The issues of Antibiotics: Cephalexin Antibiotic as emerging environment contaminant

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Abstract- Nowadays, controlling and monitoring the quality of water are very important issues, they impact potentially human and environmental health. Therefore, researches and policies are focusing on the target of the emerging environment contaminants such as antibiotics. However, there is regulatory and scientific consensus to achieve good water quality in the wide world. Variety of emerging environment contaminants are constantly reaching aquatic systems, like human and veterinary pharmaceutical substances which are reported worldwide in wastewater plant effluents, surface water, groundwater, even in tap and drinking water. Here, we present a review about Cephalexin antibiotic, focusing on its widespread detection, technologies had been described for its detection and removal from several bodies as well as highlight its effects on human health and the environment.

Index Terms- Aquatic environments, Cephalexin antibiotic, resistant antibiotics, techniques of detection and removal, human and environment health.

I. Introduction:

The practice of modern medicine cannot be imagined without pharmaceuticals. A growing world population, increasing investment in the health-care sector, advances in research and development, pervasive global market availability, and aging societies in industrialized countries have led to a significant increase in the consumption of pharmaceuticals in the last few decades [1, 2]. Moreover, due to the world's rapidly expanding human population and the growing demands for food products of animal origin, animal breeding has been practiced on an industrial scale in many developed countries of the world and the practice is being emulated by several developing countries, especially China. In 2010, China was the largest antimicrobial consumer for livestock, and it has been estimated that its livestock industry will use up to 30 % of the global antimicrobial production by 2030 [3]. And it has the highest production and consumption figures for antimicrobials in the world, releasing in 2013 more than 53000 tons of antibiotics into the environment [4, 5]. In the same year, Penicillins and Cephalosporins together represented the second most used antimicrobial groups in China [4, 6].

Besides, to their potential threats to aquatic ecological environment and human health, antibiotics have been thought as one group of emerging environment contaminants [7]. Emerging contaminants are widespread in the aquatic and terrestrial environments, and the potential to cause adverse ecological and/or human health effects even at low levels [8]. On the other hand, the estimated life-cycle of antibiotics in the environment appears to be very dynamic and complex [6, 9, 10].

Cephalexin antibiotic is a first-generation Cephalosporins [6, 11], a potent antibiotic, belonging to β-lactams, commonly used in veterinary medicine in several countries [12]. Cephalexin has good activity against Gram-positive and Gram-negative microorganisms and is relatively resistant to these β-lactamases [13, 14]. Therefore, Cephalexin is widely used as therapy for upper respiratory infections, uncomplicated pneumonia or soft-tissue infections produced by *Staphylococcus* sp., *Streptococcus* sp., *Klebsiella*, *Escherichia coli* or *Proteus mirabilis* [15], even used to treat infections of the urinary tract [16].

Cephalexin antibiotic is one of the most prescribed antibiotics and is produced in great quantities [17, 18]. It has a wide spectrum of antibacterial activity and high water solubility [19, 20], which its chemical structure is shown in figure 1. In Europe, the second most prescribed antibiotic class is Cephalosporins, and among them is Cephalexin. Since Cephalexin has a biotransformation rate of only 10%, the remaining 90% is excreted unchanged in the urine [21, 22]**.** As a consequence, The World Health Organization (WHO), published a report exclusively about the presence of pharmaceuticals in drinking water and the potential risks for human health and the environment. And classified Cephalosporins antibiotics as emergent environment contaminants, and are considered as water pollutants [23].

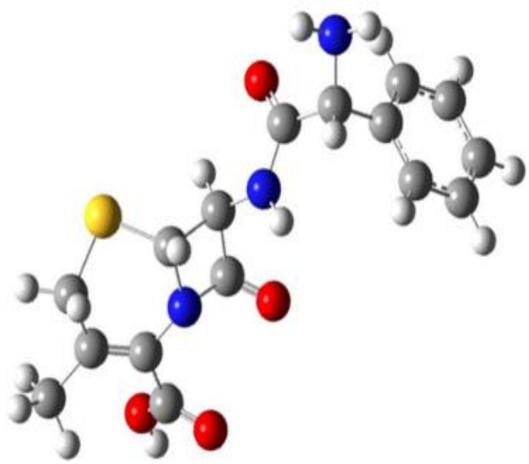

Figure 1: Chemical structure of Cephalexin Antibiotic [11].

