, rainfall-induced runoff, subsurface interflow, and soil water infiltration are additional routes via which antibiotics are transferred in soil-plant systems following the application of manure as fertilizer (Zhao et al., 2020). According to the review by Yang et al. (2021) the most common antibiotics found in water are ciprofloxacin, norfloxacin, tetracycline, trimethoprim, erythromycin, and erythromycin-H_2O. This is facilitated by their strong hydrophilicity, stability, and low volatility.

Among sewage treatment plants (STP) and the pharmaceutical industry in China, the latter is considered the most serious source of antibiotic contamination of river water (Wang et al., 2021). There are also regional differences in river input and agricultural subareas (Zhang et al., 2023). Compounds with the highest loads from STP in China are sulfonamides and fluoroquinolones (Wang et al., 2021; Linghu et al., 2023), in EU countries, these are macrolides (MLs) and fluoroquinolones (FQs) (Rodriguez-Mozaz et al., 2020).

Monitoring results of two effluent-receiving rivers in the Northern part of Pretoria, South Africa, showed maximum concentrations of doxycycline and sulfamethoxazole (Oharisi et al., 2023). FQs predominated in the Nanming River study on the distribution and prevalence of antibiotics conducted in Guiyang, China (Linghu et al., 2023). In the sites where urban areas have caused the most severe contamination, ofloxacin was the primary factor posing ecological risk.

Leachate from Municipal Solid Waste (MSW) incineration plants contains various antibiotics (Rui et al., 2023). According to the study conducted on leachate from three MSW incinerator plants in Shanghai, ofloxacin and enrofloxacin in the treated leachate pose significant risks to algae and crustaceans. Ciprofloxacin showed high residue levels (close to 20 ng·L^{-1}) in groundwater, that were comparable to those in surface water (Arun et al., 2022). It should be taken into account that consumer food safety from aquaculture is closely linked to the issue of VDs, including antibiotics, polluting the

aquatic environment (Xia et al., 2021).
Tetracyclines (TCs) are widely used in human and veterinary medicine. They have frequently been found in aquatic environments (surface water, groundwater, drinking water, wastewater, sludge, and sediment) because of the formation of stable ternary complexes with cations (e.g., Ca^{2+}, Mg^{2+}, and Cu^{2+}) in sediments or sludge particles (Khan et al., 2020a). Sulfonamides are poorly adsorbed by sediments or sludge and can rapidly pollute groundwater (Reis et al., 2020a). Sulfamethazine concentration in groundwater was a little bit higher than in the surface water (5.2 $ng \cdot L^{-1}$) (Arun et al., 2022).
It is common practice to use sewage for agriculture, but it also poses a serious risk to the spread of antibiotic resistance in the environment (Saxena et al., 2021). The presence of heavy metals can increase the toxicity of antibiotics as shown for oxytetracycline and ciprofloxacin complexes with copper, cadmium, and zinc (Khan et al., 2020a). The highest algal growth inhibition was demonstrated. Hospital wastewater is mixed with ground and surface water frequently without adequate treatment, and it contains PHs, including antibiotics, and certain heavy metals (Khan et al., 2020b). Furthermore, through co-selection, the consistent presence of heavy metals in animal dung raises the prevalence of ARB (Kuppusamy et al., 2023). Co-selection of ARG may also occur in polluted with heavy metals aquatic environments as described in Zieliński et al. (2021).
Triclosan (antibacterial), estrone, and 17α-ethynylestradiol (steroid and estrogen drug) are pervasive in all water samples from central India (Saxena et al., 2021). Exposures of hormonal PHs might cause the conversion of male fish into female (Samal et al., 2022). The mortality rate of fish is also increased by high estrogenicity.
More than 1000 tons diclofenac are used as pharmaceutical drug for humans and animals per year worldwide. It was shown that diclofenac hurts duckweed plants and freshwater fish (at a concentration of 0.1 $mg \cdot L^{-1}$ and 0.2 $mg \cdot kg^{-1}$ respectively) (Matejczyk et al., 2020a). NSAIDs have prolonged ecotoxic effects on the biotic components of ecosystems, even though their environmental concentrations are negligible. The presence of diclofenac and ketoprofen resulted in cardiovascular defects and cardiac anomalies in freshwater fish *Clarias gariepinus* and *Danio rerio* (Samal et al., 2022).
Environmental factors (pH, temperature, irradiation, and redox conditions), microbial activity, seasonal patterns, and solubility, volatility, and lipophilicity, affect the fate and transport of PHs (Khan et al., 2020a; Mooney et al., 2021; Yang et al., 2021). The cationic forms of VDs in soils have a low potential to contaminate groundwater because they are strongly retained in the soil and can form complexes with divalent ions like calcium (Rath et al., 2019). The most common families of antibiotics detected in sediments are fluoroquinolones, tetracyclines, and sulfonamides (Yang et al., 2021). This correlates with their relative content in surface waters. Additionally, sorption could facilitate AMR development by domesticating ARG and ARB. This occurs through the gentle action of PHs adsorbed on sediments and water colloids, which promote microbial adaptation (Azuma et al., 2019).

2. Veterinary drugs in manure and soil, and its influence on soil microbiome

The excretion of VDs through grazing, the application of manure as fertilizer, and the utilization of reclaimed water for irrigation lead to the pollution of soil (Al-Wabel et al., 2021; Tasho and Cho, 2016). As shown by Geng et al. (2022) numerous studies have confirmed the presence of antibiotics in livestock manure (swine, poultry, and cattle). The soil antibiotic distribution depends on its structure and physicochemical properties (primarily polarity) (Rocha et al., 2021). The soil characteristics are also important due to the adsorption properties. They are provided by soil composition, pH and organic substance content (Tasho and Cho, 2016).
In Brazilian research studies, the sorption and desorption processes exhibited by various subtropical soils towards pharmaceutical compounds belonging to identical chemical families were found to be analogous (Rath et al., 2019). Non-charged and unable to complex formation VAs will be less retained in soils than VAs in cationic forms, capable of forming complexes with divalent ions as it has been shown for enrofloxacin (ENR) retention in soils in the presence of Cu(II) (Graouer-Bacart et al., 2013).
Veterinary antibiotics have different functional groups, and are ionic, amphiphilic, or amphoteric, which allows easy adsorption to soil particles (Tasho and Cho, 2016). Ionic and cation bridging are the primary interactions involved in the sorption of ENR by humic organic matter (Martínez-Mejía et al., 2017). The lipophilicity of pharmaceuticals characterized by log *P* plays an important role in their metabolism, transformation in the environment, and bioaccumulation (López-Serna et al., 2022).

