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Review

Sources, Persistence, Ecotoxicology and Transformations of Anticancer Pharmaceutical Drug Residues in the Soil Environment: A Review

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ABSTRACT: Release and environmental consequences of drug residues pose a major challenge for soil quality management. This review aims to synthesis the literature related to the transformations of anticancer drugs at the soil-water interphase and their ecological effects. Pharmaceutical drugs including anticancer drugs originate form point and non-point sources of human and animal background. While detrimental effects of anticancer drug residues on human health are widely reported, a relatively little body of knowledge focus on their persistence, decomposition and interaction with soil biological health and quality. Assessment of potential ecotoxicological effects of the residues of anti-cancer drugs is far less frequent compared to other xenobiotics. However, a substantial concern is growing to understand the fate of these drug residues in the environment, particularly, under high environmental risk scenarios. Sewage sludge and hospital wastewaters are the primary sources of anticancer drug residues into the soil and their effects and transformations in soil depend on nature and persistence of drug residues. Depending upon their structure, anticancer drug residues can undergo biodegradation and biochemical transformations to form highly mobile molecules, which move into surface and ground waters, ultimately end up in the soil to alter microbial communities and their functions associated with flow of energy, nutrient cycling and ecosystem functions. This manuscript reviews the behavior of anticancer pharmaceutical residue in the soil environment in terms of effects on soil functions and quality by summarizing the limited available data.

KEYWORDS: Anticancer drugs, Microbial transformation, Drug degradation, Soil biological health, Soil quality

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1. Introduction

The presence of pharmaceutical residues and their possible negative effects on non-target organisms have become an area of emerging concern in basic and applied research in environmental sciences over the last decade (Vazquez-Roig et al., 2010; Negreira et al., 2014). A global review has suggested the presence of 631 out of 713 pharmaceuticals and their metabolic products above detection limits in the environment (IWW, 2014). Cancer has become the second most dangerous and death-causing disease, and this has led to an enormous increase in the development and use of anticancer drugs and, consequently, their release into environment on global scale (Besse et al., 2012; Booker et al., 2014). Presence of anticancer drugs, also considered as emerging contaminants, is fetching a global concern due to their consistent release into the environment and potential adverse effects on ecosystems (Yadav et al., 2021). Emerging

contaminants are defined as any synthetic or naturally occurring chemical that is not commonly monitored in the environment, although it has the potential to enter soil and aquatic ecosystems, causing known or suspected adverse ecological and/or human health effects (USGS, 2009). Unlike the pharmaceutical used in other therapeutic fields, anticancer drugs have quite different toxicological properties (Seira et al., 2013). Most of these drugs interfere with genetic material and consequently have carcinogenic, mutagenic and teratogenic potential and their residues represent hazardous contaminants that may enter water cycle and biosphere (Kümmerer and Al-Ahmad, 2010). Considering the environmental perspectives of these contaminants, the key steps in the life cycle of drug residues involve manufacturing, consumption and waste management. According to the European Environment Agency, the anticancer drug residues are identified from diffuse sources, through the discharge of human and animal excretion (EEA, 2010). In soils, residues of these drugs interact with clay minerals and organic matter following sorption and fixation processes, and these interactions are controlled by both environmental, soil and drug-based characteristics (Kumar et al., 2005). Many drug residues in the soil are directly ingested due their application via manures or sludge which increase human exposure to such drug residues and their metabolites.

1.1 Anticancer drugs in environment

The anticancer pharmaceuticals are released into the environment, mainly through municipal wastewater effluents, hospitals and live-stock activities (Kosjek et al., 2013; Isidori et al., 2016). Discharge of wastewater effluents into rivers and application of sludge amendments on the soil results in cascading drug residues through the environmental compartments (Fig. 1). Physicochemical analyses have indicated the presence of anticancer drug residues and their metabolites in aquatic environments such as wastewater, groundwater, surface water, and drinking water (Rowney et al., 2009; Besse et al., 2012). The sewage systems and wastewater from hospitals contains high concentration of drug residues because they neither undergo complete degradation during treatment process (Schuster et al., 2008; Loos et al., 2013; Zhang et al., 2013; Cesen et al., 2015). Landfills also receive pharmaceuticals from municipal waste disposal and, after the processes of biodegradation and adsorption, the pharmaceutics reach the groundwater and surface water resources (Musson et al., 2009). Extent of decomposition and biodegradation of these compounds depend on their physicochemical properties, especially during the sewage treatment processes, and when sewage sludge is applied to increase soil fertility, the residues contaminate soil and crops (Kumar et al., 2005; Gielen et al., 2009; Baresel et al., 2015; Haiba et al., 2016; Magnér et al., 2016). In addition, veterinary drugs from livestock farming also contaminate soil directly through manure and slurry (Song and Guo, 2014). The soil contamination, then, affects surface water, groundwater and the water intended for human consumption (Magnér et al., 2016). Although the drug residues occur as micropollutants and in low concentrations does not reduce their toxicological concerns because they consist of biological active mol-