The overuse of this therapeutic class leads to environmental contamination, which together with the presence of antibiotics in drinking water and food chain assure a constant, uncontrolled exposure to antibiotics. Increasing the risk of allergies and resistance to broad-spectrum antibacterial drugs, with a significant impact on economy and health. Therefore, World Health Organization (WHO) elaborated a surveillance campaign aimed to evaluate the current status of the antibiotic resistance and it has been proven that Cephalosporins are the most common drugs that have developed bacterial resistance so far [24], And classified Cephalosporins antibiotics as well as Cephalexin antibiotic as emergent environment contaminants, and are considered as water pollutants [23].

Hence, in high-income countries, such as the USA and Denmark, the use of some Cephalosporins has been banned or drastically reduced [25, 26]. During 2014, both Norway and Iceland registered no sell of first- and second-generation Cephalosporins for veterinary use [6]. However, this present review highlight the tremendous presence of Cephalexin antibiotic into the aquatics environment even in foodstuff, technologies of detection, as well as removal and its impacts on human health and environment, are described.

II. Sources and Pathways of Pharmaceuticals

Antibiotics are powerful medicines that fight certain infections and can save lives when used properly. They either stop bacteria from reproducing or destroy them, as well as they, make better health of sick people and animals. Due to the considerable proportion of antibiotics used in medicine and veterinaries, human and animal would be excreted in urine and feces as unchanged and active species.

Wastewater treatment plants (WWTPs) and livestock farms do not have enough capacity of removing antibiotics in their effluent and sludge. Thus, antibiotics have contaminated aquatic environments. Consequently, due to their potential threat aquatic ecological environment and human health, antibiotics have been thought as one group of emerging environment contaminants [23].

The origin of antibiotics contamination in the aquatic environment (surface and groundwater) is considered to mainly point and non-point source discharges, such as human or animal excretions, municipal wastewater, landfill leachate and pharmaceutical industry wastewater [27-29]. Moreover, numerous of studies had described several main sources of water pollution with pharmaceuticals as drug manufacturing industry [22], human waste by hospitals [30], household activities [31], and animal wastes in live-stocks farming [32-34], where veterinary pharmaceuticals, for example, contaminate soil directly via manure, surface and ground waters by runoff from fields [17]. Indeed, sources and pathways of pharmaceuticals in the wide environment and ecosystem were described by several researchers, and Figure 2 describe it below;