According to Litskas et al. (2021) avermectins are anthelmintic drugs characterized by sufficiently high lipophilicity. The hydrophobic interactions of avermectins with soils with higher organic matter contents are a significant determinant of soil avermectin affinity (Rath et al., 2019). It was reported that nitrification and reduction by ammonia-oxidizing bacteria and archaea were inhibited by eprinomectin, ivermectin, and albendazole (Lagos et al., 2023). Moreover, albendazole induced consistent reduction in the abundance of total fungi and crenarchaea in soil.

The ionization of antibiotics in the soil depends on pH. In ionized forms, antibiotics interact with negatively charged clays and organic substances. Adsorption in oxides and hydroxides is caused by electromagnetic interactions as noted by Rocha et al. (2021). Authors showed maximum concentrations in soil for oxytetracycline (50 $mg \cdot kg^{-1}$), chlortetracycline (11 $mg \cdot kg^{-1}$), ciprofloxacin (5.6 $mg \cdot kg^{-1}$), sulfamethazine (0.2 to 25 $mg \cdot kg^{-1}$), and tylosin (1.3 $mg \cdot kg^{-1}$). According to Yang et al. (2021) the degree of adsorption of antibiotics in soils follows the order: of TCs > FQs > MLs > SAs. The persistence of veterinary antibiotics in the environment depends largely on soil type, temperature, animal excreta, pH, and UV light.

The highest concentrations of TCs are typically found in manure, as highlighted by Cycoń et al. (2019). The maximum concentration of oxytetracycline was identified in chicken manure at 416.8 $\mu g \cdot g^{-1}$, while pig manure contained maximum concentrations of oxytetracycline (541.02 $\mu g \cdot g^{-1}$), chlortetracycline (392.15 $\mu g \cdot g^{-1}$), and doxycycline (56.26 $\mu g \cdot g^{-1}$). The risk of TCs entering the food chain is highest in soils with low organic content, due to their low sorption according to research by Conde-Cid et al. (2019). However, TCs can exhibit strong adsorption in clay and sediments in different environmental conditions (Tasho and Cho, 2016).

SAs and FQs are also the groups of antibiotics with significant concentrations in manure, and among the MLs tylosin was determined in the highest concentration (Cycoń et al., 2019). The strong affinity of FQs could be caused by humic substances present in the soils (Rath et al., 2019; Martínez-Mejía et al., 2017). Since SAs have low sorption and high mobility in soil, they can be transported to groundwater (Bílková et al., 2019). The sorption of sulfathiazole and sulfamethazine in sandy and loamy soils is significantly influenced by pH levels (Tasho and Cho, 2016).

Long-term fertilized soils with poultry and cow manure can contain significant amounts of antibiotics (up to 137.20 $\mu g \cdot kg^{-1}$) (Kuppusamy et al., 2023). A study by Gros et al. (2019) conducted at an experimental field site investigated the behavior of 34 veterinary drugs in soil. It was discovered that various types of VDs, such as fluoroquinolones, tetracyclines, pleuromutilins, anthelmintics, analgesics, and anti-inflammatories, were present in soils treated with manure. The concentrations of these VDs ranged from 0.078 to 150 μg·kg-1 in the upper layers of soil, with the highest amounts detected in soils fertilized with swine slurry solid fraction.

The soil microbiome is a sensitive indicator of soil pollution. Biologically, soil microbiomes are the most extensive repository of microbial communities on Earth both in terms of the total mass of genetic material and its diversity. Soil bacteria are responsible for the circulation of biogenic elements (nitrogen, carbon, phosphorus), their transformation into a form available for plants, and the maintenance of soil structure (Bílková et al., 2019; Cycoń et al., 2019). Upon reaching the soil, microorganisms fix atmospheric nitrogen and carbon, produce organic substances, and immobilize nitrogen and other nutrients to initiate nitrogen cycling processes (Dubey et al., 2019). The soil serves as a reservoir of various microorganisms that play a crucial role in either facilitating or impeding plant growth, while also impacting the availability of nutrients and toxins. The enormous role of the microbiome in plant life, increasing soil fertility, and the impact on the detoxification of xenobiotics have been recognized (Tasho and Cho, 2016).

As shown by Rocha et al. (2021), ciprofloxacin disturbs the work of Calvin cycle enzymes and photochemical phases, the accumulation of reactive oxygen species negatively affects photosynthetic activity, and a decrease in the production of reducing potential on nitrogen fixation processes.

Even low concentrations of antibiotics affect the soil microorganisms' activity (Cycoń et al., 2019). As with antibiotics, soil respiration, nitrification, and denitrification are also affected, and some reduce respiration (sulfonamides, tetracyclines, aminoglycosides), while others stimulate it (fluoroquinolones) (Bílková et al., 2019; Cycoń et al., 2019; Rocha et al., 2021). The effects on soil microorganisms vary from the demise of the essential microbes necessary to supply the plants with nutrients and imbalance in microbial population due to the resistant selection of particular bacteria (Cycoń et al., 2019; Kuppusamy et al., 2023).

Species of *Actinobacteria*, *Streptomyces*, *Rubrobacter*, *Pseudonocardia*, *Pseudomonas*, and *Rhizobium* were predominant in soils long-term fertilized with poultry and cow manure (Kuppusamy et al., 2023). The main phyla that promoted ARG included *Actinobacteria* and *Proteobacteria*. Preliminary studies by Li et al. (2023) have shown that diclofenac accelerates the emergence of some resistant *Escherichia coli* strains through mutagenesis. At the same time, information regarding the joint action of VDs from various groups and their TPs on the activity and diversity of soil bacteria is currently fragmentary, incomplete, and contradictory.