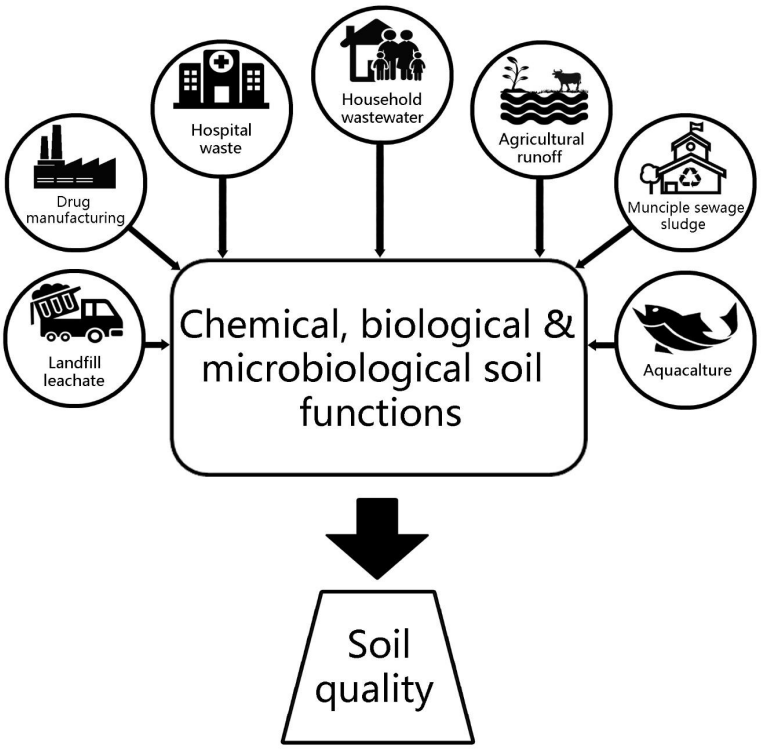

Figure 1. Schematic diagram of anti-cancer drug residue cycling in the environment.

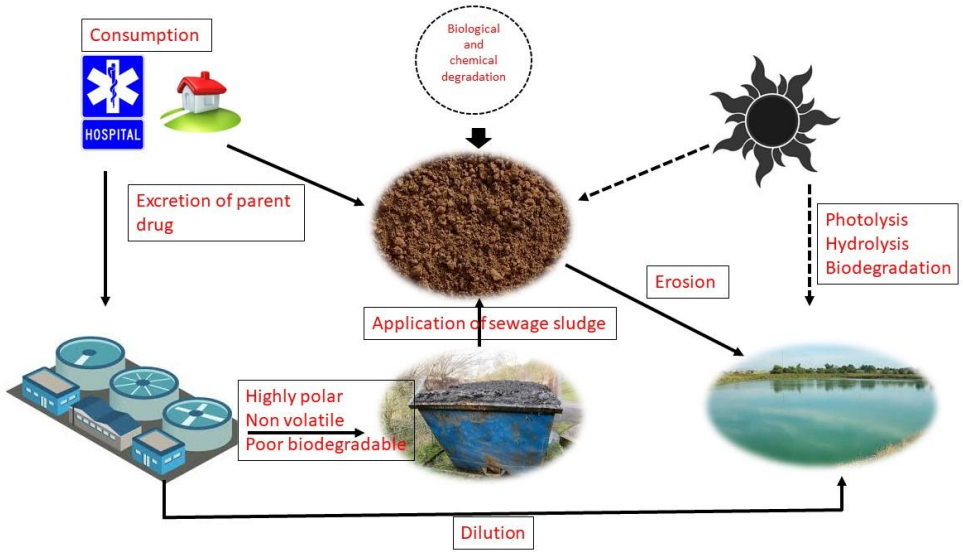

Figure 2. Conceptual diagram of anticancer drug transformation in the environment (Adapted from Booker et al. 2014).

ecules intrinsically (Allen et al., 2010). These drug residues are also considered as pseudo-persistent due to their constant discharge and accumulation into the environment (Daughton, 2003). As a consequence, uptake of pharmaceutical residues by plants from water and/or soils under sewage sludge recycling, demonstrated by soil column studies, is demonstrated an important pathway of drug residue movement into the environment (Hillis et al., 2011; Tanoue et al., 2012).

1.2 Emissions of anticancer drugs into environment

Anticancer drugs have been in extensive use for chemotheraphic treatment for many decades (Mioduszewska et al., 2016; Novak et al., 2017). However, presence of carcinogenic, mutagenic and teratogenic compounds in these drugs have fueled widespread concerns of their ecotoxicological effects and risks to the environment, especially when their potential behavoiur and associated risks are still not clear (Allwood et al., 2002; Toolaram et al., 2014). Anticancer drugs and their metabolites are released into the environment through effluents (Larsson, 2014; Ebele et al., 2017). The presence of cytostatic drugs such as oxazaphosphorine, cyclophosphamide and ifosfamide in surface and groundwater has been confirmed recently (Isidori et al., 2016). The anticancer drugs such as CP and IF generally do not undergo biodegradation during municipal sewage treatment processes. Fates and effects of such drugs in hospital wastewater has been reported recently (Prasanna et al., 2015).

The anticancer drug residues can also originate during the sewage and solid-waste treatment from the manufacturing units at industrial level to the consumption levels (e.g. excretions) (Yin et al., 2010; Xie, 2012; Baresel et al., 2015). The sources such as households, hospitals, health care centers, manufacturing facilities, and waste treatment plants contribute to the occurrence of these residues in waste streams (Ebele et al., 2017). However, a little systematic information exists about the relativeness of these resources for the emissions of drug residues into environment and the information available deals with only a small part of the actual process and/or specific substance. In addition, to a lesser level, release of such drug residues can also come from their volatilization and/or the aerial transport of dust from animal rearing units (GACE, 2007). However, the significance of such releases into the enviroment is still largely remain unknown (BIO-IS, 2013), as discussed above.