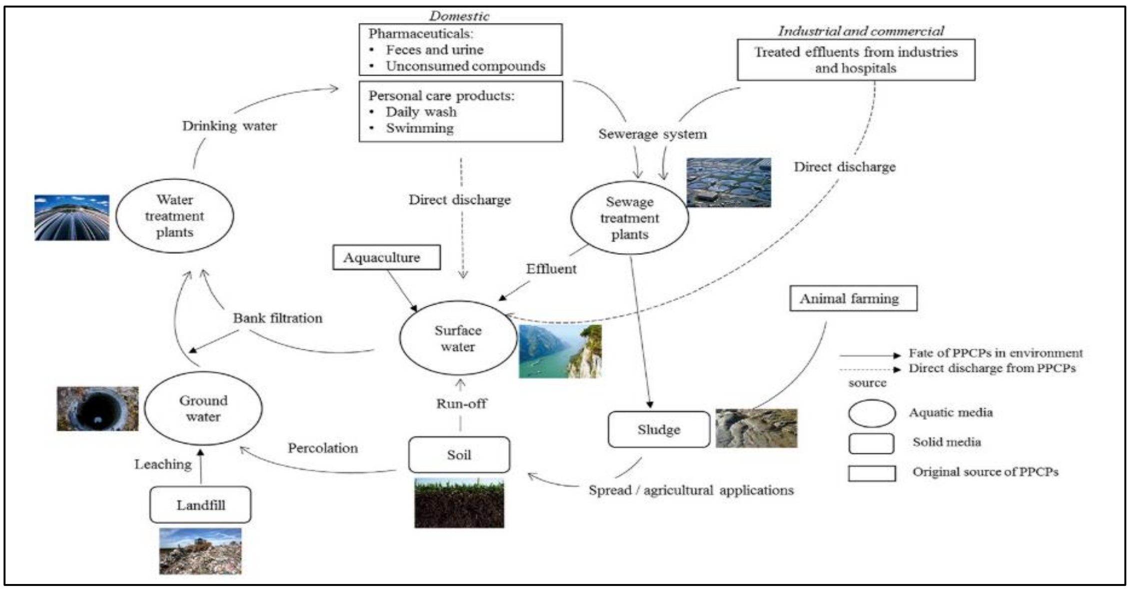

Figure 2: Sources and Pathways of Pharmaceuticals and Personal Care Products (PPCPs) in the environment [35].

III. Widespread Detection of Cephalexin Antibiotic

Contamination of surface and groundwater by antibiotics is of significant importance due to their potential chronic toxic effects on the aquatic and human lives. Surface and groundwater contamination by synthetic organic compounds is one of the main concerns faced by society in the 21st century [4, 34, 36]. Nowadays, pharmaceuticals are considered as an emerging problem [37]. Thus, the presence of these types of compounds is reported everywhere from river water to the drinking water at relatively higher concentrations and reported to pose threats to aquatic and terrestrial organisms [38-40].

In fact, pharmaceuticals have been detected in wastewater treatment plant effluents, surface water, groundwater, and drinking water. Most drug classes have been documented, including antibiotics [41, 42]. A close relationship can be assumed between occurrences in Waste Water Treatment Plants (WWTP) effluent and surface waters because most (WWTP) effluent is discharged directly into surface waters such as rivers and lakes [1]. Besides, potable water sources are contaminated by human and veterinary pharmaceuticals [43], due to incomplete removal by conventional technologies like flocculation, sedimentation, and chlorination in drinking- water treatment plants (DWTPs). Consequently, pharmaceuticals have been detected in tap water in several developed countries at levels of usually < 100 ng/L [44, 45].

In China, human and veterinary pharmaceuticals have frequently been detected in wastewater and surface waters at concentrations of generally < 1 µg/L, and levels of certain compounds, such as Cephalexin antibiotic, had been reported to be at the high of the values reported globally [46]. Moreover, Figure 3 describes the widespread Cephalexin antibiotic which had been detected in surface and treated waters influent and effluent wastewaters, river, reservoir, and sea from different sites in Catalonia (North-East of Spain) [6, 47, 48].

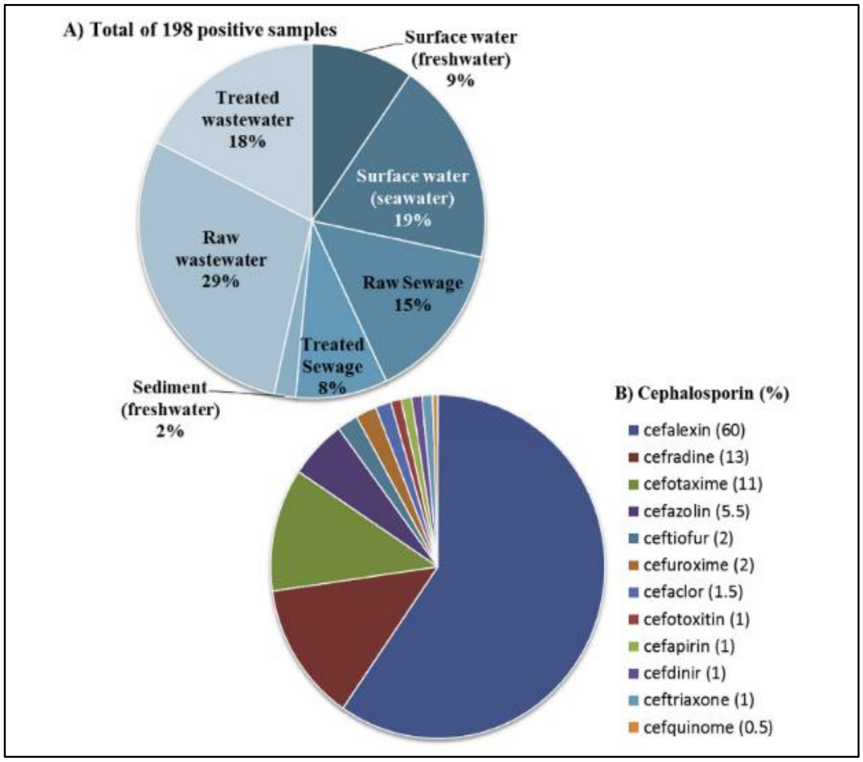

Figure 3: Relative distribution of the 198 positive samples for cephalosporin antibiotics in the aquatic environment. **A** illustrates the contribution of each environmental matrix where positive samples have been reported. **B** shows the percentage distribution of positive samples for each detected cephalosporin [6].