VD residues can reach soil organisms and plant communities and transfer into the food chain. With the development of scientific methodology and analytical equipment, an opportunity emerged for a deep study of the transformation of substances processes in the environment. The methods for simultaneous determination of antibiotics, NSAIDs, coccidiostats agents, beta-adrenomimetics, anthelmintics, and their TPs, are needed for monitoring (Lavrukhina et al., 2022; Melekhin et al., 2022).

3. Plants and plant raw materials: metabolism and accumulation of pharmaceuticals, contamination levels and immediate hazards

Various antibiotics against bacterial diseases in plants have been approved for crops in several countries. In the EU, their use for plant protection is possible only in accordance with strict regulations, as detailed by Haynes et al. (2020). Used in crop production antibiotic volumes are insignificant, therefore this manner of environment transferring does not play an important role (Makarov et al., 2023). They are used usually for expensive crops (fruits, vegetables, as well as decorative plants) because of the high cost. The main pathways of plants contamination involve the application of manure and insufficient treatment of wastewater. The widespread occurrence of antibiotics in farmland soil threatens food safety (Geng et al., 2022).

Plants can metabolize and accumulate pharmaceuticals (Table 1). Some veterinary drugs are phytotoxic and negatively affect plant physiology and metabolism (Bártíková et al., 2016; Rocha et al., 2021). Several experiments showed growth stimulation and induced flowering by the impact of exogenous mammalian sex hormones (17β-estradiol, estrone, progesterone, and testosterone) (Bártíková et al., 2016). Negative effect on production yield due to irrigation with antibiotic-contaminated water was notified by Reis et al. (2020b). The preliminary study involved experiments carried out under controlled conditions that differed from natural primarily due to the significantly high concentrations of antibiotics (Bártíková et al., 2016; Tasho and Cho, 2016).

Table-1. PHs determined in plants (Makarov et al., 2023)

PHs group	Substances	Plant (tissues)	Ref.
VAs	34 Substances: TCs, FQs, LAs, SAs	Vegetables, fruits, grains	Ben et al., 2022
VAs	28 Substances: TCs, FQs, LAs, MAs, SAs, aminocoumarin novobiocin	Wetland plant tissues (roots, stem, leaf and seeds)	Chen et al., 2020
VAs	Chlortetracycline, enrofloxacin, sulphathiazole	Radish	Chung et al., 2017
NSAIDs	Paracetamol	Corn and barley	Dolu and Nas, 2023
ATs	Albendazole and its metabolites	Alfalfa and clover	Navrátilová et al., 2021
VAs	Ciprofloxacin, azithromycin	Radish, lettuce	Sidhu et al., 2019
VAs	Tetracycline, sulfamethazine, norfloxacin, erythromycin, chloramphenicol	Carrots, lettuce	Pan and Chu, 2017
VAs	16 Substances: TCs, FQs, SAs	Peach trees (roots, stem, shoots, and leaves)	Zhao et al., 2020

ATs – anthelmintics; LAs – lincosamides; MAs – macrolides; NSAIDs – nonsteroidal anti-inflammatory drugs; VAs – veterinary antibiotics

In edible vegetables and crops grown under more realistic farming scenarios, tetracyclines exhibited higher residue levels in plants (median values 5.10–15.4 μg·kg^{-1} dry weight) than quinolones, sulfonamides, and macrolides (Geng et al., 2022). This could be attributed to their soil level and significant potential for bioconcentration. Research investigating the impact of VAs on agroecosystems through prolonged manure application in agricultural settings concluded that the direct negative effects of antibiotics on peanut harvests were more pronounced than their indirect effects (Zhao et al., 2022). Moreover, the analysis indicates their important role in the negative impact on peanut grain yields via damage produced by microbes and earthworms.

Morphophysiological alteration caused by irrigation water containing ciprofloxacin resulted in diminished seed production in maize (Rocha et al., 2021). In Bártíková et al. (2016) overview was provided regarding the impacts of ciprofloxacin on plant photosynthesis, chlorophyll content, production rate, plant growth and development, and root activity. In a more recent study, enrofloxacin and its metabolite ciprofloxacin harmful impact on crops was verified (Gros et al., 2019). Although ciprofloxacin interferes with the photosynthetic metabolism of plants, enrofloxacin does not. Other antibiotics that are associated with the photosynthesis include tetracyclines and beta-lactams (Bártíková et al., 2016).

Investigation of the absorption of antibiotics by vegetables in fertilized livestock manure soil showed the maximum contamination risk for root crops because of its direct contact (Chung et al., 2017; Tasho and Cho, 2016). However, other experiments resulted in high relatively median concentrations of antibiotics (0.400–203 μg·kg^{-1} dry weight) for corn also (Geng et al., 2022). The greenhouse conditions are more significant for antibiotics bioconcentration, probably due to the higher residue levels of antibiotics in soil.

Root absorption is one of the main pathways of antibiotics contamination of plants and substances accumulate in greater quantities in them (Rocha et al., 2021). This was discovered by authors for cucumber, corn plants, and the rhizomes of ginger. Estimation of the half-lives and trace amounts of chlortetracycline, enrofloxacin, and sulphathiazole in contaminated soil and radish roots and leaves indicate that antibiotics were taken from soil via roots and entered the leaves of radishes in concentrations of <2.73%, 0.08–3.90%, and <1.64% for chlortetracycline, enrofloxacin, and sulphathiazole (Chung et al., 2017).

The research of alfalfa (*Medicago sativa* L.) exposure to oxytetracycline, ofloxacin, and sulfamonomethoxine by using swine manure indicated oxytetracycline and ofloxacin were detectable in the root, stem, and leaf, but sulfamonomethoxine was detected only in the root (Huang et al., 2021). In this study, ofloxacin concentration decreased by 68.7% and oxytetracycline concentration was insignificantly decreased for 60 days of ensiling.

Paracetamol was detected in corn (up to 43.3 ng·kg^{-1}) and barley (up to 16.8 ng·kg^{-1}) (Table) within the irrigation with treated wastewater, and naproxen was detected in sugar beet (up to 11.2 ng·kg^{-1}) through sewage sludge application (Dolu and Nas, 2023).