1.3 Behavior of anticancer drugs in environment

The residues of anticancer drug of various therapeutic categories e.g. hormones, cytostatics, antidepressants and antibiotics have been observed in the environment at the soil-biota-water-air interphase; although the data on the presence of these drug residues in soil, air and biota are still scarce. These drug residues can generally degrade following both biotic and abiotic paths in soils and water (BIO-IS, 2013). Transformations of anticancer drugs and their metabolites can lead to their movement within different parts of the environment such as from wastewater to sludge/sediments to soils to water bodies (Table 1). This movement, however, depends on various factors including molecular characteristics of drugs, retention behavior (a-

Table 1 Summary of major transformation processes of drug residues in environment **(**Modified from Haddad et al. 2015).

Mechanisms	**Transformation products**	**Activity hotspots**
Biodegradation	Microbial metabolites, Biodegradation products, Biotransformation residues, Complex metabolites	Water and wastewater treatment plants, Surface water systems, Anaerobic digesters, Bacterial and fungal dominated hot-spheres in soil
Photolysis, Photocatalysis	Photo-degradation products, Photoproducts	Surface water bodies, Water and wastewater treatment
Chlorination, Ozonation, Advanced oxidation	Metabolites from chlorination, Products of oxidation and photo-oxidation,	Water and wastewater treatment
By products of xenobiotic nature	Biotransformation products, Metabolites, Recalcitrant products	Occur in majority of transformation products

bsorption/adsorption), properties of soils and sediments, pH, quantity of organic molecules, water saturation and aerobic properties (Wang and Wang, 2015). The sorption rate of drug residues is a fundamental factor which influences their transportation rates and, as a result, the products with non-sorptive behavior are rapidly transported to the surface and groundwater whereas sorptive substances follow a much slower transportation mode (Holten-Lützhøf, 1999; Doretto and Rath, 2013; Wegst-Uhrich et al., 2014). Nevertheless, these properties of drugs and soils control the leaching of drug residues into subsurface soil and groundwater (Dolliver and Gupta, 2008; Kwon, 2011). Higher polarity and lower volatilization potential of the most of pharmaceuticals also make them more susceptible to be leached down with water (Breton and Boxall, 2003). Both abiotic and biotic pathways are responsible for degradation of drug residues and converting them into less potent yet hazardous byproducts (Halling-Sørensen, 2002). The degradation rates of these drug residues depend largely on environmental factors including temperature, pH, soil type, and the nature of the pharmaceutical under consideration (BIO-IS, 2013). Interaction of pharmaceuticals with clay minerals and soil

organic matter through sorption, binding and fixation determine their persistence and decomposition in the soil matrix (Avisar et al., 2010; Liu et al., 2011). The strength of the interactions also depends on the chemical species and the soil characteristics (Kumar et al., 2005). Other factors regulating environmental fate of anticancer drugs include carbon and energy sources, mineral nutrients, growth factors, ionic composition, water availability, pressure, air composition, electromagnetic radiation, pH, oxidation–reduction potential, spatial relationships, and genetics and interaction of the microorganisms which can alter the microbial diversity and activity.

1.4 Transformations and persistence of anticancer drugs

Since anticancer drugs are excreted with faeces and urine, and composed of xenobiotic-nature parent compounds and metabolites, they enter into the soil by means of aquatic environment through hospital and wastewater treatment plant wastes, landfill leachates and, to a minor amount, in the discharge from the pharmaceutical industry. For example, the platinum-based anticancer drugs including cisplatin, carboplatin and oxaliplatin, and their residues enter into the soil mainly through the municipal wastes containing excretions from patients undergoing chemotherapy (Ferrando-Climent et al., 2014; Petrie et al., 2015). Transformations of anticancer drugs are directly linked to the fate of parent compounds (Haddad et al., 2015). Different environmental processes are linked with wastewater and potable water treatment plants (Zwiener, 2007). During aerobic wastewater treatment or anaerobic digestion of sludge, transformation of these drugs and their metabolites may take place, and, as a result, bacterial metabolite-based biotransformation products are formed (Längin et al., 2009). The formation of several biotransformation products, having genotoxicity and mutagenic potential, during these processes are related to the anticancer drugs (Table 2). It must be noticed these anti-cancer drugs have significant potential to cause cytotoxic, genotoxic, mutagenic and teratogenic effects, however, studies on such effects are confined to aquatic environments (Touraud et al., 2011; Turner and Mascorda, 2015; Heath et al., 2016; Novak et al., 2017). Booker et al. (2014) summarized the discharge of some anticancer drugs including capecitabine, imatinib, sorafenib, lapatinib, and mitotane to the soil via sewage sludge and showed that sorption potential of these drugs ranged from 6 (imatinib) to 92% (lapatinib) whereas some of them have very high bioaccumulation potential such as lapatinib and mitotane. The pharmaceutical residues with neutral to alkaline characteristics are retained more strongly by soil compared to the those more mobile in soil with acidic properties because:

- Pharmaceuticals having neutral chemistry are more hydrophobic and partition to soil organic matter (Schwarzenbach et al., 2003);
- Basic chemical nature pharmaceuticals are dominated by cationic groups with positive charges and are held strongly by negatively-charged soil particles (Magnér et al., 2009); and,
- Pharmaceuticals with acidic functional groups are anionic having negative

charge and tendency to be repelled by soil (Magnér et al., 2016).