Pharmaceuticals persist in the environment mainly because of its incomplete elimination in sewage treatment plants (STPs), remaining between 60% and 90% of them after the action of biodegradation, deconjugation, sorption and photodegradation steps [49]. The STP effluents then contain biorecalcitrant unmetabolized and metabolized pharmaceutical residues that are released in the receiving surface waters, mainly rivers [17, 50].

Cephalexin antibiotic has been ubiquitously found in the aquatic environment, with one report indicating concentrations from (151 to 182 ng/L) in the coastal waters around Hong Kong [51]. Cephalexin had been also detected in municipal wastewater from (339.4 to 375 ng/L) [20, 52], even in the sewage of Shenzhen (>1 µg/L) [53], in New York City Watershed from (80 to 502 ng/L) [42], and in India where the effluent concentration from a Cephalosporin factory after treatment is approximately 29 mg/L [54]. These examples are evidence of one of the biggest hurdles of dealing with Cephalexin antibiotic in wastewater management, with its high resistance to biodegradation [22].

Antibiotic residues and illegal additives are among the most common contaminants in milk and other dairy products, and they have become essential public health concerns [12]. Hence, the occurrence of antimicrobial drug residues in food carries potential risk by a selection of resistant pathogenic organisms and causes adverse effects on intestinal microflora and decreases the quality of animal products. Thus, accumulation of residues is mainly in products of animal origin such as milk and beef. Consequently, it had been described that Cephalexin antibiotic residue had been detected in milk and beef [12, 55, 56], eggs [46], and even in potato [16].

Furthermore, antibiotics had been detected in children's urine reaching low-dose; the origin of this occurrence could be from the exposure to low-level residues of antibiotics in food or the metabolic gradients of exposure to high-level antibiotics, such as direct antibiotic use [7]. Additionally, Cephalexin antibiotic was carried out in urine from human volunteers [57].

IV. Effects of Cephalexin Antibiotic

The presence of these pharmaceuticals in surface and drinking water has several negative effects on humans and ecosystems. In fact, pharmaceuticals in surface waters exhibit toxic effects on aquatic organisms while their presence in drinking water can cause an increase in the incidence of some diseases such as cancer (female sex hormones). Antibiotics can lead to an increase in drug resistance of microorganisms, including pathogenic microorganisms. Also, their presence in drinking water can pose a threat to infants, babies, the elderly, and people who suffer from kidney or liver failure and cancer [31]. Indeed, despite its efficient, excessive use of Cephalexin antibiotic is extremely harmful to the human body, for example, it is well known that excessive use of Cephalexin will cause acute renal failure in humans and experimental animals [16].

Nevertheless, the presence of antibiotics in the aquatic environment has created two concerns. The immediate one is the potential toxicity of these compounds to aquatic organisms and humans through drinking water. The second one is the growing release of antibiotics to the environment contributes to the emergence of strains of disease-causing bacteria that are resistant to high doses of these drugs [29, 58]. Absolutely, the wide application of antibiotics in human and veterinary medicine has led to large-scale dissemination of refractory and even toxic pollutants in the environment. In many countries, a multitude of extremely resistant antibiotics has been found in treated sewage, industrial effluent, the aquatic environment and even in drinking water [50]. They are extremely resistant to biological degradation processes and because of their continuous input they could remain in the environment for a long time; their presence in the environment is considered dangerous in both low and high concentrations [20].

Nowadays, antibacterial resistance is one of the most concerning health issues and represents a considerable medical challenge for the clinicians [59]. Antibiotics are extensively used in humans and animals, for prophylactic and treatment purposes, and in agriculture, to promote crop growth. Unfortunately, the overuse of this therapeutic class leads to environmental contamination, and increasing the risk of allergies and resistance to broad-spectrum antibacterial drugs, with a significant impact on the economy and health [24]. In consequence, currently it is difficult to treat infections due to the increase in antibiotic-resistant bacterial strains [24, 60].

