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Review

A Review on Cytotoxic Antibiotics: Occurrence in Water Matrices, Degradation by Advanced Oxidation Processes, and By-Product Formation

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Abstract: Cytotoxic antibiotics (CA) present a pressing environmental concern due to their persistence and potential adverse effects on ecosystems and human health. Conventional wastewater treatment methods often fail to effectively remove these compounds, making it necessary to explore advanced oxidation processes (AOPs) as promising alternatives. This review aims to synthesize global data on the dosages and environmental concentrations of common CA in diverse water sources, while evaluating the efficacy of AOPs in degrading these contaminants. Various AOPs, including photocatalysis, ozonation, and Fenton-like processes, or their combination, are discussed, highlighting their mechanisms and efficiency in eliminating cytotoxic antibiotics from aqueous environments. In addition, information about the degradation by-products is provided. The rising consumption of cytotoxic drugs underscores the need for this up-to-date review, as diseases were CA are used as treatment, show increasing numbers. By consolidating recent developments and outlining challenges and opportunities, this review serves as a valuable resource for researchers, engineers, and policymakers involved in mitigating the environmental impact of cytotoxic antibiotics through AOPs.

Keywords: cytostatic drugs; emerging pollutants; pharmaceutical compounds; wastewater treatment; excretion rates; anticancer drugs; advanced oxidation processes

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1. Introduction

Emerging pollutants (EP), are defined by the United States Environmental Protection Agency as chemical compounds whose behavior, environmental and public health impacts remain poorly understood [1]. EP have been found in various aquatic matrices such as surface water, groundwater, drinking water and wastewater treatment plants (WWTP) at low concentrations in the range of ng/L and µg/L [1,2]. In addition to the above, the use of contaminated water for agriculture can introduce EP to the food chain [3]. These compounds can migrate to different water bodies through direct or indirect routes, introducing polluting substances into natural environments [4,5]. The most common sources that cause these contaminants to be found in surface water are WWTP effluents, industrial activities and agriculture [6,7]. WWTP are not totally effective in removing EP

since they were designed primarily for the elimination of macropollutants [8], organic matter, nitrogen, and phosphorus [9]. For the treatment of these contaminants, different technologies have been explored, such as: activated carbon, flocculation, enzyme-based methods, nano-bioremediation, and advanced oxidation processes (AOPs) assisted by nanomaterials [3,4,6,8].

The consumption of EP has increased along with population and economic growth, at least 700 substances classified as EP have been detected. In addition, their metabolites and conversion by-products have been identified in the European aquatic environment [10,11]. In Latin America, 197 different types of EP were identified between 1999 and 2018 in eleven countries [12]. All different inorganic, organic, and particulate pollutants can be classified as EP based on their physicochemical properties [13]. They are also classified into various groups and subgroups, such as pharmaceutically active compounds, personal care products, plasticizers, brominated flame retardants, perfluorinated compounds [14], hormones, industrial additives, endocrine-disrupting chemicals, nanomaterials, pesticides [10], and microplastics [11], among others.

Among the EP that represent a water contamination problem is the group of pharmaceutical compounds (PhACs) [15]. These are widely used in human and veterinary medicine and aquaculture [16]. PhACs have been classified as one of the most important groups of emerging aquatic contaminants because of their widespread presence and persistence in aquatic environments in the world [17]. The high consumption of PhACs ultimately results in their widespread presence in the environment [16–18]. They have been found in drinking water and freshwater sources, and their impacts on the ecosystem have made them a critical group of contaminants [19].

Adequate sanitation structures are scarce or even absent in developing communities, so the sources of pollution that introduce drugs into the environment are very varied [20,21]. These sources include municipal wastewater, improper disposal of medications, dumping of expired or leftover medications, intensive livestock farming, hospital effluents, and the pharmaceutical industry [20–22]. Hospitals are the main contributors of drugs discharged into the environment [18]. Several studies have detected the presence of PhACs not only in urban wastewater, hospital drainage, and surface water; they have also been detected in groundwater and drinking water, which can reach the ground due to the use of wastewater for irrigation [23].

PhACs were discovered in aquatic systems in the 1980s, since then many pharmaceutically active compounds have been detected in water [24]. These compounds are grouped into categories based on their properties such as chemical structure, therapeutic class, significance and physical properties [25]. The main PhACs of environmental concern identified in aquatic environments can be classified as: antibiotics, hormones, anti-inflammatories, analgesics, β-blockers, lipid regulators [18,20,23–27], antiepileptic medications, contrast media [23,24,27], and chemotherapy products (anti-cancer agents) [18,23].

During recent years, several AOPs have been used for the degradation of emerging and recalcitrant contaminants, including drugs for cancer treatment. However, the degradation of cytotoxic antibiotics (CA) such as anthracyclines has not been widely studied, except for some scarce works. A search was performed in the SCOPUS database with the following keywords: “advanced oxidation process” AND “cytostatic drugs” AND PUBYEAR > 2003 AND PUBYEAR < 2025 AND PUBYEAR > 2005 AND PUBYEAR < 2025 AND (LIMIT-TO (DOCTYPE, “re”)). The search yielded a total of 138 REVIEW-type articles between the years 2006 to 2024. Figure 1 shows the number of publications per year corresponding to the search performed; it demonstrates a notable increase in interest in cytostatic drug (CD) degradation by AOPs from 2015 onwards, reaching a maximum in 2022.

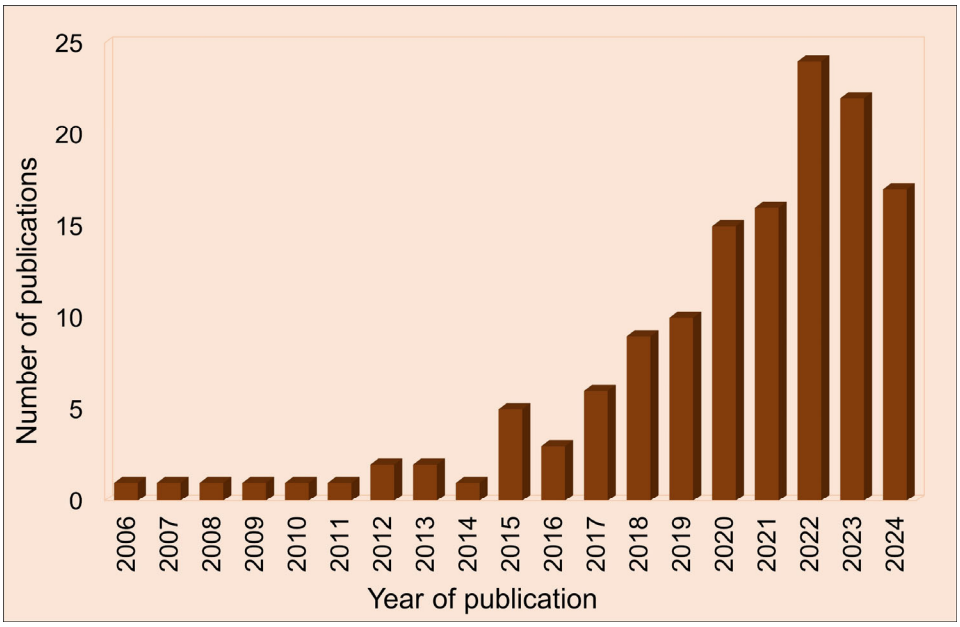

Figure 1. Number of REVIEWS published each year between 2006 and 2024 about cytostatic drugs degradation by advanced oxidation processes according to a search in the SCOPUS database with the following keywords: "advanced oxidation process" AND "cytostatic drugs" AND PUBYEAR > 2003 AND PUBYEAR < 2025 AND PUBYEAR > 2005 AND PUBYEAR < 2025 AND (LIMIT-TO (DOCTYPE, "re")).

Although the past two decades have seen an increase in reviews on CD, reviews specifically dedicated to CA contaminant degradation by means of AOPs, do not appear to generate the same level of interest. During the same time period (2006–2024), only 13 studies were found that address the degradation of cytotoxic antibiotics through AOPs. Interest peaked in the years 2019, 2021, 2022, and 2023, but there were only two mentions of CA contaminants in each of these years.

Several reviews have investigated the progress and current status of the degradation of pharmaceutical contaminants, including cytostatic drugs, by means of various AOPs, presenting the applications and novelty of the methods (Table 1). However, there are still drawbacks, persistent challenges that must be faced, and areas of opportunity towards which new research should be directed.