Some of these drugs undergo fractional elimination during activated sludge treatment which is the most common wastewater treatment system (Lutterbeck et al., 2015; Kosjek et al., 2016). Hydraulic retention time and age of sewage sludge are important factors for biological transformations of pharmaceuticals during sewage treatment (Kreuzinger et al., 2004). During this treatment process, trace toxins are generally affected by three mechanisms of volatilization, biodegradation or sorption onto sludge, however, relative strength of these pathways depend on the physicochemical properties of compound and sludge (Seira et al., 2013). Due to the direct and indirect interactions of these highly active compounds, unsafe levels of the drug residues often occur in the environment (Kummerer et al., 2016).

2. Experimental parameters

Several experimental parameters have been used to define distribution and the fate of anticancer drugs in the environment. These parameters predict the behavior drug residues based on their chemical structures and physicochemical properties such as dissociation constant (pK_a), octanol-water partition coefficient (K_{ow}), bioconcentration factor (BCF), atmospheric OH rate, organic carbon partition coefficient (K_{oc}), solid water distribution coefficient (K_d), n-octanol or water distribution coefficient (D_{ow}), vapor pressure (P), degradation half-life (DT_{50}) and Henry's coefficient (KH). A number of studies have used these parameters to describe the physicochemical nature, occurrence and fate of various anticancer compounds. For examples, comparison of dissociation constant of five anticancer drugs e.g. 5-Fluorouracil (5-FU), Gemcitabine (GEMc), IF, CPA and Methotrexate (MTX) showed that MTX had low pKa value and higher polarity than others (Besse et al., 2012; Xie, 2012; Zhang et al., 2013). According to the Guideline of Medicinal Products on the environmental risks associated with anticancer drugs, European Medicines Agency (EMA) requires K_{ow} to be greater than 4.5 as a pre-requisite for further screening of drugs for their toxicity, persistence and bioaccumulation in environment (European Commission, 2011; Vestel et al., 2016).

2.1 Dissociation and sorption mechanisms

For dissociation of drugs, the constant pK_a is used as equilibrium constant which defines the degree of dissociation at a specific pH of compounds. Dissociation increases the polarity and mobility of drug residues and affect their environmental fate at a broader pH range of 5–9 (Kosjek and Heath, 2011).

The sorption of drug residue is one the fundamental factor affecting transformation of anticancer drugs in the environment. Anticancer drugs can be degraded both abiotically or biotically at the soil-water interphase and these transformations generally reduce their harmful effects by converting them into less hazardous products (BIO-IS, 2013). The sorption rate on organic matter is determined by using two types of coefficients i.e. K_{ow} and K_{oa} which are derived from the D_{ow} and K_d coefficients. D_{ow} coefficient specifies the affinity of an organic substance to allocate between lipids and fats while sorbing to particulate matter (Kosjek and

Heath, 2011). For example, aromatic amines bind strongly to soil organic matter or humic substance because of higher reactivity of their aromatic amino groups (Richnow et al., 1997). This mechanism results in lowering mobility of these compounds than predicted from the physicochemical parameters. However, in contrast, anthracyclines, vinca alkaloids and their correspondent mitoxantrone adsorb freely to steel, glass, and plastics, and also show their potential for sorption by the sludge and sediments (Kümmerer, 2008).

Interaction of the drug residues with soil organic matter and clay particles take place through processes such as binding, sorption and fixation of these substances within the soil matrix (Thiele-Bruhn et al., 2004). Sorption of the anticancer drugs residues to the soil matrix depend greatly on the properties of soil and chemical species along with the temperature, moisture and the soil solution chemistry (Xu et al., 2021). For sorption and/or interaction of these drug residues with soil, the distribution coefficient (K_d) is used which measures sorption of a solute in soil medium. K_d indicates the ratio between the quantity of an adsorbate per unit mass of sorbent to the concentration of the adsorbate in solution at equilibrium. Soil organic matter (SOM) being the key determinant of the fate of organic pollutants in soil (Nowara e al., 1997), K_d is modified as K_{OC} which takes into consideration the role of soil organic carbon (SOC) for pollutant sorption (Song and Guo 2014). If the $K_{OC} > 5$, the drug residues have high bioaccumulation potential e.g. lapatinib and mitotane has high bioaccumulation potential with $K_{OC} > 5$ (Booker et al., 2014). In addition, sorption potential of anticancer drugs increases linearly with the increase in K_{OC} values. Sorption of the drug residues to soil has been shown to be governed by SOM quantity and quality (Gruber et al., 1990; Chefetz et al., 2008).