Figure 4 highlight the antibiotics resistance hotspots, which are found not only in medical settings but also in environmental compartments that are subjected to anthropogenic pressure, such as municipal wastewater systems, pharmaceutical manufacturing effluents, aquaculture facilities, and animal husbandry facilities [61].

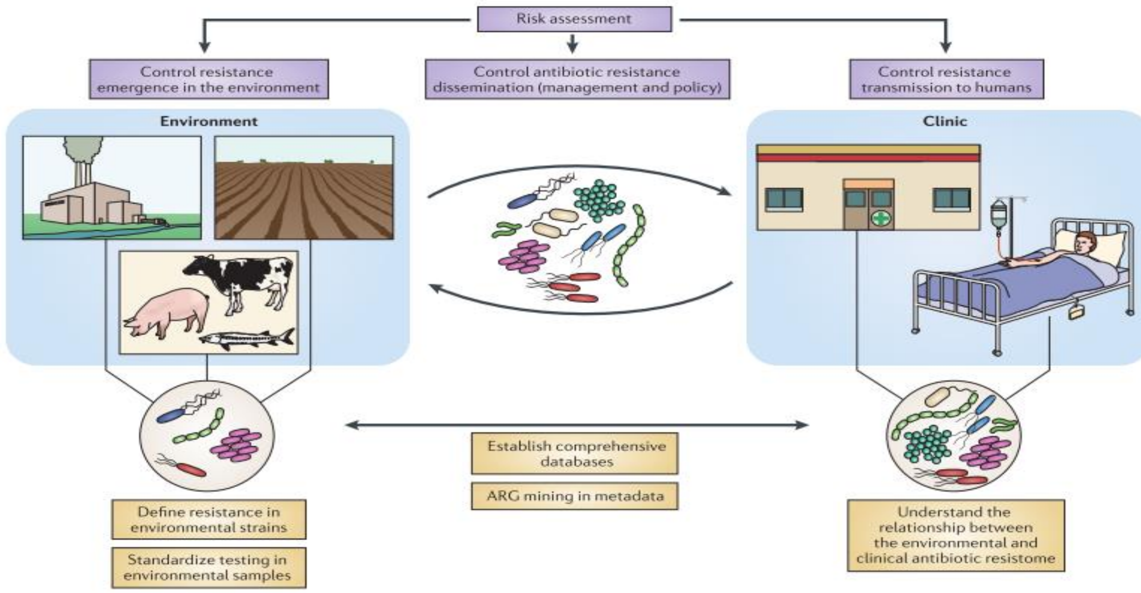

Figure 4: Minimizing the spread of antibiotic resistance in the environment [61].

In fact, antibiotic-resistant bacteria are rapidly selected in individuals exposed to antibiotics and may persist for extended periods [62]. Antibiotic resistance becomes a problem when resistant strains persist in individuals, human populations and/or in the environment to the extent that the efficacy of antibiotic treatment is compromised. It is currently estimated that in the European Union antibiotic-resistant bacteria cause 25000 deaths a year, and contribute a yearly cost in US dollars of $ 21-34 billion [30, 63]. As well, antimicrobial-resistant infections already claim at least 700 000 lives each year across the world with dire prospects of 10 million people dying every year by 2050 [64, 65].

Consequently, The World Health Organization (WHO) declared in the guidelines for drinking-water quality, that access to safe drinking water is essential to health, a basic human right and a component of effective policy for health protection. The importance of water, sanitation, and hygiene for health and development has been reflected in the outcomes of international policies [23]. Moreover, the World Health Organization (WHO) has been leading multiple initiatives to address antimicrobial resistance, such as changing prescription policies, reduction of preventive use in animal feed, improved disposal control, and implement better mechanisms for surveillance and monitoring antibiotics in our environment, aimed at rapid, sensitive, and selective detection of antibiotics [65, 66].