The challenges associated with AOPs for wastewater treatment extend beyond their operational complexity to their limited applicability for diverse pharmaceutical contaminants. While real-world applications provide valuable insights, a deeper understanding of specific contaminants and their behavior under oxidative treatments remains indispensable. This understanding is particularly critical when addressing persistent toxic by-products, which often exert unforeseen toxic effects on both ecosystems and human health [28]. For example, while advancements in photocatalysis have highlighted the potential of solar-driven catalysts to lower operational costs, the scalability of these solutions remains constrained by the energy requirements and infrastructure upgrades necessary for industrial implementation [29].

Despite the promising results obtained with hybrid systems combining AOPs and biological processes, a significant limitation lies in the restricted scope of contaminants analyzed. Pharmaceutical wastewater often contains a broader spectrum of pollutants than those traditionally studied, creating a gap in knowledge essential for advancing these technologies [30]. Moreover, current reviews often focus on the classification of AOPs without delving into the characteristics of the processes or materials used, hindering the comparison between established techniques and emerging innovations.

To overcome these challenges, novel combinations of AOPs, such as Fenton-based and UV-driven systems, have been proposed as cost-effective and environmentally friendly solutions for handling wastewater contaminated with antibiotics and other pharmaceuticals [31]. Nevertheless, their successful application hinges on addressing the variability of wastewater effluent concentrations and improving process scalability. Laboratory-scale studies demonstrate the feasibility of cost-efficient setups using simple equipment, but transitioning to industrial-scale operations requires further technological refinement.

Ultimately, a holistic approach incorporating both innovative materials and integrative methodologies is needed to enhance the performance of AOPs while minimizing their environmental footprint. Comprehensive studies that evaluate both the degradation of complex contaminant mixtures and the behavior of resulting transformation products under realistic conditions will be pivotal in developing scalable, green, and effective water treatment systems [32].

Table 1. Summary of various recent review articles on cytostatic drug degradation or PhAC degradation by AOPs, highlighting its focus and novelty in contrast to this review.

Review	Focus and Novelty	This Review
Occurrence and fate of pharmaceutical pollutants in wastewater: Insights on ecotoxicity, health risk, and state-of-the-art removal [33].	Occurrence and impacts of PhACs, along with their treatment by different methods, are extensively analyzed, offering an in-depth and comprehensive overview of their environmental implications.	Occurrence and impacts of CA, along with its treatment using AOPs, which are underrepresented in the literature. This highlights the limitations of AOPs, particularly by demonstrating their inability to achieve complete pollutant mineralization.
Challenges and Emerging Trends in Advanced Oxidation Technologies and Integration of Advanced Oxidation Processes with Biological Processes for Wastewater Treatment [32].	Extensively reports on real wastewater degradation processes and addresses a broad range of pollutants. Establishes the challenges of wastewater treatment and highlights the introduction of contaminants into water bodies from various sources.	Focus on the degradation of specific pollutants, providing detailed insights into their behavior at each stage of various degradation processes. It also offers a comprehensive analysis of CA consumption and its concentrations detected in different aquatic and solid matrices.
Anticancer drugs in wastewater and natural environments: A review on their occurrence, environmental persistence, treatment, and ecological risks [34].	Emphasizes the importance of generating transformation products through physicochemical processes and provides a state-of-the-art review on the application of AOPs for the degradation of cytostatic drugs.	Presents various transformation products of CA and establishes its generation pathways through different AOPs. It also provides a state-of-the-art analysis of the application of AOPs and their combinations, incorporating the use of novel nanomaterials.
Critical review of technologies for the on-site treatment of hospital wastewater: From conventional to combined advanced processes [35].	Includes an extensive characterization of the main chemical parameters in hospital influents and reports the concentrations of a wide range of PhACs in hospital wastewater.	Provides a systematic analysis of the presence of CA in various water matrices and WWTP sludge, offering a broader perspective on the issue and establishes the causes of CA removal through transfer between matrices and traces the route of contaminants throughout their cycle.

Table 1. *Cont.*

Review	Focus and Novelty	This Review
Trends in Fenton and photo-Fenton processes for degradation of antineoplastic agents in water matrices: current knowledge and future challenges evaluation using a bibliometric and systematic analysis [36].	A systematic bibliometric analysis to assess trends in the use of Fenton and photo-Fenton processes. Additionally, it focuses on the identification of transformation products and their subsequent toxicological evaluation.	Highlights the persistence, toxicity, and specific transformation routes of CA, providing detailed information on its excretion and environmental impact. It also analyzes a wider variety of AOPs, including photocatalysis, ozonation, electro-oxidation, and combined processes.
Wastewater treatment by anodic oxidation in electrochemical advanced oxidation process: Advance in mechanism, direct and indirect oxidation detection methods [37].	Details anodic oxidation mechanisms, highlighting both direct and indirect oxidation methods. It also explores specific electrode materials and conditions aimed at improving the efficiency of anodic oxidation.	Addresses CA, focusing on global data, environmental persistence, and transformation pathways through a wide range of AOPs, describing the fabrication of materials used and listing the experimental parameters involved.

This review aims to synthesize global data on dosages and environmental concentrations of common CA in diverse water sources, while evaluating the efficacy of AOPs in degrading these contaminants. The study explores photocatalysis, ozonation, electrochemical oxidation and Fenton-like processes, both individually and in combination, assessing recent advancements in AOPs technologies for cytotoxic antibiotic degradation. By examining these aspects, the review seeks to highlight the potential of AOPs technologies for water treatment applications and contribute to the growing body of knowledge on managing pharmaceutical pollutants in aquatic environments. The methodology used for this review includes the identification of relevant scientific material that meets a specific criterion established by the authors within the scope of this work. Databases were consulted using search engines such as: Google Scholar, Science Direct, Scopus, and NCBI. For updated population data, the websites of international organizations such as the International Diabetes Federation and the World Health Organization (WHO) were consulted. The most relevant works on degradation of cytotoxic antibiotics through advanced oxidation processes between the years 2013 and 2024 (November 2024) were considered, using keywords such as: "cytotoxic", "advanced oxidation processes", "degradation", "pathways", and "by-products" and each of the drugs in the group of CA and Related Substances. For the first sections, the search range extended to 2011 with the keywords: "emerging contaminants", "pharmaceuticals", "presence", "occurrence", "wastewater", "dose" and "excretion". Each of the articles found were analyzed thoroughly and critically to be organized into different groups depending on the section of the review to which they correspond. Studies that did not clearly state that the process was AOPs, whether specified by the authors or if the mechanism reaction was described within the article, were excluded.

This review article offers a unique contribution to the field by synthesizing recent advancements, identifying key research gaps, and providing a comprehensive framework for future studies, thus offering new perspectives and guiding further developments in the area.

2. Cancer and Anticancer Drugs

Cancer represents a significant and increasing cause of mortality worldwide, responsible for approximately 10 million deaths in 2022. According to the WHO, the number of registered cases worldwide exceeded 19 million in 2023. Data reported indicate that

the highest recovery rates of patients are observed in North America and Oceania, at approximately 73%, followed by Europe, with a recovery rate exceeding 65%. In contrast, the remaining regions (Latin America and the Caribbean, Asia, and Africa) exhibit disease recovery rates between 52% and 35% [38]. The most common new cancer cases were breast cancer, with 2.29 million cases, followed by lung and prostate cancer, with 2.48 million and 1.46 million cases, respectively. Lung, liver, and colorectum cancer caused the highest number of deaths, with more than 3.4 million victims [39]. In their 2024 study on cancer statistics, Bray et al. [40] projected an increase of 35 million new cases worldwide by 2050. This projection was made assuming that cancer incidence rates will remain constant. This represents an increase of approximately 86% compared to the 19 million cases reported in 2023. However, the precise increase for each country will be determined by its Human Development Index level, with increases ranging from 42% to 142%.

CD are natural or synthetic substances used in chemotherapy for the treatment of different types of cancer [41,42]. Increments in cancer cases in recent years, together with early diagnosis and treatment, are directly correlated with the increase in various treatments, including use of CD globally [43,44]. Consequently, it can be reasonably assumed that the presence of these substances in the environment will also increase. According to Villarini et al. [45], the list of anti-cancer agents contains more than 100 drugs used in clinical practice, these include the CA, for which the mechanism of action is not specific to the cell cycle, and they interfere with deoxyribonucleic acid (DNA)/ribonucleic acid (RNA). These drugs act by intercalating into DNA, inhibiting its replication and transcription, blocking the activity of topoisomerase and the joining of base pairs [46]. CA and related substance (category L01D according to the WHO), are divided into three groups: actinomycines (L01DA), anthracyclines and related substances (L01DB) and other cytotoxic antibiotics (L01DC) [47]. In each subgroup, different CA have been categorized according to the WHO, collaborating with the Centre for Drug Statistics Methodology. Data are presented in Table 2.