2.2 Biodegradation and decomposition

Anticancer drugs and their metabolites are released into rivers and pose a serious risk of contaminating aquatic and terrestrial ecosystems (Fig. 2). Mostly diverse classes of anticancer drugs have low biodegradability but varied and wide range of persistence patterns through (Toolaram et al., 2014; Kosjek et al., 2016). Booker et al. (2014) summarized a number of studies indicating relatively low biodegradation of the majority of anticancer. The biodegradability of anticancer drugs has been shown to be lower in soils compared to water. For example, Zahn-Wellens/EMPA test along other studies suggested that there was little CP degradation in swage water treatment plants and, also, when it enters into water cycle (OECD, 1992; Steger-Hartmann et al., 1997; Kiffmeyer et al., 1998). Similar degradation behavior was observed for IF in both wastewater treatment and Zahn-Wellens experiments (Steger-Hartmann et al., 1996). The data showed that etoposide biodegrade slowly in the environment whereas vincristine, vinca alkaloids, vinblastine and vindesine lack inherent biodegradability (Al-Ahmad and Kümmerer, 2001). Despite most of the anticancer drugs exert low biodegradability (Table 1), some of them show substantial biodegradation e.g. cytarabine decomposed up to 70% after 10 days in activated sludge and similarly, 5-FU was completely eliminated from a spiked influent under laboratory

conditions within days (Kiffmeyer et al., 1998). These differences in biodegradation suggested that 5-FU was resistant to degradation both in the closed-bottle and Zahn–Wellens tests. A general trend in biodegradability of 5-FU, cytarabine and gemcitabine is related to their chemical structures. For example, molecules of 5-FU contain no easily biodegradable sugar while cytarabine consists of a pyrimidine with arabinose and gemcitabine groups, and arabinose being fluorinated shows resistant to biodegradation due to high redox potential (Kümmerer and Al-Ahmad, 1997). CPA and IF are other widespread anticancer drugs in the environment with little tendency for biodegradation. For example, Buerge et al. (2006) conducted laboratory simulation tests using lake water under dark conditions to investigated degradation of CPA and IF, and found a half-life of 80 days for CPA whereas IF followed incomplete degradation pathway. However, under irradiated conditions of lake water, degradation of CPA and IF proceeded at half-life of 44 and 144 days respectively. MET is another anticancer drug which show little biodegradation and 7-hydroxymethotrexate is the major byproduct resulting from its degradation (Kiffmeyer et al., 1998). Johnson et al. (2008) suggested that these compounds at higher concentrations results in cytotoxic effects microbial populations. In addition, following conditions limit removal of anticancer drugs during wastewater treatment processes:

- Hydrophilic nature of the drugs does not allow sorption to the sludge;
- Presence of halogen atoms within molecules of some compounds which hinder biodegradation; and,
- Intrinsic toxicity of compounds to bacteria.

Chee-Sanford et al. (2009) suggested hydrolysis as an important phenomenon of pharmaceutical transformation in the environment as water is always an integral part of animal manures and sludges which are the major source of the drug residues. Hydrolysis of various veterinary drugs have already been reported under acidic and alkaline environments (e.g. Doi and Stoskopf, 2000; Huang et al., 2001). Nevertheless, biodegradation represents the major mechanism of drug transformation in soil. Biodegradation pathway is controlled by enzymatic degradation and addition of microbial inoculants with wastewater, sewage sludge and sediments enhanced microbial degradation of drug residues (Al-Ahmad et al., 1999; Gartiser et al., 2007). However, abiotic degradation of the drug residues is more dominant in soils compared to the biodegradation processes (Clarke and Smith, 2011). The persistence and biodegradability of the drugs in soils depends on number of soil and environmental factors, as discussed above. While many drugs are degradable in soils with a half-life <30 days under controlled experimental conditions, a few such as sarafloxacin, roxithromycin, and virginiamycin exhibit higher persistency and stay in the soils unchanged over the scale of months (Song and Guo, 2014). These drug residues have been shown to be taken up by plants such as corn, onion and cabbage, and can also by other organisms such as earthworms (Kumar et al., 2005; Carter et al., 2016).

2.3 Stability towards photolysis

Photolysis is considered a major pathway for abiotic transformations of anticancer drugs in the environment (Calza et al., 2014). Photolysis can be both direct and indirect i.e. direct photolysis results from the direct absorption by solar light through the substrates whereas indirect photolysis occurs due to natural photosensitizers such as dissolved organic matter (DOM) which can produce species with strong oxidation potential including hydroxyl radicals (HO) upon irradiations (Nikolaou et al., 2007; Michael et al., 2014). For example, functional groups on molecules can absorb light in the range of 200–800 nm region having pi electron functionalities and hetero atoms containing nonbonding valence shell electron pairs. Other light absorbing groups may include chromophores with C=C, C=O, N=O and C–X (X = I, Br) functional groups. Indirect photolysis depends on the physicochemical characteristics of organic compounds determined from a rate coefficient called ‘‘atmospheric OH rate’’. For example, atmospheric OH rates of vincristine and vinblastine are 200 times higher than that of carmustine which suggest that vinblastine and vincristine possess more potential for advanced oxidation processes than the compounds having lower atmospheric OH rate constants (Shi et al., 2013). MET is susceptible to photolysis because of its potential to absorb ultraviolet (UV) light of wavelengths greater than 290 nm compared to 5-FU which do not absorb light of wavelength greater than 290 nm and resist direct photolysis, however, it can be degraded by ozonation process. (Pérez Rey et al., 1999). In contrast, 5-FU was sensitive to light at remained 266 nm and followed photodegradation under Hg medium pressure lamp in solution (Straub, 2010). Capecitarabine (CAP) showed slow abiotic degradation in solution at low wavelengths (<190 nm) indicating the needs to analyze stability of drug compounds exposed to low wavelength light (Baumann and Preiss, 2001). CP can also degrade via hydrolysis at temperature above 30 °C due to presence of chlorine atoms and slow dark chemical degradation whereas IF did not follow such degradation mechanism (Bicer et al., 2013). The indirect photochemical degradation due to OH radicals resulted in relatively faster degradation rates in treated lake water samples which highlighted the significance of transitory photo oxidants responsible for the degradation processes (Buerge et al., 2006). However, photodegradation of drug residues could be limited under field conditions due to restricted exposure to light (Beausse, 2004). Nevertheless, biodegradation and photolysis are the most important primary pathways of degradation (Booker et al., 2014).