Furthermore, the release of antibiotics into the aquatic environment [67], impacts the ecosystems [31]. Besides, the photolytic transformation products of Cephalexin antibiotic presented increased acute toxicity to *Vibrio fischeri* [68], showing again the importance of assessing the ecotoxicological effects of treatment strategies [6]. As well as, the increasing of the luminescence inhibition was observed during sunlight simulated photolysis of Cephalexin antibiotic in *Vibrio fischeri* [68].

V. Technologies of Detection Cephalexin Antibiotic

The presence of pharmaceuticals in environmental waters has become more apparent in the past decade due to the improvements in selectivity and sensitivity of modern analytical techniques [69]. Besides, with the latest increasing interest in fighting antimicrobial drug resistance a great deal of attention has been focused on detecting antibiotics in waters as well as in foodstuff and biological samples [31]. Over the past years, the detection of Cephalexin antibiotic has been achieved by many analytical methods, applied to water samples, food, pharmaceuticals, and biological samples. Hence, these techniques present different difficulty, accessibility, cost, the limit of detection or analysis time and can be divided into four main groups: microbiological tests, instrumental methods, biosensors and electrochemical techniques [24, 70].

Number of effective analytical methods for the sensitive detection of Cephalexin antibiotic was described in the literature, such as the solid phase extraction (SPE) followed by ultra-high-performance liquid chromatography coupled to quadrupole linear ion trap tandem mass spectrometry (UPLC-QqLIT) [71], solid-phase extraction (SPE), moleculary imprinted solid-phase extraction (MISPE) [72], UV spectrophotometry [73], mass spectrometry (MS) [74], and capillary electrophoresis (CE) [75]. Unfortunately, all these methods are laborious, time-consuming, require complex analytical equipment, very qualified staff. [24] and high-cost [76]. Therefore, A novel method was developed for rapid and quantitative determination of Cephalexin antibiotic, including fluorescence quenching of L-cysteine capped core-shell CdTe/ZnS nanoparticles (NPs) [76], photoluminescence carbon dots [16], electrocatalytic oxidation at a carbon paste electrode modified with cobalt salophen (CoSal) by cyclic voltammetry [77], anodic oxidation at high potential by differential pulse voltammetry (DPV) using bare boron-doped diamond electrode (BDDE) [24], differential pulse polarograms (DPP) [78], differential pulse polarograms (DPP) and linear sweep voltammetry (LSV) methods [79]. Further methods have been described in various researches in the last decade which are defined in Table 1.

Table 1: Different techniques for the detection of Cephalexin antibiotic

Detection methods	Detection limit (10^{-6} M)	Type of simples	References
Reverse phase HPLC	-	aqueous solution	[80]
HPLC	3.00	aqueous solution	[81]
Polarographic method	0.05		[82]
HPLC - UV	10.00	Bovine milk	[83]
Microbiological system	128.00	Ovine milk	[84]
Spectrophotometry	168.00	Pharmaceutical formulations (capsules)	[85]
Electrochemical reduction by CV using a dropping mercury electrode	17.37	Pharmaceutical formulations (tablets) Human serum	[86]
Electrochemical oxidation by SWV using heated glassy carbon electrode	52.00	Pharmaceutical formulations (capsules)	[87]
Electrochemical oxidation by DPV (Differential Pulse Voltammetry), using the BDDE	34.74	Pharmaceutical formulations (capsules) Urine River water	[24]
Ninhydrin quantitative method	-	aqueous solution	[82]
UPLC-MS/MS	0.10	Effluent and influent wastewater	[52]

VI. Technologies of Removal Cephalexin Antibiotic

Antibiotics such as Cephalexin is a group of pharmaceutical compounds in human medicine practice that has been entered in water bodies (wastewater, surface and groundwater) at different concentrations can affect the quality of the water and impact the supplies of drinking water, the ecosystems, and the human health. The presence of Cephalexin antibiotic in the environment has raised concerns regarding the toxicity to aquatic organisms and the emergence of strains of antibiotic-resistant bacteria. Therefore, removal of this substance before entering the aquatic environment as well as water reuse plants is very important [29]. As consequence, over the last decades, research efforts have been made at developing more effective technologies for the remediation of waters containing pharmaceuticals such as Cephalexin antibiotic, its removal being achieved by three main methods: physical, biological and chemical [31, 88].