In the study of albendazole and its metabolite circulation in real agriculture conditions, unexpectedly high concentrations of the active metabolite albendazole sulphoxide were discovered in all samples (dung, plants, ovine plasma, rumen content, and feces) (Navrátilová et al., 2021) and albendazole sulfoxide and inactive albendazole sulfone persisted in soil (up to 25 cm from feces) and in plants for 3 months since the experiment ended (Navrátilová et al., 2023).

Crop plants also could be a pathway for ARB and ARG into the human microbiome, but to date, this problem didn't attract enough attention (Xiao et al., 2023). ARG are found in microorganisms of vegetables (cilantro, endive, lettuce, pak choi, tomato, cucumber, pepper, carrot, and radish) and crops (rice and wheat). It should be noted that some soil and plant microorganisms are able to produce antibiotics, e.g., streptomycin and penicillin (Chen et al., 2023). They may apply selective pressure on the microbial community, increasing the resistance of susceptible microorganisms.

As shown in Table 1, the main study concerns the determination of veterinary antibiotics in plants, therefore, TPs may be a supplemental serious hazard for the environment, animals, and humans. Since the synergistic effect of PHs and TPs on plant growth and development is possible, the simultaneous presence of transformation products remains an urgent problem.

4. Transformation of pharmaceuticals in environment: translocation and ecotoxic potential of transformation products

PHs should be detoxified in the transformation process. They are excreted and may persist in the environment as parent compounds or metabolites (Geng et al., 2022). Transformation products in the environment can be generated through various processes including oxidation, hydroxylation, hydrolysis, conjugation, cleavage, dealkylation, methylation, and demethylation of PHs. Classification of TPs is discussed in studies by Bílková et al. (2019), Reis et al. (2020b) and Zhong et al. (2022). They can be categorized according to the processes of their degradation – biotic (human, animal, and microbial metabolites) and abiotic (hydrolysis, photolysis). TPs could be equally or more toxic or persistent than the parent compounds in several cases (Maculewicz et al., 2022; Zhong et al., 2022) (Fig. 2).

TPs with higher toxicity than parent PHs

- Photodegradation products of cephalosporins;
- Several photodegradation products of sulfamethoxazole;
- Several degradation products of carbamazepine;
- Some hydrolysis and photodegradation products of tetracyclines;
- Photodegradation products of acyclovir, prednisolone, dexamethasone, diclofenac

Figure-2. Transformation of pharmaceuticals into products with higher ecotoxicity (based on Maculewicz et al., 2022)

It is proven that SAs photolysis processes both by natural light and UV irradiation generate persistent and toxic intermediates (Reis et al., 2020a). However, for many groups of drugs data on toxicology, bioconcentration, and stability in the environment is still insufficient for the risk assessment (Matejczyk et al., 2020a).

Nevertheless, metabolites of antibacterial drugs could be less toxic but maintain antibacterial activity in the environment. For example, during the enrofloxacin transformation, not only the well-known antibiotic ciprofloxacin is formed, but desethylene-ciprofloxacin (M_1), sulfo-ciprofloxacin (M_2), oxo-ciprofloxacin (M_3) and N-acetyl-ciprofloxacin (M_4) have also been identified (Al-Omar, 2005). They exhibit microbiological activity less than the parent compound, but equal to or greater than some other quinolones (for example, the antibacterial effect of M3 and M_4 is comparable to norfloxacin for some organisms).

Hydrolysis is the major transformation process in the aquatic environment. As Zhong et al. (2022) noted that their efficiency depends on depth, organic carbon content, sandy sediments, bacteria communities, turbidity, etc. Winter in temperate latitudes countries is characterized by low illumination and temperature and correspondingly decreased efficiency of photo- and microbial degradation (Bernot et al., 2019). In countries with milder climates, the increase in pharmaceutical pollution in the winter months is more noticeable.

Hydrolytic transformation processes of TCs may include epimerization, dehydration, decarbonylation, hydroxylation (followed by rearrangement), and deamidation (Zhong et al., 2022). Their hydrolysis-derived products are predicted to have higher toxicity than the parent compounds and should be considered in monitoring programs and risk assessments. First, epi-TCs are more toxic. In addition to parent TCs (53–137 $\mu g \cdot L^{-1}$) in swine manure slurry their degradation products (4-epi-, 4-epianhydro-, and anhydrotetracyclines) were detected in the range of 118–663 $\mu g \cdot L^{-1}$ (Yang et al., 2021).

It was claimed that antimicrobial properties decreased with hydrolysis progress in the example of salinomycin (ionophores) hydrolysis, but some intermediate TPs would retain antimicrobial activity (Reis et al., 2020b). Antimicrobial active ciprofloxacin and norfloxacin were detected as biodegradation intermediates of enrofloxacin in the microbial cultures (Alexandrino et al., 2017).

The role of sorption on solid particles is also important. It depends on temperature, pH, and properties of the particles (including cation exchange). Aquatic colloids (minerals, organic particulates, metal oxides, and bio-colloids) have been proven as a powerful sorbent for pharmaceutical compounds (Khan et al., 2020a). A stronger tendency to be absorbed by sediments and colloids is observed for beta-adrenomimetics.

The pH, ionization of adsorbate, and surface charge have an impact on the back-releasing of substances from colloids into water. The residues of some antibiotic metabolites in groundwater may be higher than the parent compounds due to their higher solubility and persistence (Zainab et al., 2020). According to studies of natural water TPs, reached concentrations several times higher than their parent compounds (Matejczyk et al., 2020a).

In aquatic settings, certain transformation products undergo the process of reversing back to their parent compounds. SAs are metabolized in humans and animals primarily by N4-acetylation and excreted in urine and feces (Cui et al., 2021). Furthermore, hydroxylated and glucuronide-conjugated forms of sulfonamides were discovered in water, although in smaller quantities. Numerous studies have confirmed the deconjugation of the main metabolite N4-acetyl-sulfamethoxazole during wastewater treatment (Polesel et al., 2016). Therefore, glucuronide conjugates can be transformed back to the parent compound, but this process has been very limitedly studied (Cui et al., 2021). The conversion to the biologically active parent compound not limited to SAs has been demonstrated during wastewater treatment processes. Reverse transformation has also been observed for photodegradation byproducts of trenbolone acetate (steroid) (Khan et al., 2020a).