3. Effect of anticancer drugs on soil quality indicators

Since the soil quality is of significant importance, researchers have proposed a large number of soil quality indicators and indices since soil quality cannot be estimated directly. Majority of these soil quality indicators integrate changes in soil physical, chemical and biological properties over time in response to natural and anthropogenic factors. Use of such soil quality indicators has generally been applied at pilot, field and global scales (Karlen et al., 2001). However, recently, the concept of soil quality index has been suggested as a more comprehensive tool

to describe soil quality that integrates soil physical, chemical, microbiological and biochemical properties (Halvorson et al., 1996; Torres et al., 2015). Soil biological and microbiological parameters are considered sensitive and relatively quick response soil quality indicators as they represent microbially mediated soil processes. Soil microorganisms are directly related to soil quality as they are responsible for organic matter turnover, biogeochemical C, N and P cycling, soil structural stability and fate of xenobiotics applied to the soils (Turco et al., 1994; Wardle and Giller, 1996).

4. Effects on soil microbial activity and microbial communities

Microorganisms are an extremely diverse group of organisms constituting about 60% of the total Earth's biomass . According to an estimate, about 1.2×10^{29} and $4\text{-}5 \times 10^{30}$ microorganisms are inhabitant to aquatic and terrestrial environments respectively (Singh et al. 2009). Microorganisms play an integral part in biogeochemical nutrient cycles, flow of energy and matter, plant biomass production and environmental health in majority of ecosystems (Desai et al., 2009; Grenni et al., 2018). Therefore, biological and biochemically processes in soil and water mediate ecosystem functions (Zabaloy et al., 2008). As a result, microbes are critical for carbon and nutrient transformations, and any change in their community structure may alter the cycling and recycling of nutrients, and thus affect soil and water functions indirectly (Wang et al., 2008). The soils, the ultimate sink of pollutants, are generally contaminated with pharmaceuticals drugs through the following channels (Oppel et al., 2004):

a) Using of activated sewage sludge as organic amendment and fertilizer on agricultural fields;
b) Irrigation of agricultural fields with wastewater containing drug residues;
c) Contaminating groundwater from wastewater drainage; and
d) Leakage from drains and sewage treatment works.

Soils are the ultimate sink of drug residues where they can cause strong effects on soil such as inducing antibiotic resistance in soils (Kemper, 2008; Marti et al., 2013). Environmental factors, microbial communities and interactions between microorganisms can alter microbial diversity, activity and community composition in soil which regulate soil functions. The soil solid surfaces containing 80–90% of the microorganisms are hotspots of positive (symbiosis and metabiosis) and negative (competition, parasitism, and predation) microbial interactions which control the secretion of the bioactive compounds. As a result, some microbes secret compound that affect their competitors negatively under conditions of limited resources. Antibiotic resistance genes (ARGs) have also been reported in soil receiving antibiotic rich wastewater which have potential to affect human health (Amarasiri et al., 2020). There is evidence that antibiotic resistance bacteria could alternative microbial community structure and composition (Negreanu et al., 2012; Meena et al., 2015), however, very little is known on how antibiotics and antibiotic resistance bacteria may affect the soil processes and nutrient cycling. For example, oxytetracycline decreased activities of soil enzymes including urease, sucrase and

phosphatase but increased microbial biomass N (Yao et al., 2010). Kotzerke et al. (2008) found significant effect of sulfadiazine on N cycling. Similarly, negative effects of sulfadiazine on soil bacteria and their diversity have been reported (Hammesfahr et al., 2008). However, such type of studies is few and far between especially with reference to anticancer drugs.

Environmental pollution has the substantial potential to adversely affect and/or alter the microbial communities playing a vital role in provision of important ecosystem processes such as biomass decomposition and nutrient cycling (Fig. 3). Microbes are the most important biological agents responsible for degradation and recycling of waste materials in the environment. They colonize the polluted sites and enable biodegradation of recalcitrant xenobiotics (Galvao et al., 2005). Application microbial ecology approaches help in environmental risk assessment of soil and water contamination from pharmaceuticals pollution. Grenni (2011) investigated the effects of anticancer drugs from waste disposal/manufacturing on bacterial populations and linked the change in microbial community to soil and groundwater quality. The bacterial community was analyzed using fluorescence in situ hybridization (FISH) and their abundance was measured by using the epifluorescence direct count method. The results demonstrated negative effects of trace pollution from antibiotics and chlorinated volatile organics as indicated by the change in microbial communities. A recent review by Grenni et al. (2018) has highlighted direct and indirect the effects of various antibiotics including anticancer drugs on structure and functioning of microbial communities. Such changes in microbial diversity and structure hinder ecosystem processes including nitrogen cycling, sulphur transformations and organic matter decomposition (Laveman et al., 2015; Roose-Amsaleg and Laveman, 2016).