Table 2. Classification of cytotoxic antibiotics in their different subgroups and codes for each one according to WHO collaborating Centre for Drug Statistics Methodology, Oslo, Norway [48].

Group		Sub-Group		Cytotoxic Antibiotics	
Name	**Code**	**Name**	**Code**	**Name**	**Code**
Cytotoxic antibiotics and related substances	L01D	Actinomycines	L01DA	Dactinomycin	L01DA01
		Anthracyclines and related substances	L01DB	Doxorubicin	L01DB01
				Daunorubicin	L01DB02
				Epirubicin	L01DB03
				Aclarubicin	L01DB04
				Zorubicin	L01DB05
				Idarubicin	L01DB06
				Mitoxantrone	L01DB07
				Pirarubicin	L01DB08
				Valrubicin	L01DB09
				Amrubicin	L01DB10
				Pixantrone	L01DB11
		Other cytotoxic antibiotics	L01DC	Bleomycin	L01DC01
				Plicamycin	L01DC02
				Mitomycin	L01DC03
				Ixabepilone	L01DC04

CA are compounds with complex chemical structures, high molecular mass, and varying excretion rates (Table 3). Specialized literature shows that bleomycin (BLEO) has an excretion rate of 60% to 70%, being classified as very toxic [49], followed by doxorubicin (DOX) with a maximum of 45% detected in urine without any change after passing through the body [50]. In addition, the amount excreted through feces represents half the compound administered [51]. Daunorubicin (DAU) has a similar behavior to DOX with the same maximum excretion in feces (50%) [52]. Within the L01DB subgroup, other anthracyclines present similar excretion percentages, in the range of 2% to 11% for idarubicin (IDAU), mitoxantrone (MXT), and pirarubicin (PRB) [53–55]. The excretion range with the lowest maximum value was exhibited by ixabepilone (IBP), with only 5–6% as reported by Benet et al. [56].

Table 3. Excretion percentages of cytotoxic antibiotics through feces and urine, chemical formula, and molar mass.

Cytotoxic Antibiotics	Chemical Formula	Molar Mass	Excretion (%)		Reference
			Urine	Feces	
DOX	$C_{27}H_{29}NO_{11}$	543.52	3.5–45	40–50	[50,51,57]
EPI	$C_{27}H_{29}NO_{11}$	543.52	6–20	40	[50,52]
DAU	$C_{27}H_{29}NO_{10}$	527.52	3–25	40–50	[52,53]
BLEO	$C_{55}H_{84}N_{17}O_{21}S^{3+}$	1415.55	60–70	-	[49]
MXT	$C_{22}H_{28}N_4O_6$	444.48	6–11	25	[55]
IDAU	$C_{26}H_{27}NO_9$	497.49	2–7	-	[53]
IBP	$C_{27}H_{42}N_2O_5S$	506.69	5–6	-	[56]
PRB	$C_{32}H_{37}NO_{12}$	627.64	5–9	-	[54]
MIT	$C_{15}H_{18}N_4O_5$	334.33	10	-	[58,59]
DAC	$C_{62}H_{86}N_{12}O_{16}$	1255.42	10	-	[56]

The consumption and dosage of CA are dependent upon the specific type of cancer. Dactinomycin (DAC) is used for the treatment of rhabdomyosarcoma, Wilms' tumor, and Ewing's sarcoma with a maximum dose of 15 µg/kg. DAC is also used to enhance the effects of radiotherapy [60]. DOX is used in doses of 30–75 mg/m^2 [61] and 30–80 mg/m^2 [50]; the dose is limited due to its cardiotoxicity, especially due to its metabolite doxorubicinol, which is 10 times more potent than its parent compound [61]. However, DOX is still used around the world for treatment of cancer-related conditions; Besse et al. [53] reported a consumption in France of 7.94 kg in 2004 and 16.82 kg in 2008 according to data from the specialized cancer care center Léon Bérard in Lyon, France. In 2010 and 2014, consumption figures were reported in Catalonia (Spain) of 0.19 kg and 0.094 kg, respectively [62]. In Latin America, there are also records of the use of this medication: in Rio de Janeiro, as part of the public cancer treatment network between 2010–2017, an average of 0.11 mg/day was consumed [63].

Epirubicin (EPI) is another anthracycline used widely mainly for the treatment of breast, lung, stomach and ovarian cancer [64]; for this purpose, 130 g/year are administered at the Vienna University Hospital with a therapeutic dose of 60 to 150 mg/m^2 as reported by Mahnik et al. [61]. In several places throughout England, application of doses of 0.90 µg/day per patient led to EPI consumption of 16 kg/year in 2005 [50]. At the Catalan Institute of Oncology, between 353 to 1235 mg is administered weekly [64], while in the

Iranian city of Shiraz, 17,700 mg was prescribed between the June and August 2011 [65]. The highest consumption for EPI, also in the case of DOX, was reported in the Léon Bérard center, with 18.8 kg and 17.59 kg administered in 2004 and 2008 [53].

In Spain, Ortiz de García et al. [66] calculated that the consumption of mitomycin (MIT) was 13.32 kg in 2010 based on the population in January of that same year. For refractory stomach and pancreatic cancer treatment [67], the dose used is 20 mg/m^2, administered in cycles of 42 to 56 days [60,67]. The quantities of other reported CA range from a few milligrams per year to several hundred grams per year, with variations depending on the country. For example, BLEO is a glycopeptide antibiotic used primarily for the treatment of testicular cancer and lymphoma with an overall consumption of less than 1 g/year up to 7 g/year [49], with a therapeutic dose of 10 to 20 mg/m^2 per week [60]. High doses of DAU chemotherapy have been used for the treatment of acute lymphocytic anemia and acute myeloid leukemia—45 mg/m^2 and 30–45 mg/m^2, respectively—during the first three days of the therapy cycle [68]. With similar doses of 40 mg/m^2 IBP is administered every three weeks for the treatment of metastatic breast cancer [69,70].

3. Occurrence of Cytotoxic Antibiotics in Water

CA has been observed to persist in a variety of environmental matrices over extended periods of time. The estimated half-life times in water for DAU, DOX, EPI, and BLEO were found to be 180 days, indicating that they are persistent organic pollutants. As a result, these compounds are able to continue their path through the ecosystem and reach the soil, where their half-life is 360 days. It is also expected that the sediments will have a prevalence of 1620 days for DAU, DOX and EPI and 1583 days for BLEO [34,71]. Low biodegradability of these compounds, combined with their consumption around the world due to their high rates of administration to patients suffering from cancer, leads to the presence of some of them in hospital and WWTP influents and effluents, as in natural water bodies, like rivers.

DOX is the most detected CA in different water matrices. In the oncology ward at the Vienna University Hospital, the total amount of wastewater from 18 patients was collected over 24 h. In four analyses carried out over 98 days, DOX was only detected in Analyses 1 and 3, with concentrations of <0.26–1.35 µg/L and <0.26–0.5 µg/L, respectively [57]. Negreira et al. [72] analyzed the influents and effluents of 12 WWTP located throughout 4 Mediterranean basins in Spain and analyzed the effluent of a large general hospital. Samples were collected between September 2011 and January 2012. DOX was only found in the influent of two WWTP at concentrations of 2.5 and 2.7 ng/L. Also in Spain, but in the Seville region, Martín et al. [73] performed analyses for the presence of CD in samples obtained from a WWTP that consists of a sedimentation treatment and activated sludge in 2011. In the first work carried out in January, as part of the CA, only DOX was found in the influent of the WWTP, at a concentration of 4.5 ng/L. Subsequently, between August 2011 and July 2012, DOX was detected only in the WWTP effluent, with a concentration range of 20.3 to 42.4 ng/L. In 48 samples analyzed, DOX was detected in two and it was determined that the degradation of this contaminant was null in the WWTP evaluated [74].

A similar study was conducted in Iran, where the effluent from the hospital in Sari was studied for the presence of different types of medication, including DOX, to determine the concentration of the contaminant at various stages of the wastewater path, including the WWTP. In the untreated wastewater coming from the common hospital ward and the oncology wing, DOX was reported with concentrations of 0.29 and 2.69 mg/L, respectively. After treatment with activated sludge and in the sludge tank, a similar concentration of 0.95–0.96 mg/L of the drug was found. Even after chlorination, 0.81 mg/L of DOX was found, indicating that the treatment train with conventional methods was not effective [51].