Biodegradation primarily occurs in soil and is largely influenced by bacterial activity, the presence of organic carbon, and various environmental factors such as temperature, humidity, and pH, as suggested by Reis et al. (2020b). Photolysis is limited to surface. The biodegradation pathway of TC in water by strain *Klebsiella* sp. SQY5 suggested that mycelium contributed the most to the degradation, and nine biodegradation products were identified (Shao et al., 2019). Biodegradation includes the removal of methyl, carbonyl, and amine groups. Degradation of TCs was also reported in fungal species from phyla *Basidiomycota* and *Ascomycota*, and in bacterial strains from *Stenotrophomonas* and *Sphingobacterium* (Reis et al., 2020a). Diclofenac is less subject to biodegradation and as molecules of most biodegradation pathways are established 4'-hydroxy and 5-hydroxydiclofenac (Maculewicz et al., 2022; Matejczyk et al., 2020a,b). In addition to *Actinoplanes*, *Brevibacterium*, and microorganisms of activated sludge, and alphaproteobacterial strains *Labrys portucalensis* F11, *Klebsiella* sp., *Enterobacter hormaechei*, and *Raoultella* sp., are effective for diclofenac degradation (Matejczyk et al., 2020a).

The dominant metabolite of ibuprofen in raw and treated wastewater and sewage sludge is 2-hydroxyibuprofen, but 1-hydroxyibuprofen was determined as the primary transformation product of ibuprofen in soil (Dolu and Nas, 2023; Maculewicz et al., 2022). In the corn plant, 1-hydroxyibuprofen shows a high translocation potential. Among the metabolites of ibuprofen, at least one was determined in crops, especially during the periods of treated wastewater and sewage sludge application.

Veterinary drugs and their TPs have become a growing environmental concern. It is not only because of their possible biological activity. In real conditions, the presence of several substances (from the same or different classes) and their TPs is possible. They can have synergistic or antagonistic mutual effect, strengthening or weakening each other's actions and changing detoxication pathways (Matejczyk et al., 2020b; Xu et al., 2022). As described, current studies have demonstrated that, for example, ampicillin and kanamycin individually and in combination with their metabolites enhance the toxicity of diclofenac for *E. coli*. Similar effect was noted for genotoxicity (Osińska et al., 2020). Other studies have shown that doxycycline inhibits the metabolism of florfenicol, and this could increase the content of florfenicol residues in edible animal tissues (Xu et al., 2022). According to the study findings, the first reason for this outcome is the suppression of CYP3A29 expression, which may result in impaired metabolism of florfenicol. In addition, competition for the binding site of R372 and a 'steric-like effect' were also found. Thus, it is crucial to evaluate the possible breakdown or alteration of PHs in water, sediment, soil, and living organisms as this could lead to the creation of harmful substances and impact the overall toxic outcomes. Most of the results of PHs and VDs transformation were obtained in laboratory experiments. In perspective, the study of transformation products (TPs) in environmental risk assessments is especially important. The environmental toxicity of these substances under actual conditions has not been largely investigated. Moreover, in the development of analytical methods, TPs can be proposed as specific PHs markers.

5. Sample preparation and analysis in qualitative and quantitative determination PHs and their TPs (recent advances)

Pharmaceuticals are transferred in the aquatic environment and bioaccumulated in different fish tissues, algae, bivalves, and aquatic invertebrates due to insufficient wastewater treatment, ground runoff from livestock farms, agricultural, and aquaculture facilities. The use of innovative instruments, such as portable devices, is a prerequisite for the identification and measurement of PHs in environmental samples (Rezazadeh et al., 2019). Digital colorimetry mainly with smartphone use is a popular method (Huang et al., 2018; Rezazadeh et al., 2019). Their major advantage is the high speed of transmission of the data to almost anywhere in the world. The increase in the resolution of digital cameras expands the locality of colorimetric analysis, opening prospects for the study of small samples and inclusions (e.g., precipitation of