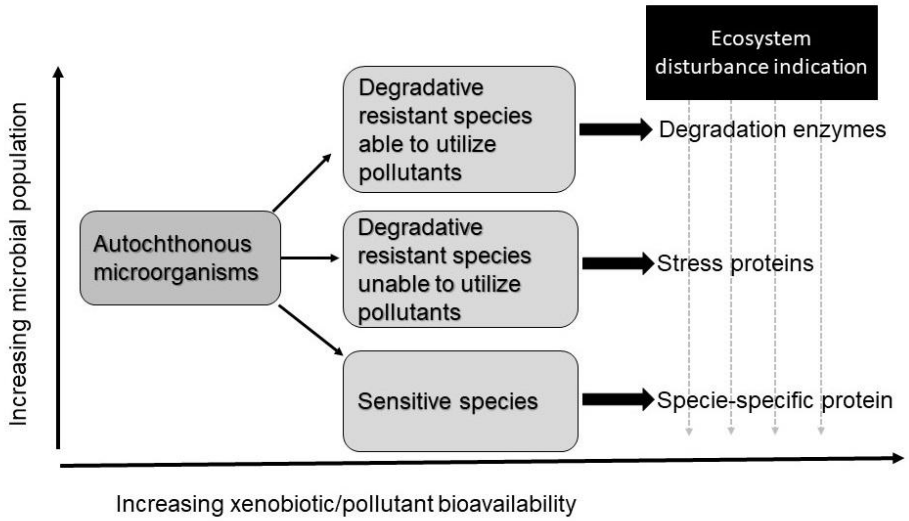

Figure 3. Schematic diagram of microbial response to environmental xenobiotics/pollutants (Modified from Ogunseitan 2000).

Table 2. Summary of degradation and transformation of some anticancer drugs in environment.

Anticancer drug	Elemental formula/Group	Environmental fate			
		Biodegradability	Adsorption onto sludge/sediments	Direct photolysis	Indirect photolysis
Cyclophosphamide (CP)[2,3,5,11,13]	$C_7H_{15}C_{l2}N_2O_2P$/Alkylating agent, nitrogen-mustard analogue	No	No	No	Yes
Ifosfamide (IF)[2,3,4,7,11,13]	$C_7H_{15}C_{l2}N_2O_2P$/ Alkylating agent, nitrogen-mustard analogue	No	No	No	Yes
Cytarabine[5,7]	$C_9H_{13}N_3O_5$/Antimetabolic agent, pyrimidine analogue	Yes	--	--	--
Gemcitabine[7]	$C_9H_{11}F_2N_3O_4$/Nucleoside analogue	Yes	--	--	--
5-fluorouracil (5-FU)[5,9,10]	$C_4H_3FN_2O_2$/Antimetabolic agent, pyrimidine analogue	Yes	No	No	Yes
Capecitarabine (CAP)[12]	$C_{15}H_{22}FN_3O_6$/Antimetabolic agent, pyrimidine analogue	Yes	No	--	--
Methotrexate (MET)[5]	$C_{20}H_{22}N_8O_5$/Antimetabolic agent, folicacid analogue	Yes	--	Yes	--
Vinblastine[1]	$C_{46}H_{58}N_4O_9$/Plant alkaloids and other natural products, vinca alkaloid	No	Yes	Yes	Yes
Vincristine[1]	$C_{46}H_{56}N_4O_{10}$/Plant alkaloids and other natural products, vinca alkaloid	No	Yes	--	--
Etoposide[9]	$C_{29}H_{32}O_{13}$/Plant alkaloids and other natural products, podophyllotoxin derivative	No	--	Yes	Yes
Doxorubicin[8,9]	$C_{27}H_{29}NO_{11}$/Cytotoxic antibiotics, anthracycline	No	Yes	--	--
Epirubicin[6,8,9]	$C_{27}H_{29}NO_{11}$/Cytotoxic antibiotics, anthracycline	No	Yes	--	--
Daunorubicin[8,9]	$C_{27}H_{29}NO_{10}$/Cytotoxic antibiotics, anthracycline	No	Yes	--	--
Mitoxantrone[6]	$C_{22}H_{28}N_4O_6$/An anthracenedione-derived antineoplastic agent	No	Yes	--	--
Cisplatin[5]	$C_{12}H_{19}N_3O$/ Other antineoplastic agents, methylhydrazine	No	--	--	--

[1]Al-Ahmad and Kümmerer (2001), [2]Baumann and Preiss (2001), [3]Buerge et al. (2006), [4]Halling-Sørensen et al. (1998), [5]Kiffmeyer et al. (1998), [6]Kümmerer (2008), [7]Kümmerer and Al-Ahmad (1997), [8]Mahnik et al. (2006), [9]Mahnik et al. (2007), [10]Pérez Rey et al. (1999), [11]Steger-Hartmann et al. (1996), [12]Straub (2010), [13]Ternes et al. (2005).

A significant body of knowledge shows change in microbial community structure and function as a result of exposure to antibiotics designed with selective mode of operation (Mohamed et al., 2005; Yang et al., 2009; Ding and He, 2010). These drugs change the microbial community abundance and their interactions with other microbial species, however, the effects depend on soil characteristics, drug dose and native microbial populations (Zielezny et al., 2006). Effects of such anticancer drug pollution to soils are largely unknown (Boxall, 2004; Bérdy, 2012; Larsson, 2014). For example, drugs induce a significant threat to the edaphic and aquatic organisms because of their significant bioavailability.