In Portugal, an investigation was conducted to detect CD in surface water and wastewater in various hospital effluents to determine its presence. Sampling was conducted at five distinct locations within the Aveiro Central Hospital on a monthly basis between May 2019 and February 2020, with the exception of August. DOX was found in 12 of the 129 samples, with a detection of 9% and concentrations ranging from 37 to 46 ng/L in the months of June, December, January, and February [75]. Gouveia et al. [76] took samples from six rivers in Portugal at points close to potential sources of drugs such as hospitals, cancer centers, and WWTP discharges. DOX was one of the 13 drugs detected with a concentration of 4.0 ng/L in the Arade, Cávado, and Douro rivers.

DAU and EPI are anthracyclines with structures similar to that of DOX and have also been detected in wastewater and effluents from WWTP. At the University Hospital of the Federal University of Santa Maria (HUSM) in Brazil, a study was carried out on the daily presence of anti-cancer drugs in the treated effluent over one week in 2017. The treatment plant at HUSM consists of tanks where an aerobic/anaerobic microbiological process is carried out; at the outlet, there are two effluents (A and B), from which samples were taken every two hours. DOX was the detected to be high at both points, with concentrations of 2.43 to 4.64 μg/L at Point A and 2.08 μg/L at Point B. DAU was reported with maximum concentrations of 3.69 and 1.08 μg/L for points A and B, respectively. EPI was the least detected but presented the highest concentration in A, with a maximum of 6.22 μg/L [77]. Further analysis at the same location in 2022 revealed that the lower concentrations measured after biological treatment for DOX, DAU, and EPI were 4.64, 3.69, and 6.22 μg/L, respectively [52]. EPI was also identified in urban effluents in Catalonia, Spain prior to any treatment at a concentration of 24.8 μg/L [64].

BLEO is a highly toxic CA substance. It has been detected in a number of water matrices, including hospital effluents with concentrations ranging from 30 to 124 ng/L and at WWTP with concentrations from 11 to 19 ng/L at the inlet and outlet without change [49], which indicates that conventional degradation processes are unable to effectively degrade BLEO as a contaminant. Its presence has been reported in river water, with a maximum concentration of 17 ng/L, and it has even been detected in drinking water in concentrations between 5 and 13 ng/L [78].

It is well documented that antibiotics have been identified in a range of water matrices and aquatic environments. In recent years, some reviews have been published on this topic, reporting the detection of antibiotics in seas, rivers, lakes [79,80], and sediments [80] as well as in biosolids, compost, and soil [81]. Similarly, research has been conducted on CD; for example, in 2020, Jureczko et al. collected data on the presence of these drugs in effluents and influents from hospitals and WWTP, rivers, surface water, and drinking water [42].

Despite the critical importance of CA as environmental contaminants, data on their occurrence and quantification remain scarce. There is a significant gap in the availability and coverage of data on the presence of contaminants in water in various regions of the world, which hinders an accurate global assessment of water quality and its impact on public health. In the course of preparing this review, an extensive search was conducted across various academic databases in the last decade using keywords such as “occurrence”, “water”, “soil”, “wastewater”, “river”, and “water matrices”, in combination with each substance listed in Table 2. However, the search did not yield any results. This highlights an urgent need to prioritize research in this area to better understand the current scope of contamination and to drive the development of innovative treatment strategies capable of mitigating this pressing environmental challenge. Table 4 presents the data obtained on the occurrence of DOX, EPI, DAU, and BLEO in different water and solid matrices.

Table 4. Occurrence of cytotoxic antibiotics in aquatic and solid matrices across various locations worldwide.

Cytotoxic Antibiotics	Location	Concentration (ng/L)	Source	Reference
DOX	Vienna, Austria	260–1350	Hospital effluent	[57]
	Spain	2.5–2.7	WWTP influent and effluent	[72]
	Seville, Spain	4.5	WWTP influent	[73]
		20.3–42.4	WWTP effluent	[74]
	Mazandaran, Iran	290,000	WWTP effluent 1	[51]
		2,690,000	WWTP effluent 2	
		950,000	After activated sludge	
		960,000	Sludge collection depot	
		810,000	After chlorination	
	Aveiro, Portugal	37–46	Hospital effluent	[75]
	Portugal	4.0	River	[76]
	Rio Grande do Sul, Brazil	2080–4640	WWTP effluent	[77]
		<4640		[52]
EPI	Rio Grande do Sul, Brazil	2270–6220	WWTP effluent	[77]
		<6220		[52]
	Catalonia, Spain	24,800	Urban effluent	[64]
DAU	Rio Grande do Sul, Brazil	1800–3690	WWTP effluent	[77]
		<3690		[52]
BLEO	-	30–124,000	Hospital effluent	[49]
		11–19	WWTP influent	
		11–19	WWTP effluent	
		5–17	River water	
		5–13	Drinking water	

3.1. Cytotoxic Antibiotics Degradation by Biological Methods

The detection of CA in various water matrices underscores a critical gap in the effectiveness of conventional methods for its degradation. These substances are introduced into aquatic environments and water bodies primarily through hospital and household effluents as well as effluents discharged from WWTP. The environmental behavior of CA within these systems is dependent on both the properties of the compound itself and the specifics of the treatment processes it undergoes. In some cases, CA may be adsorbed by sludge, volatilized, or remain in the dissolved phase of the treated effluent, which ultimately influences its distribution and persistence in the environment (Figure 2) [82].

Figure 2. Proposed route of cytotoxic antibiotics during their use and disposal cycle.

It is important to note that certain CA compounds exhibit distinctive behavior due to their relatively low solubility in water. This property enables these compounds to adsorb more readily to solid matrices, including sludge and sediments. Such sorption interactions inhibit their biodegradation, thereby rendering traditional wastewater treatment less effective in their complete removal. Instead of undergoing degradation, these compounds are often removed alongside the sludge from WWTP and transported away from the aqueous phase but not chemically transformed or neutralized [83,84].

Although the transfer of CA compounds into sludge may represent an initial removal mechanism, this process does not constitute true degradation but rather a spatial displacement of contaminants. This transfer from water to sludge highlights the need for comprehensive management strategies, as untreated sludge can reintroduce CA compounds into other environmental compartments if disposed of improperly. To prevent unintended ecological and human health risks, it is therefore essential that sludge containing CA undergo further treatment processes or secure containment at its ultimate disposal site. By ensuring that such measures are in place, WWTP can mitigate potential environmental contamination that might otherwise occur from the subsequent release or leaching of CA into the environment [63,82,84]. In addition to this, a saturation of the biomass in the sludge may occur, causing an increase in the concentration of the effluent, as seen with DOX as reported by Kelbert et al. [85]. Similar behavior is expected for other CA found in sludge and sediments such as EPI, DAU, MXT and IDAU [63,82–85].

These observations are supported by previous studies, such as the work conducted by Franquet-Griell et al. [86]. In their study, they treated real wastewater samples from a WWTP containing DOX using an aerated sequential batch reactor inoculated with activated sludge. This approach allowed for the evaluation of degradation processes under realistic conditions, offering valuable insights into the behavior and fate of such contaminants during treatment. They found that the contaminant could not be detected after 30 min of treatment. However, they established that the reason was due to the adsorption of DOX in the activated sludge.

Additionally, Wang et al. [87] carried out a study in 2018 to degrade DOX and EPI present in domestic synthetic wastewater using an osmotic membrane anaerobic bioreactor. They reported a 100% removal for both contaminant compounds, although 90% was

attributed to removal through the anaerobic sludge and retention by the osmotic membrane. At the federal university of Santa Maria, the wastewater from its WWTP was subjected to treatment; a wetland was built to degrade CA, where the removal efficiency was determined with a polar organic chemical integrative sampler (POCIS) and an epilithic biofilm that were exposed to influent and effluent. The wetland proved to be inefficient in degrading DOX, EPI, and DAU. POCIS accumulated these compounds in amounts of 863.1 ng/g, 124.2 ng/g, and 215.2 ng/g, respectively [88].

Other methods that have been tested to degrade CA in water are some types of fungi and enzymes that have shown some favorable results. Jureczko et al. [89] degraded BLEO in water models with initial concentrations of 10 mg/L using white rot fungi (WRF); five strains of the fungus were used, but only two demonstrated the ability to degrade the contaminating compound. *Trametes versicolor* and *Hypholoma fasciculare* achieved degradations of 64.1% and 58.57%, respectively, after two weeks of treatment. That same year, Rybczyńska-Tkaczyk [90] used immobilized mycelium to degrade several anthracyclines. In the case of MXT, a maximum degradation of 99.09% was reached after five days of treatment, this being the best result reported. DAU and DOX showed to be more resistant to the fungus, with degradations of 92.5% and 87.2%, respectively.