small volumes) (Monogarova et al., 2018).
The need for qualitative and quantitative determination of PHs and their TPs in the environment is evident. This is possible only with the development of instrumental analysis: gas and liquid chromatography, capillary electrophoresis, and mass spectrometry (MS). Analytical techniques coupled with MS detection are characterized by high specificity, simultaneous multicomponent determination opportunities, and low detection limits.
Furthermore 'green chemistry' principles are preferred both in on-site and instrumental analysis, which is why fewer toxic reagents and solvents are needed – primarily in sample preparation. The most significant illustration of the successful application of green chemistry principles is exemplified in the sample preparation process known as QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe). The procedure originally is outlined in the established protocol for the evaluation of pesticide residue levels in fruits and vegetables (Socas-Rodríguez et al., 2017). The QuEChERS method reduces the time needed for the initial preparation of specimens by eliminating the requirement for supplementary purification techniques, which could introduce potential errors. This method is known for its high recovery rates for various antibiotics across a broad spectrum and promotes the use of fewer organic solvents. In a previous review by Lavrukhina et al. (2022), the efficacy of employing QuEChERS for the analysis of antibiotics was highlighted.
Digital colorimetry is proposed for the determination of phenol (Moslemzadeh et al., 2020), formaldehyde (Shahvar et al., 2018), pesticides (Sankar et al., 2020), as well as antibacterial drugs (Amelin et al., 2022). A characteristic feature of such techniques is the development of colorimetric sensors based on common laboratory components that are affordable, easily handled, and do not affect the mobility of the system. Using sensitive techniques for generating an analytical signal in combination with a high locality of measurements (sorbents and precipitation of small volume) allows to reach low detection limits.
Currently, the functionalities of contemporary digital colorimetry with smartphone, are in line with traditional spectral techniques. Compared with other options, they offer the advantages of ease of use, portability, and user-friendly characteristics. This is mainly due to the development and improvement of specialized software products, mobile applications with graphics editors, and devices for recording an analytical signal and interpreting the data.
The further development of digital colorimetry using smartphone and chemometric analysis is associated with the range of practical scientific fields as well as with the possibility of analyzing video files, which will allow kinetic studies, especially relevant for PH degradation in environmental objects. In the case of drug residue monitoring in the environment and plant, the multi-residue analysis methods are of great interest. The variety of organic pollutants increases steadily. In considering the physicochemical properties differences, it is necessary to apply the general conditions of extraction, chromatographic separation, and subsequent detection (Lavrukhina et al., 2022). Solid-phase extraction (SPE) and QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) are the commonly used approaches in multi-residue analysis.
High-performance liquid chromatography (HPLC) and ultra-high-performance liquid chromatography (UHPLC) allow the analysis duration to be reduced and in combination with MS/MS to develop simple, inexpensive methods characterized by high accuracy (Jongedijk et al., 2023). HPLC with tandem mass spectrometric detection is the preferred method for analyzing aqueous media and bottom sediments in polar PHs due to its exceptional selectivity and sensitivity (Lavrukhina et al., 2022). The lower limits of detection and quantification for antibiotics in soil, manure, biosolids, waste, and natural waters are set at 0.01 and 0.05 $\mu g \cdot kg^{-1}$ ($\mu g \cdot L^{-1}$) respectively. The identification of compounds is primarily carried out in the multiple reaction monitoring (MRM) mode, utilizing at least two of the most distinct precursor ion/product ion transitions. To ensure the accuracy of the findings, the retention time is determined, and characteristic ions are used. There is a growing interest in UHPLC as it offers enhanced resolution and speed of analysis. To mitigate and assess matrix effects, particularly in the examination of seawater and bottom sediments, dilution after extraction and the use of isotopically labeled standards are employed, despite the potential increase in cost and/or duration of the analysis. Nevertheless, the utilization of these methodologies is essential for ensuring the reliability of the results.
Special attention should be payed to analytical techniques for extracting and identifying residue analytes in experiments related to the degradation of VDs. Some methods can't distinguish between decomposition and sorption. Insufficient or incorrect

extraction may result in misinterpretation of the antibiotic's fate in soil because antibiotics that bond with solid particles may be considered transformed or degraded by mistake (Cycoń et al., 2019).

Baseline procedures such as MS/MS are often not sufficient for the simultaneous determination of pharmaceuticals, VDs, and their TPs. In this case, high-resolution mass spectrometry (HRMS) has been proven to be effective (Kish et al., 2023). The ability to detect compounds without standards and conduct retrospective analysis is one of the most effective tools for identifying drugs and their metabolites. This requires the further development of UHPLC-HRMS for simultaneous PHs and TPs determination and methods integration in routine analysis.

6. Treatment strategies in pharmaceuticals removal from water and soil

Sorption, photo-degradation, and biodegradation are the key processes that determine the fate of PHs, including VDs, and their metabolites in the environment (Maculewicz et al., 2022; Reis et al., 2020a). The biotic and abiotic processes in water and soil reduce their amount. The PHs removal efficiency was influenced by pH, exposure time and microbial activity.

6.1. Water treatment

Conventional activated sludge treatment, activated carbon treatment, and membrane filtration are simple physical methods for wastewater treatment with the absence of toxic by-products as the main advantage (Yang et al., 2021). Contemporary wastewater treatment procedures for removal of antibiotics and ARG are presented by anaerobic biotechnology treatment, solar/ferrioxalate photocatalysis, electrochemical removal, membrane bioreactor process, microalgal bioremediation process, constructed wetland, bio-nanotechnology, eco-friendly adsorbent, and carbon filtration (Samal et al., 2022; Yang et al., 2021; Zhou et al., 2023).

As Singh et al. (2021) reported adsorption methods are more effective than simple physical purification through more intense electrostatic interaction, hydrophobic interaction, hydrogen bonds, π-π interactions, and cation exchange, but they are limited by one layer. The use of adsorbent could be a very effective water treatment, e.g. $ZnCl_2$ modified biochar efficient for TCs removal, multi-walled carbon nanotubes are a good adsorbent for chloramphenicol and SAs (Yang et al., 2021). However, its regeneration is required to prevent secondary pollution.

In recent years, various advanced technologies for water purification from pharmaceutical residues have been studied: chemical oxidation using ozone and ozone/hydrogen peroxide, membrane filtration such as nanofiltration, and reverse osmosis (Matejczyk et al., 2020a). Photodegradation is a universal method for organic pollutant decomposition (Yang et al., 2021). Ozonation and photocatalysis are preferred practices as shown for carbamazepine, diclofenac, and ketoprofen complete mineralization example within a short time (6–8 min) (Khan et al., 2020a). Photolysis depends on many factors, but mainly on the structure and property of substances, water composition (inorganic compounds and dissolved organic matter), and properties (pH and temperature), photosource, and photocatalyst (Meyer and Lundy, 2014). Among the procedures, there are direct photodegradation, sensitized photodegradation, and photo-oxidation process. These approaches are effective, for example, for FQ decomposition due to their light sensitivity (Yang et al., 2021).

Advanced oxidation processes (AOPs) for water treatment development such as photo-Fenton, sonolysis, electrochemical oxidation, radiation, and ozonation are actual at present but studying the ecological risks of antibiotics degradation products is of great significance to water environment security (Matejczyk et al., 2020a; Zheng et al., 2023). It was reported that the water treatment with UV/H_2O_2 led to rapid full degradation of ionophores monensin, salinomycin, and narasin (Reis et al., 2020b). The efficiency of the hybrid ozonation-ultrasound process for PHs removal can reach 90% (Khumalo et al., 2023). Different combined strategies as shown in Ghazal et al. (2022) and Alsalihy et al. (2024) reviews are the most promising for water treatment. The degradation of targeted contaminants may occur either sequentially or simultaneously, depending on the specific design of the system. The reactor, that combines combined up-flow anaerobic sludge bed, anoxic-oxic tank, and different AOPs, is effective for antibiotics and ARG removal, the effectiveness in combination with Fenton/UV is higher (Hou et al., 2019). However, studies for other PHs showed the capacity not only of parent compounds (e.g. tetracyclines) but also their degradation intermediates (TPs, generated in AOPs with differential free radicals) to significantly change the microbial community in actual water in microcosm experiments (Zheng et al., 2023).