Since then, many electrochemical technologies have been devised for the remediation of wastewaters [89, 90]. They can be classified into two main categories, the first one is the separation technologies, which isolate the xenobiotics from the aqueous medium without altering their chemical structure, and the second one is the degradation technologies, which cause the cleavage of structural bonds inducing the conversion of the initial pollutant into by-products. The main advantage of the electrochemical technologies is their environmental compatibility because the main reagent, the electron, is a clean reagent. Other advantages include their versatility, high energy efficiency, amenability to automation, easy handling because of the simple equipment required and safety because they operate under mild conditions [91]. Nevertheless, In the last years, the decontamination and disinfection of waters by means of direct or integrated electrochemical processes are being considered as a very appealing alternative due to the significant improvement of the electrode materials and the coupling with low-cost renewable energy sources [17].

As a concern, extensive research has been made in recent years on antibiotics removal from waters by electrochemical conversion an combustion employing strategies such as direct electron transfer, generation of •OH, H_2O_2 or active chlorine species, EAOPs based on Fenton's reaction or using "active" or "non-active" anodes to name a few. The comparative degradation behavior of Cephalexin antibiotic using advanced oxidation processes (AOPs) with the aim of improving Cephalexin biodegradability was studied. Among the AOPs used, RuO2/Ti anodic oxidation (AO), AO in the presence of electro-generated H_2O_2 (AO- H_2O_2), and the electro-Fenton (EF) process, the EF process was the most effective. In the EF process, an activated carbon fiber (ACF) was used as a cathode [22, 31]. Additionally, using the same degradation route of electrogenerated active chlorine, the initial concentration of Cephalexin antibiotic decreased by more than 90% after treatment using an electrochemical system with a Ti/IrO 2 anode and a Zr cathode in the presence of NaCl [92]. Moreover, the electrolysis with a boron-doped diamond anode electrode was used with more than 99% of elimination [34].

Besides, natural zeolite (NZ) and zeolite coated with manganese oxide nanoparticles (CZ) have been used for removal Cephalexin antibiotic from aqueous solutions with significant increase of remediation from (28 to 89%) [93]. As well, to illustrate, activated carbon prepared walnut shells were used [94]. Even, two activated carbons from agricultural wastes were prepared, by KOH and K_2CO_3 activation, where the adsorption mechanisms of Cephalexin antibiotic onto both carbons namely KAC and KCAC have been compared [95]. Additionally, original and Cu (II)/Fe (III) impregnated activated carbons developed from lotus stalks were used [96], also wine wood which demonstrated great potential for Cephalexin adsorption from aqueous solutions, with high removal yields of more than 80% [97].

Anaerobic membrane bioreactor specifically submerged flat sheet membrane under the condition of bioaugmentation technique was also used to treat high-concentration of Cephalexin antibiotic in wastewater [54]. As well, supported liquid membranes (SLMs) with strip dispersion and carrier, Aliquat 336, were used for the selective recovery of Cephalexin from simulated enzymatic solutions of Cephalexin synthesis [98]. Furthermore, nanofiltration (NF) membranes (TFC-SR2 and TFC-SR3) have been used as an attractive technology for removal of Cephalexin antibiotic [29].

In the same way, several techniques had been demonstrated for removal Cephalexin antibiotic from aqueous solutions such as chlorination [99], combined system using green algae and active sludge giving a high removal efficiency with more than 95% [100], UV 254 and persulfate activated by UV 254 (UV/PS) [101], UV-visible light and photocatalysis by removal efficiency ranging from (70 to 95%) [102], even the ultrasound irradiation [20].

VII. Conclusion

Aquatic resources are required to be free from any contaminant which may be hazardous to human health and environmental aspect. Contaminated water, as well as foodstuff, play an important role in the transmission of diseases to humans even treat the whole ecosystem. Despite the international organization of health and food safety have been established a number of monitoring programs in order to prevent or to reduce the risk of contracting infections. The increasing concentration of antibiotics even the release of antibiotics resistance in an aqueous environments are registered. Hence, the value of this review was to identify Cephalexin antibiotic to acquire a more comprehensive understanding by given the detection and removal techniques which were described in order to provide further opportunities for controlling and assessing the quality of water resources and foodstuff and offer opportunities to monitor and mitigate any further health impacts threat human and environment as well.

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