Fungal treatments appear to be superior in degrading cytostatic compounds in water when compared to conventional WWTP. However, the degradation is not total, and experimentation times are relatively long. In contrast, enzymes, particularly laccase oxidoreductase, have been demonstrated to degrade DOX in water models with up to 500 mg/L of contaminant. Laccase has been shown to effectively remove DOX from water, even at the lowest enzyme concentration, within a time frame of 10 to 16 h. Increasing the enzyme concentration has been observed to reduce the required time to four hours [91].

3.2. Cytotoxic Antibiotics Degradation by Advanced Oxidation Processes

AOPs have been widely used in the degradation of recalcitrant organic contaminants due to the creation of reactive oxidant species such as the hydroxyl radical ($HO^{\bullet}$), which has a high redox potential. AOPs based on sulfate radical ($SO_4^{\bullet-}$) have also attracted attention for the removal of recalcitrant organic contaminants due to their high oxidative potential. These radicals are the key to processes that can reduce toxic pollutants into simpler non-toxic substances [92,93]. In addition to radicals $HO^{\bullet}$ and $SO_4^{\bullet-}$, other reactive species can be produced in AOPs, such as the superoxide radical ($O_2^{\bullet-}$) and singlet oxygen ($^1O_2$). Although the redox potential of these substances is lower than their precursor radicals, they can degrade some recalcitrant organic contaminants by providing an alternative degradation pathway [93]. AOPs include several technologies for water treatment, the most frequent being Fenton-like processes, ozonation, catalytic wet peroxide oxidation, heterogeneous photocatalysis, electrochemical oxidation, sonolysis, γ-ray radiation, microwave, and pulsed electron beam [94].

One of the main advantages of AOPs over conventional treatments is that they can degrade recalcitrant organic compounds without generating secondary waste derived from the degradation process. This is particularly important against processes such as chlorination, which has the potential to produce organochlorine species [95]. On the other hand, there are disadvantages or considerations to take into account with AOPs, in disinfection to inactivate pathogens they are rarely used because the half-life of the radicals produced is too short, so the long retention times required make these technologies restrictive in these cases [96]. Furthermore, AOPs are poor at treating real wastewater due to complex organic systems. For matrices with individual contaminants, degradation is affected by dissolved organic ions and organic matter. It is easy to conclude that operational conditions affect the performance of AOPs, and a distinction must be made between the

different technologies available for different organic contaminants. To overcome these limitations, the combination of different methodologies has been used to improve the oxidation efficiency of recalcitrant organic compounds; some of these combinations can be UV/H_2O_2, ultrasound/photocatalytic oxidation, UV/ozone, and UV/Fe^{2+}/H_2O_2, to highlight a few [97].

During recent years, several AOPs have been used for the degradation of emerging and recalcitrant contaminants, including drugs for cancer treatment. However, the degradation of CA such as anthracyclines has not been widely studied, except for some scarce works. One of the most common processes is electrochemistry, the use of different electrodes that—through an electric current—promote the degradation of some contaminants. In the past, graphite electrodes have been used for DOX degradation. It was determined that the AuO-TiO_2@graphite anode degraded almost 100% of the contaminant in 40 min, defining the process as highly efficient, even after several reuse cycles. This method is low-cost and does not generate organic waste. Furthermore, the utilization of NaCl as an electrolyte enhanced the degradation process due to the generation of active chlorine, which possesses a high oxidizing capacity [98]. Ferreira Garcia et al. [99] experimented with non-active boron-doped diamond (BDD) anodes in an electrolytic process with Na_2SO_4 and NaCl, by which it was confirmed that in the presence of NaCl, the degradation of DOX was fast and efficient with a low power consumption, reaching 99.9% degradation in 60 min. In the same year, De Souza Gil et al. [100] conducted a comparative analysis of the electrodes previously mentioned. The findings revealed that the BDD electrode demonstrated enhanced degradation times and energy consumption in comparison to AuO-TiO_2@graphite, with a current of 5 V and a voltage of 1 mA. The complete degradation of DOX was observed within a period of 20 min.

In the past decade, Fenton-like processes have primarily focused on the degradation of MXT, some combining it with other types of AOPs, such as electrochemical removal. Jafarizad et al. [101] combined these two processes using an electrode containing magnetite (Fe_3O_4@GO/CC) and compared it with common graphene oxide (GO) and coated carbon cloth (CC) electrodes. The Fe_3O_4@GO/CC electrode exhibited the most favorable performance, achieving a 90% degradation of the contaminant within 30 min of treatment and a total organic carbon (TOC) removal of 96.9%. Another combined process used in the past involves pre-absorption and Fenton-type oxidation in a hybrid system of reduced graphene oxide together with iron nanoparticles (rGO/FeNPs). MXT was degraded up to 99.8% under acidic conditions and by adding 30 mM H_2O_2, the authors attribute the degradation efficiency to the production of $HO^{\bullet}$ due to the heterogeneous catalysis supported by the homogeneous Fenton reaction [102].

Wu et al. [102] investigated the DB generated during the Fenton-like oxidation of MXT using a hybrid rGO/FeNPs system. HPLC-MS identified several compounds formed through complex chemical transformations, including cyclization, oxidation of side-chain amino groups, side chain deletion, and the destruction of the anthraquinone core. The proposed degradation pathway illustrated in Figure 3 highlights the complex degradation mechanism facilitated by rGO/FeNPs, which acts as both adsorbent and catalyst where MXT is concentrated on the catalyst surface for targeted oxidation by $HO^{\bullet}$. This mechanism is particularly relevant for understanding the behavior of CA in water matrices, the potential detoxification of the by-products and highlights the environmental relevance of this AOP.

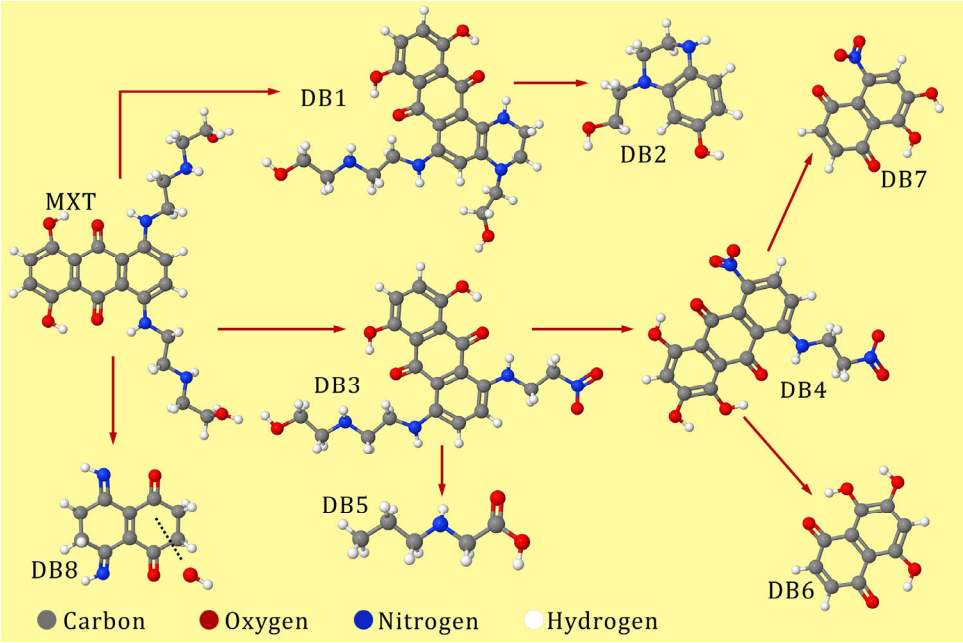

Figure 3. Proposed degradation pathway for MTX using a hybrid rGO/FeNPs system.

Another possibility for the preparation of rGO is the use of green technology. In this case, it was prepared using green tea extract as a reducer. rGO/Fe nanoparticles reached the maximum removal of 98.5% with a loading of 800 mg/L of the particles and an initial MXT concentration of 10 mg/L. Tests showed that the efficiency of rGO/FeNPs decreases after six cycles up to 76.8% degradation [103].

Ozone as a degradation source for CA showed 100% efficiency for DOX, EPI, and DAU with pH magnitudes of 9 for the first two and pH 7 for the third one in experiments carried out with pollutants with an initial concentration of 10 mg/L and an ozone flux of 1.5 g/h [52]. In contrast, in 2022 García-Costa et al. [104] investigated the degradation of real wastewater from a WWTP containing multiple contaminants, including DOX. The study employed ozonation systems with an O_3 flow rate of 150 cm^3N/min and an inlet concentration of 85 mg/L, combined with H_2O_2 at a concentration of 7.45 mg/L.