Diclofenac, naproxen, and 2-hydroxyibuprofen were detected in all sewage sludges. Diclofenac is poorly eliminated (7.9–52.2%) during wastewater treatment opposite to other NSAIDs paracetamol, ibuprofen, naproxen, and their main metabolites (93.4 – >99.9%) (Dolu and Nas, 2023). According to other authors, the removal efficiencies by WWTPs range from 21 to 40% (Matejczyk et al., 2020a). Remediation potential of green alga *Chlamydomonas reinhardtii* from contaminated water was able to remove 37.7% of diclofenac and maintained alga vitality at NSAIDs concentration 32.7 $mg \cdot L^{-1}$ (Liakh et al., 2023). During AOPs, such as ozonation and UV/H_2O_2 for water treatment from diclofenac, 2-hydroxyphenylacetic acid, 2,5-dihydroxyphenylacetic acid and 2,6-dichloroaniline (highest toxic effect) could be formed as the TPs (Fig. 3).

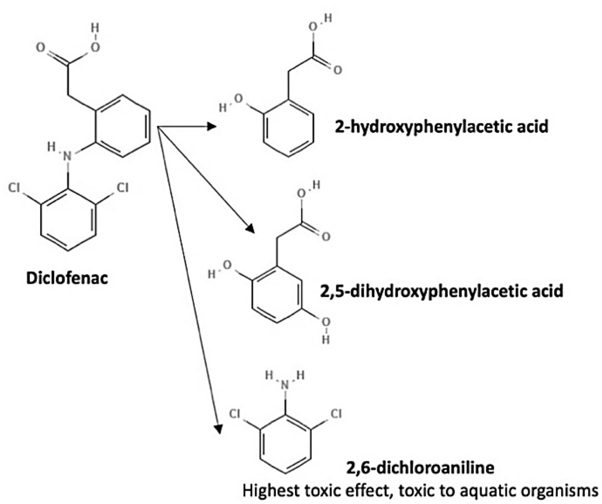

Figure-3. Diclofenac transformation during water treatment by UV/H_2O_2 (based on Matejczyk et al., 2020a; National Center for Biotechnology Information, 2023a, 2023b, 2023c, 2023d)

Biological processes (membrane bioreactor, bio-filtration, microbial, and enzymatic processes) have some advantages over physical methods for wastewater treatment due to less energy and less or no waste, but toxic by-products are also the problem (Kumar et al., 2023). Microalgae are effective in wastewater treatment procedures because of the ability to eliminate xenobiotics, but the process is quite long (Sodhi et al., 2021). Relevant technologies mainly remove pharmaceutical compounds through biosorption, bioaccumulation, biodegradation, photodegradation, and co-metabolism in microalgae (Zhou et al., 2023). Ciprofloxacin, enrofloxacin, tiamulin, and progesterone were detected exclusively in the microalgae biomass of piggery wastewaters by other assays which agrees with their high log *P* values (López-Serna et al., 2022). The adsorption mechanism was found to be a relevant phenomenon in the process of water purification according to the relationships established with log *P*.

The wastewater treatment from PHs by bio-nanotechnology provides an alternative to conventional treatment approaches. The bio-nanomaterials are produced from bacteria, fungi, yeast, algae, and plants, which grow and produce enzymes and other compounds that promote biomineralization (Kumar et al., 2023).

The wastewater treatment plants should be considered as a reservoir of ARG (Zieliński et al., 2021). Ordinary wastewater treatment procedure plants are inefficient in fully removing pharmaceutical compounds (Saxena et al., 2021; Yang et al., 2021). For example, most WWTPs cannot effectively remove amoxicillin and TCs from wastewater (Sodhi et al., 2021). As it observed TCs have longer half-life in the aquatic environment (34–329 h) and may aggravate the development of AMR. Additionally, many sewage treatment plants are not equipped with advanced treatment facilities (Saxena et al., 2021). Alternative approaches are required to be created to effectively eliminate PHs. For effective removal of ARG aerobic-anaerobic reactors can be used (Sodhi et al., 2021).

6.2. Manure detoxification

The degradation of VDs in manure and soil due to abiotic and biotic pathways is possible (Fig. 4).

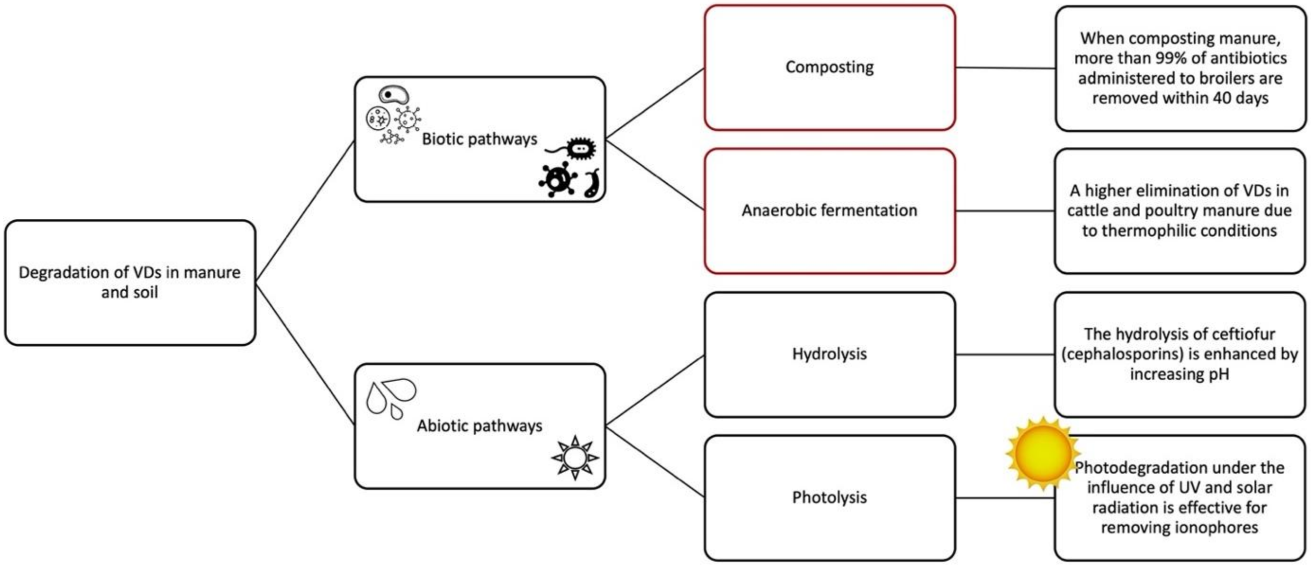

Figure-4. The most accessible technologies for the removal of VDs from manure (based on Geng et al., 2022; Yang et al., 2021, 2023; Zhong et al., 2022)