However, such effects are overshadowed due to occurrence of the co-contaminants e.g. metoprolol strongly sorbs to soil particles and reduces bioavailability but not the persistence levels of CP and IF in the environment (Turner and Mascorda, 2015). In another study, transport and mobility of CP and IF with MET anticancer drugs was negatively correlated with the turbidity of the solution in a soil column (Mioduszewska et al., 2016). Some previous studies have indicated higher persistence levels of the two oxazaphosphorines, however, these studies were performed at relatively higher concentrations which affected the microbial activities negatively leading to increased persistency of these compounds (Steger-Hartmann et al., 1996, 1997; Kiffmeyer et al., 1998). In contrast, a number of studies have reported the effects of veterinary drugs residues on soil biodiversity e.g. Thiele-Bruhn (2003) found noticeable effects of veterinary drug monensin on soil respiration. Similarly, Patten et al. (1980) observed an increase in soil respiration after application of beef cattle feces on a sandy loam soil. However, Bauger et al. (2000) did not find any negative effects of antibiotics on soil fauna even at concentrations higher than 100 mg kg^{-1}. Data on tetracyclines toxicity to soil fauna/flora and plants showed non-substantial environmental risk whereas the drug has noticeable effects on soil microorganisms and enzymatic activities at realistic concentrations (BIO-IS, 2013). However, association of such observations with soil and ecosystem functions are still not clear.

The effects of drug residue on microbial communities generally involve changes in phylogenetic structure, resistance and ecological functions at micro-ecosystem level (Ding and He, 2010). However, our understanding of the direct and indirect effects of drug residues on ecosystem functioning is very limited whereas it has been established since long that such disturbance could significantly alter microbial and enzymatic activities to modify the ecosystem functioning and stability on long-term basis because of changes in biomass synthesis and nutrient transformations (Perry et al., 1989; Koike et al., 2007; Martinez et al., 2009).

5. Ecological and toxicological effects of drug residues

Pharmaceuticals cascading through the ecosystem behaves as an “ecological factor” which generally change the community structure of the ecosystem and alter ecological functions of water and soil at ecosystem levels (Aminov and Mackie, 2007; Kotzerke et al., 2008). Despite of the clear evidences of

persistence and stability of the anticancer drugs in the environment and their potential ecological effects on soil and water, studies investigating their chronic and acute ecological effects are not very common. Consequently, both short and long-term ecological effects of pharmaceuticals in soil, water and plants are largely unknown (Brain et al., 2006; Song and Gao, 2014). However, an escalating trend in research advocating effects of these drug residues on terrestrial and aquatic environment has been observed (Isidori et al., 2016). For example, the US FDA guidelines for drugs safety include both the toxicity at environmental biodiversity and ecological community and ecosystem level (FDA 1998). In another study by Lutterbeck et al., (2015), the author found significant inhibition of lettuce seed germination when exposed to anticancer drugs (CP, MTX, 5-FU and IM). Their study also indicated mutagenic and cytotoxic potential of these anticancer pharmaceuticals. A limited number of studies have evaluated the long-term ecological risks of pharmaceutical drug residues; however, little focus was given to the potential effects of the metabolites and intermediate products of these drug residues (e.g. Cleuvers, 2003; Bound and Voulvoulis, 2004; Fatta-Kassinos et al., 2011). Since the pharmaceutical residues are generally present in the environment as mixture, therefore, despite of the sub-optimal concentrations of individual compound, the so-called "cocktail effect" might pose a significant ecological and ecotoxicological concern (Heath et al., 2016). A few recent studies have reported ecotoxic effects of anticancer drugs on zebrafish (Kovacs et al., 2016), fertility in higher plants (Misik et al., 2016) and green alga and cyanobacterium (Elersek et al., 2016).

6. Conclusions and limitations

Pharmaceuticals including anticancer drugs are being recognized a significant environmental concern because of their increasingly widespread use and potential ecological effects on terrestrial and aquatic biodiversity. Hospital, household and sewage treatment plants are the major point sources of anticancer drug residue discharge into the environment. Once these pharmaceuticals enter the environment, their fate depend on the physical, chemical, biological and biochemical processes such as photolysis/photodegradation, biodegradation/biotransformation in soil and water, sorption to soil particles and sediments and direct uptake by flora and fauna. However, a little knowledge exists on the behavior of these drugs residues to processes occurring in the soil and water. There are limited studies describing effects of these drugs on microbial communities inhabiting in soil and water at micro-ecosystem scale. There is literally very little information available on the behavior these drug residues in soils, especially soil function and, hence, the ecosystem response. As a result, it is apparently difficult to apply mitigative measure for restricting their emissions into water and soil. Poor removal of some anticancer during the treatment process and their high resistance to biodegradation suggest the need for other methods to eliminate these compounds from wastewater. There are no research studies that would clearly indicate the effects of the prolonged exposure of organisms to anti-cancer drugs. Therefore, it is difficult to

introduce measures restricting their emissions into surface waters. The appearance of some high-profile publications over the recent years has started to fill in existing knowledge gaps and provide a more reliable information about the environmental and human health risk assessment associated with the use of anticancer drugs and their metabolites and transformation products (TPs). However, effects of these drug residues on soil processes and functions, soil quality and, hence, the ecological role of ecosystem remain largely unknown.

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MA & MR Conceived the idea; MA wrote the first draft; MR, MA and KA edited the final version.

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