Initially, the O_3/H_2O_2 process achieved a DOX degradation efficiency of 8% and a TOC reduction of 40%. Subsequently, the integration of UV light enhanced DOX degradation to 52% and further decreased TOC levels, reaching a reduction of 59%. This improvement is attributed to the interaction between UV radiation and ozone, which generates additional $HO^{\bullet}$, thereby accelerating the degradation process.

Although the addition of UV light nearly doubled the operational costs, the results demonstrated that the extent of DOX degradation was more than six times greater compared to the ozonation process without UV irradiation.

Cavalcante et al. [105] degraded MXT through photolysis using a 125 W medium pressure lamp and compared the differences between the experiments when adding H_2O_2 as an oxidizing agent. While the lamp alone degraded only 65% of the cytostatic contaminant, when hydrogen peroxide was added, the degradation was total and TOC removal reached 90% after 140 min of treatment. Authors stated that the UV/H_2O_2 process is usually slower than photo-Fenton processes, but they were able to prove that UV-C photolysis is more efficient. DOX, DAU, and EPI were also subjected to photolytic degradation with a UV-C lamp. When subjected to the process, the maximum degradations obtained were 97.3%, 88.3%, and 99%, respectively. Using UV-C radiation can reduce the concentration of the pollutants studied, but it is not enough to eliminate them in relatively short times (60 min).

For this particular case, ozonation appears to be a superior process in the degradation of CA [52].

In the degradation of CA by homogeneous and heterogeneous photocatalytic processes in the last decade, most of the work was conducted on DOX. The search yielded additional contaminants, including EPI, MIT, and MXT. However, only photoelectrocatalysis was employed in the degradation of MXT. Calza et al. [106] investigated the photocatalytic degradation of DOX using TiO_2 and identified fourteen major DB by LC-HRMS. The degradation pathway shown in Figure 4 indicates that the main transformation mechanisms include (poli)hydroxylation, oxidation, and cleavage of the sugar moiety. Two isobaric species with [M + H]+ 560.1755 were attributed to monohydroxylated DOX, differing by hydroxylation on either the aromatic ring or the sugar moiety. Further oxidation produced dihydroxylated derivatives and other hydroxylated/oxidized compounds, demonstrating complex oxidative processes. The study also identified by-products resulting from the detachment of the sugar moiety, highlighting significant molecular fragmentation. These transformations suggest that the photocatalytic degradation of DOX involves multiple oxidative reactions that affect the structural integrity of the anthraquinone core. The degradation of this core indicates potential detoxification as the complex structure is progressively destroyed, as seen in MXT degradation by ozone-based processes (Figure 3). The degradation pathway highlights the complexity of by-product formation and underscores the importance of TiO_2-mediated photocatalysis in the degradation of cytotoxic compounds.

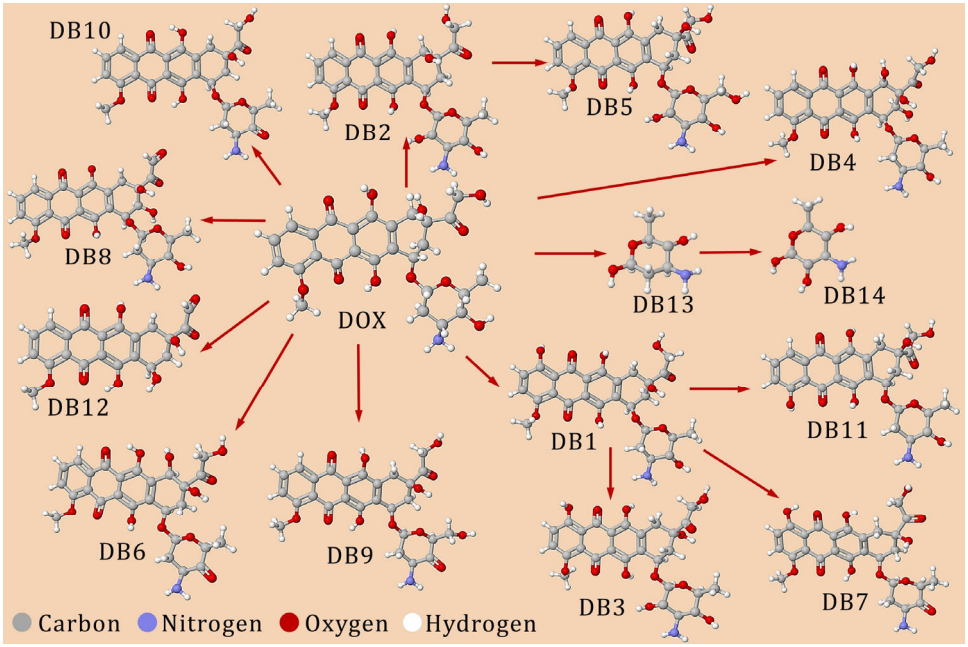

Figure 4. Possible transformation by-products and proposed degradation pathways of DOX through photocatalysis and photolysis.

In 2017, two research teams degraded DOX with different catalysts reaching an efficiency of 100% degradation in both cases. In the initial case, TiO_2 was activated through the use of UV lamps, and the surface area and total pore volume of the catalyst were reported to provide evidence supporting the results of the removal capacity achieved through the adsorption of TiO_2 (51%) [107]. In the second, a nano-photocatalyst was manufactured with iron nanoparticles (α-Fe_2O_3/SAPO-34) which demonstrated the best results with the addition of H_2O_2 and alkaline conditions [108].

Many authors have chosen to use novel catalysts rather than conventional ones, most of them using synthesis of their own structures using metals and compounds with carbon

as precursors. One of the most recent works was published by Zhao et al. [109] and developed a 0D/3D Nb_2O_5 quantum dots/C-doped g-C_3N_4 heterojunction catalyst for the degradation of DOX. The degradation efficiency increased with pH 8, peaking at 97.36%, due to favorable electrostatic interactions between the catalyst and the pollutant. The catalyst's unique 3D hollow porous structure and Nb_2O_5 quantum dots significantly enhanced photocatalytic activity by promoting charge separation and increasing active sites.

In other research published the same year, Garg et al. [110] reported a 95% degradation efficiency of the contaminant with $SnO_2/CoFe_2O_4$ as catalyst in a 2:1 ratio. In this case, an acidic medium showed the best performance.

In addition to metal complexes with tin and iron, other materials have been employed in the synthesis of photocatalysts for the degradation of DOX. The results of these studies have been variable. Racles et al. [111] used coordinated copper polymers as a photocatalyst activated by sunlight; the total degradation of the contaminant was achieved in 20 min without adding an oxidizing agent or adjusting the magnitude of the pH. While Abbasi et al. [112] reported favorable outcomes with complexes synthesized using cerium (IV) oxide and graphene oxide (GO-CeO_2), the most optimal efficiency was observed at a pH of 8.3, with a degradation rate of 97% over the course of 240 min. Although the behaviors of GO and CeO_2 were investigated separately, with 44% and 67% efficiency, respectively, it was evident that the combined GO-CeO_2 complex exhibited the highest efficiency.

EPI was degraded in two studies that reported similar results but employed entirely different photocatalysts. In 2017, TiO_2 was activated with a lamp that emits UV radiation at 365 nm, resulting in approximately 98% degradation. The authors analyzed the properties of the titania sample, reporting high crystallinity and confirming the presence of spherical anatase nanoparticles approximately 7–8 nm in size. The efficiency degradation of EPI and DOX, noted in the previous paragraph, was attributed to the catalyst's BET surface area of 318.9 m^2/g and total pore volume of 0.2347 cm^3/g [107]. Furthermore, EPI was degraded by up to 99.5% when treated with carbon nano-onion (CNO) composites comprising dendritic Ag nanostructures and MoS_2 nanoflowers under visible light at neutral pH for 50 min. However, a decline to 76.8% was observed during the fourth reuse cycle of the catalyst. To justify the use of the CNO/MoS_2/Ag composite, the degradation reaction with CNO/MoS_2 and CNO was evaluated with results between 36% to 73% removal of EPI [113].

Within the search for this review, only one work on photoelectrocatalysis to degrade MXT was found; authors used assisted photocatalysis (APC) and assisted photoelectrocatalysis (APEC) using CuO thin films deposited on silicone (Si). The experiments were carried out under UV-A radiation for 180 min, and H_2O_2 was added to enhance the reactions. For APC, the CuO/Si/H_2O_2 complex showed only 50% removal of contaminant, but when switching to APEC with the same conditions, the degradation increased by 25% [114]. Table 5 includes work on CA degradation using photocatalytic processes.