Ceftiofur (cephalosporins) rapidly degraded to inactive metabolites when unsterilized bovine feces are added and its hydrolysis and photolysis increase with increase of pH and exposure to light (Tasho and Cho, 2016). Composting and anaerobic fermentation can decrease the antibiotic concentration in animal manure by more than 99% as demonstrated in study Ho et al. (2013).

The half-life of antibiotics is an important indicator of persistence. It could vary from a few days (chloramphenicol, ceftiofur) to as high to 300 days (oxytetracycline, sarafloxacin) (Tasho and Cho, 2016), the half-life of tetracycline in the soil is up to 10 months (Tan et al., 2022). Antimicrobials can persist for a long time in deeper soil and water layers due to the increase of half-life at low temperatures and in the dark. The degradation of antibiotics can be enhanced through oxidation with ozone and other factors such as UV radiation and hydrogen peroxide. For example, ionophores can be effectively removed through photodegradation under UV and solar irradiation (Tasho and Cho, 2016).

Biodegradation, including composting, activated sludge, and degrading strains, is the most interesting technology for the detoxification of manure and removing antibiotics from the soil due to its environmental friendliness, high efficiency, low energy consumption, and absence of secondary pollution by TPs (Tan et al., 2022).

The removal of ARG currently has gained increasing attention of researchers and composting is an effective but not well-studied method in this field. As a rule, the concentrations of antibiotics in compost samples are relatively lower than in manure, indicating the degradation of some of the antibiotics during the composting process (Al-Wabel et al., 2021). In soil and ryegrass experiments, the compost posed the highest environmental risk of ARG (with the most abundant types of multidrug resistance) initially and further the risk decreased to the original level at the end (25^{th} day) (He et al., 2023). Meanwhile, Xu et al. (2022) experiments showed that not only the microbial community changed but also the relative abundance of multidrug resistance genes and mobile genetic elements (MGEs) increased during composting. In the case of anaerobic digestion of poultry and cattle manures thermophilic conditions resulted in higher elimination of VAs, but only one out of five ARG was completely removed (Zahedi et al., 2022).

Aerobic composting of manure (except cattle manure) showed good results in reducing the diversity and abundance of ARG (Yang et al., 2023). The dominant bacteria which are key potential hosts of ARG were *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*. The role of MGEs and heavy metals in the ARG dynamics was indicated by Yang et al. (2023).

For large-scale use, electron irradiation is highly effective but expensive, and the standardization of radiation procedure and intensity is required. The phytoremediation potential of some woody plants in the removal of SAs has been reported, and it has been improved by inoculation of some phosphate-solubilizing bacteria such as *Pseudomonas* sp. and *Bacillus* sp. (Tasho and Cho, 2016). However, composting and anaerobic fermentation remain the primary and easily accessible methods for the removal of veterinary drugs from manure (Ho et al., 2013). Further development of technologies for manure detoxification and VDs removal is required.

Conclusion

The lasting impacts of small amounts of antibiotics, antiparasitic and antifungal drugs, hormones, anti-inflammatory, sedatives, and their byproducts, as well as various veterinary drugs in combination with other substances such as pesticides, on ecosystem behavior, warrant thorough and systematic investigation. A common problem of uncertainty in the prediction of VD emission to soil is the lack of reliable information. Synergistic interaction between PHs of different classes and their TPs should also be studied. Additionally, there is limited availability of data on hazardous effects of antibiotic metabolite mixtures.

Although numerous processes suggested by nanotechnology for the elimination of PHs from water sources remain in the experimental phase, many of the research endeavors remain in the experimental phase. The main problem of the chemical process of wastewater treatment is the generation of toxic TPs and high energy consumption. AOPs are effective techniques, however at the same time toxic TPs formation also indicates the necessity of development of additional wastewater treatment systems from pharmaceutical residues. Biodegradation is a promising technology. Among the advantages, it is cost-effective and environment friendly. The need for efficient conventional manure detoxification technologies with complete removal of antibiotics and their TPs is increasing. The combination of microbiological destruction with other technologies may be the most effective approach. TPs could be used as specific markers of water treatment and manure detoxification effectiveness control using advanced analytical strategies and instrumental methods. The development of this methodology may be a particularly promising step in future research.

Simple methods based on smartphone are proposed for water analysis. For more complex objects, accurate and reliable techniques have been considered. HRMS is required to determine the parent compounds and their TPs. The use of TPs as specific markers of PHs could be considered as an important research prospect for future.

Even in small quantities and in conjunction with other classes of pharmaceuticals and toxins, exposure to antibiotics in the diet has the potential to disturb the metabolism of intestinal bacteria, consequently impacting the occurrence of ARB and ARG. The data regarding plant uptake and accumulation of PHs and their TPs are still insufficient and limited. Future extensive works should be focused on all aspects considered in this review including foremost developing of efficient technology of PHs and their residues removal and TPs determination methods.

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Contribution of Authors

Lavrukhina OI, Kish LK & Tretyakov AV: Conceived idea, designed study, data analysis and interpretation of results, manuscript draft preparation and final proof reading
Amelin VG & Makarov DA: Data collection, analysis and interpretation of results and final proof reading
Kozeicheva ES & Khishov AS: Data collection and final proof reading
Borunova SM: Data analysis and interpretation of results

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