In 2019, Da Rosa et al. [114] applied APEC in the degradation of MXT; a total of 10 DB were identified by LC/MS analysis in samples taken at 60, 90, and 180 min during the process. The compounds proposed by the authors were based on knowledge of the degradation of PhACs and other organic compounds and on the study of published data. In Figure 5, it can be seen that most of these by-products were hydroxylated because the $HO^{\bullet}$ radicals attacked the carbon chain of the aromatic part of the molecule. DB formed demonstrated an enhanced toxicity profile in toxicity tests with *Artemia salina* and *Allium cepa*. Treatment resulted in a reduction in acute toxicity, although the toxicity classification remained in Class III. Consequently, while less harmful forms for the environment are obtained, considerable risk persists.

Table 5. Degradation of cytotoxic antibiotics by advanced oxidation processes in the last decade.

Process	Cytotoxic Antibiotics	Specifications	Degradation (%)	Parameters	Reference
EC-O [1]	DOX	AuO-TiO_2@G TiO_2@G G [3]	97 90 82	$[DOX]_0$ = 5 mg/L 5 volts NaCl 10 mmol/L	[98]
		BDD-Na_2SO_4 BDD-NaCl	99 99.9	Na_2SO_4@0.637 Ah/L NaCl@0.318 Ah/L	[99]
		AuO-TiO_2@G BDD [4]	100 100	$[DOX]_0$ = 1.25 mg/L 5 V & 1 mA	[100]
	MXT	Fe_3O_4@GO/CC [5]	90 TOC 96.9	$[MXT]_0$ = 5 mg/L pH = 3; 0.2 mM Fe	[101]
Ozonation	DOX	Ozone	100	pH = 9; O_3 = 1.5 g/h $[DOX]_0$ = 10 mg/L	[52]
		O_3/H_2O_2 O_3/H_2O_2/UV	8 52	O_3 = 85 mg/L $[H_2O_2]_0$ = 7.45 mg/L	[104]
		Ozone	9 41	O_3 = 0.5 mg/L $[DOX]_0$ = 30 µg/L	[115]
		O_3/Sonolysis	17 47.5	Sonolysis = 70 W/L pH 3 & 9	
	DAU	Ozone	100	pH = 7; O_3 = 1.5 g/h $[DOX]_0$ = 10 mg/L	[52]
	EPI	Ozone	100	pH = 9; O_3 = 1.5 g/h $[DOX]_0$ = 10 mg/L	
Fenton	MXT	H_2O_2 rGO/FeNPs/H_2O_2	11.3 99.8	$[H_2O_2]$ = 30 mM pH = 3	[102]
		FeNPs [6] rGO [7] rGO/FeNPs	53.1 77.5 98.5	$[MXT]_0$ = 10 mg/L rGO/FeNPs = 0.8 g/L pH = 9	[103]
		UV/H_2O_2/Fe^{3+} UV/H_2O_2/FeOx UV/Fe^{3+}	77 82 13.25	All degradation percentages correspond to TOC	[105]
Photolysis	DOX DAU EPI	UV-C	97.3 88.3 99	$[AC]_0$ = 10 mg/L pH = 9 UV-C Lamp 254 nm	[52]
	MXT	UV-C UV-C/H_2O_2	65 100	$[H_2O_2]$ = 18 mmol/L Hg lamp 125 W	[105]
PhCat [2]	DOX	TiO_2 P25	100	$[DOX]_0$ = 15 mg/L [Cat] = 200 mg/L Philips TLK/05 lamp 40 W	[106]
		α-Fe_2O_3/SAPO-34	100	$[DOX]_0$ = 20 mg/L [Cat] = 150 mg/L $[H_2O_2]_0$ = 4 mol/L; pH = 8	[108]
		TiO_2	100	$[DOX]_0$ = 2 mg/L UV lamp 365 nm, 13 W	[107]

Table 5. *Cont.*

Process	Cytotoxic Antibiotics	Specifications	Degradation (%)	Parameters	Reference
PhCat [2]	DOX	$BiFeO_3$	79	$[DOX]_0$ = 2 mg/L; UV radiation	[116]
		Cu-A	100	$[DOX]_0$ = 30 mg/L; Sunlight H_2O_2~1% volume 2 mg Cat added	[111]
		PAN [8]/CEA [9]/MIL-125/TiO_2	100	$[DOX]_0$ = 50 mg/L [Cat] = 500 mg/L UV lamp 365 nm, 30 W pH = 3	[117]
		TiO_2	62	Xe visible lamp 300 W pH = 8	[118]
		Pt/TiO_2	88	30 mg Cat added Sonication added	
		GO	44	$[DOX]_0$ = 0.5 mM pH = 7 LED light 9 W–800 lumens	[112]
		CeO_2	67		
		GO-CeO_2	97		
		BCN [10]	9.2	$[DOX]_0$ = 10 mg/L 0.04 g Cat added pH = 8 Reactor LabSolar 6a Metal halide lamp 500 W Radiation 30 mW/cm^2	[109]
		PCN [11]	59.8		
		CPCN [12]	65.3		
		NOCN-1 [13]	96.2		
		NOCN-2 [14]	98.6		
		NOCN-3 [15]	96.6		
		CN [16]	40.86	[Cat] = 25 mg/L pH = 2.5 Mercury lamp (λ > 420 nm) H_2O_2 100 µL added	[110]
		SnO_2	20.22		
		$CoFe_2O_4$	38.62		
		CSn-20	64.05		
		CSnCo-0.5	94.95		
		CSnCo-1	90.29		
		CSnCo-2	90.24		
	EPI	TiO_2	98	$[EPI]_0$ = 2 mg/L UV lamp 365 nm, 13 W	[107]
		CNO	36.4	$[EPI]_0$ = 10 mg/L; [Cat] = 150 mg/L Visible light pH = 7	[113]
		CNO/MoS_2	72.4		
		CNO/MoS_2/Ag	99.5		

Table 5. *Cont.*

Process	Cytotoxic Antibiotics	Specifications	Degradation (%)	Parameters	Reference
PhCat [2]	MXT	APEC Si/H_2O_2	14	$[MXT]_0$ = 20 mg/L	[114]
		APEC CuO/Si	14	Ag/AgCl reference electrode	
		APC $CuO/Si/H_2O_2$	50	UV-lamp 18 W, 350–400 nm	
		APEC $CuO/Si/H_2O_2$	75	Potential 1.5 V	
		TiO_2	93.6	$[MXT]_0$ = 2 mg/L; [Cat] = 500 mg/L Lamp Narva 365 nm, 13 W	[119]
	MIT	TiO_2 P25	100	$[MIT]_0$ = 20 mg/L; [Cat] = 200 mg/L Lamp TLK/05, 40 W/m^2	[120]

Note(s): [1] Electrochemical oxidation, [2] photocatalysis, [3] graphene, [4] boron-doped diamond, [5] graphene oxide/carbon cloth, [6] nanoparticles, [7] reduced graphene oxide, [8] polyacrylonitrile, [9] cellulose acetate, [10] bulk g-C_3N_4, [11] polymeric g-C_3N_4, [12] C-doped g-C_3N_4, [13] 1.6 g CPCN, [14] 1.9 g CPCN, [15] 2.2 g CPCN, [16] metal-free graphitic nitride.

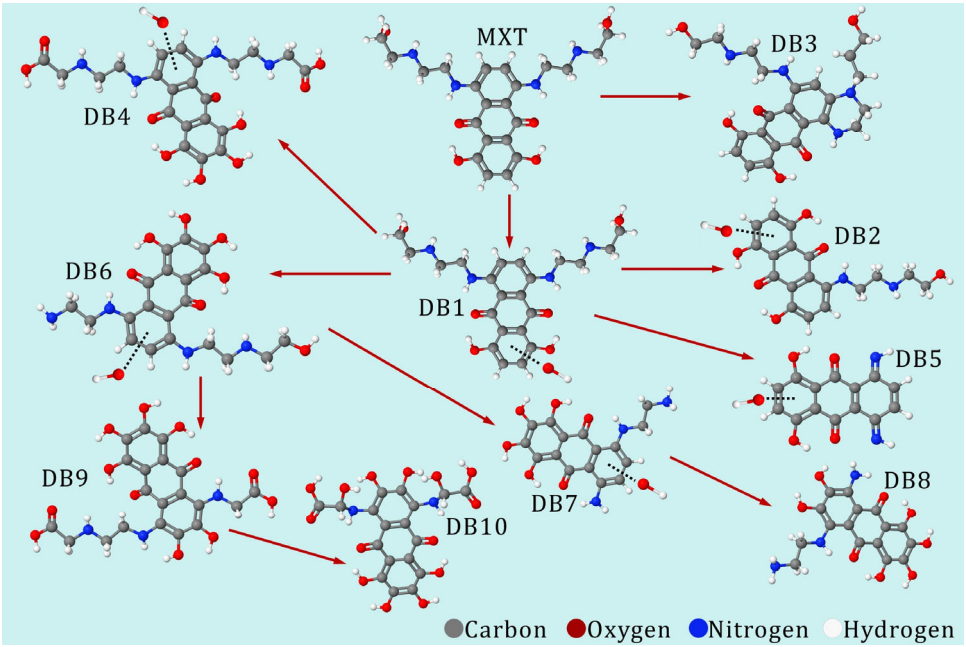

Figure 5. Degradation by-products and proposed degradation pathway of MTX through the APEC $CuO/Si/H_2O_2$ process.

Throughout this review, the presence of cytotoxic antibiotics in aqueous and solid matrices has been analyzed and attributed to their increased use due to the rising number of cancer patients. The main challenges associated with their potential impact on ecosystems and human health, even at low concentrations, have been highlighted, as well as the difficulties faced by WWTP in addressing these persistent contaminants. Additionally, the efficacy of advanced oxidation processes for their removal has been evaluated, with

significant variability observed in degradation efficiency depending on the method and experimental conditions applied.

These findings help identify key trends and provide a solid foundation for future analyses, emphasizing the need to explore innovative approaches that address both the technical limitations and environmental impacts of these emerging contaminants. The first step in this endeavor involves deepening research into their presence, behavior, and persistence.

Based on these considerations, key conclusions can be drawn to guide future research and mitigation strategies, highlighting the relevance of the most effective methods and their potential applications in the treatment of pharmaceutical contaminants.

4. Issues and Prospects

Water scarcity has become a global problem in the last century. The water supply in the future will depend on the reuse of wastewater from treatment plants. However, new technologies with low operational and investment costs must be the center of attention to counteract the presence of emerging contaminants, resistant to conventional processes due to their refractory nature [121]. In addition to the intrinsic effect that these substances can cause on their own, when water is subjected to disinfection by chlorination, organic compounds can react with chlorine, leading to the formation of disinfection by-products. Drinking water with trace concentrations of these contaminants may have a chronic adverse effect on human health [122].

In general, scaling up AOPs from lab-scale to real-scale applications involves several challenges, including technical, economic, and operational factors. For example: technologies such as ozonation and photocatalysis require significant initial investments due to the complexity of the equipment, energy consumption for UV lamps, ozone production, and catalyst regeneration, in addition to maintenance expenses, including catalyst replacement, periodic system inspections, and repairs [123]. Factors like corrosion, degradation of materials, and wear and tear can affect performance over time and should be considered. Although solar energy offers cost reduction opportunities, its intermittent nature necessitates energy storage systems, which increases costs. Innovations in immobilized catalysts and advanced reactor designs are crucial for improving scalability and cost efficiency [124].

Key reagents, such as H_2O_2, account for a substantial share of operational costs, a challenge further intensified by supply chain dependencies. Variations in the availability and pricing of these chemicals create significant hurdles, particularly in regions with constrained supply chains. Minimizing reagent consumption not only reduces costs but also lowers the environmental footprint, offering both economic and ecological benefits [125].

By-products and partially oxidized organic compounds may persist in the environment and pose toxicological risks. Large-scale AOP applications might lead to the generation of by-products, which may require additional treatment, increasing the overall complexity and costs of the treatments. These compounds are often formed due to incomplete oxidation or secondary reactions. Optimizing parameters such as pH, reaction time, and reagent concentration can help minimize by-product formation. Secondary treatments, such as biological degradation or activated carbon adsorption, and advanced filtration technologies like reverse osmosis, further enhance by-product removal [126].

In laboratory settings, photoreactors are small and ensure uniform UV irradiation, while industrial-scale photoreactors must efficiently handle larger volumes, ensuring effective mixing and turbulence for consistent reagent contact across the reactor. They also maintain uniform UV radiation distribution, avoiding diminishing light penetration due to the liquid's depth [127]. Maintaining high reaction efficiency at large scales can be challenging, as AOPs often require precise control over factors like pH, temperature, and flow rate to ensure consistent results.

Finally, environmental regulations, different in every country, are key when designing a wastewater treatment method intended to solve a common problem around the world.

In summary, successfully scaling AOPs requires innovation in reactor design, energy management, reagent supply, and by-product handling along with a deeper understanding of AOP mechanisms under diverse large-scale conditions.

5. Conclusions

The presence of cytotoxic antibiotics in various environmental matrices poses a significant challenge to public health and ecosystems, primarily due to their high persistence, which can last for months as a result of their low biodegradability. This issue has been aggravated by the increased use of these compounds, driven by the rising number of cancer cases and high patient recovery rates. Additionally, up to 70% of the administered drug can be excreted unchanged, leading to increased environmental release, with some of these compounds being classified as highly toxic. Conventional treatment methods have proven insufficient in effectively removing or degrading these compounds, as evidenced by their detection in WWTP effluents, the sludge generated by these processes, and surface water bodies and even drinking water. In this context, hospitals and domestic effluents stand out as the main sources of these pollutants.

Although studies have been conducted to detect CA in water bodies and solid matrices, these are limited and often do not cover the full range of compounds within this group of drugs. Furthermore, many studies lack recent updates, highlighting the need for more comprehensive research to better understand the occurrence, fate and impacts of these substances. Such understanding is crucial for the development and implementation of more effective removal processes. In this regard, biological methods have shown promising potential for the degradation of CA, with notable examples such as the use of enzymes and fungi achieving degradation efficiencies exceeding 99%. However, in some cases, efficiencies did not exceed 58%, and the time required to complete the processes remains long, underscoring the importance of further research and optimization of these alternatives.

Furthermore, AOPs have emerged as effective tools for the degradation of persistent contaminants, including CA. Processes such as Fenton-like oxidation, photocatalysis, electrochemical oxidation, and ozonation have achieved complete removal of certain CA under controlled optimal conditions. Nevertheless, some studies report efficiencies below 75% even under ideal conditions, while others yield negligible results. Additionally, the application of these processes can generate transformation by-products that are more toxic and stable than the original compound, adding complications to the problem.

The application of AOPs to degrade real effluents remains limited due to the complexity of the organic matrices present in such discharges. Therefore, it is essential to expand research on these processes, exploring their combinations and integration with innovative biological methods to maximize their capacity for removing pharmaceutical contaminants such as CA. This integrated approach will contribute to the development of more sustainable technologies and innovative materials that can be implemented on a larger scale and under real conditions, promoting more effective environmental management and significantly reducing the risks associated with these contaminants.

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Abbreviations

The following abbreviations are used in this manuscript:

AOPs	Advanced oxidation processes
APC	Assisted photocatalysis
APEC	Assisted photoelectrocatalysis
BCN	Bulk g-C_3N_4
BDD	Boron-doped diamond
BLEO	Bleomycin
CA	Cytotoxic antibiotics
CC	Carbon cloth
CD	Cytostatic drugs
CEA	Cellulose acetate
CN	Metal-free graphitic nitride
CNO	Carbon nano-onions
CPCN	C-doped g-C_3N_4
DAC	Dactinomycin
DAU	Daunorubicin
DB	Degradation by-products
DNA	Deoxyribonucleic Acid
DOX	Doxorubicin
EC-O	Electrochemical oxidation
EP	Emerging pollutants
EPI	Epirubicin
GO	Grapheme oxide
HUSM	Federal University of Santa Maria
IBP	Ixabepilone
IDAU	Idarubicin
HRMS-ESI	High-resolution mass spectrometer with an electrospray ion source
MIT	Mitomycin
MXT	Mitoxantrone
NOCN-1	1.6 g CPCN
NOCN-2	1.9 g CPCN
NOCN-3	2.2 g CPCN
NPs	Nanoparticles
PAN	Polyacrylonitrile

PCN	Polymeric g-C_3N_4
POCIS	Polar organic chemical integrative sampler
PRB	Pirarubicin
rGO	Reduced graphene oxide
RNA	Ribonucleic Acid
TOC	Total organic carbon
WHO	World health organization
WRF	White rot fungi
WWTP	Wastewater treatment plants
PhACs	Pharmaceutical compounds
PhCat	Photocatalysis
Si	Silicone

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