

Occurrence and Removal of Macrolides in Municipal Wastewater Treatment Plants: A Review

Zahra Abbasi¹, Mehdi Ahmadi^{2, 3*}

¹ Department of Chemistry, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran.

² Environmental Technologies Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

³ Department of Environmental Health Engineering, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

ARTICLE INFO

REVIEW ARTICLE

Article History:

Received: 19 September 2021

Accepted: 20 November 2021

*Corresponding Author:

Mehdi Ahmadi

Email:

Ahmadi241@gmail.com

Tel:

+989126779273

Keywords:

Wastewater Treatment,
Macrolide,
Environment.

ABSTRACT

Introduction: Macrolides are a group of antibacterial agents. Given their clinical importance, and the consistent rise in resistance among pathogenic bacteria, macrolides have been the targets of extensive research.

Materials and Methods: This review considered the number of macrolides in different wastewater and the removal of these drugs. The antibiotics were frequently detected in influents and effluents, ranged from ng/L up to lower µg/L. In influent, the highest concentrations of clarithromycin (6080 ng/L), roxithromycin (>103 ng/L), erythromycin (3900 ng/L), and azithromycin (1949 ng/L) were detected in Croatia, Chinese, USA, and Singapore municipal wastewater treatment plants, respectively.

Results: The removal efficiency of macrolides during wastewater treatment processes varies and is essentially dependent on a combination of macrolides physicochemical properties, location of municipal wastewater, and the operating conditions of the treatment systems. The application of alternative techniques, including membrane separation, activated carbon adsorption, advanced oxidation processes, biodegradation, and disinfection were the dominant removal routes for macrolides in different wastewater treatment processes. A combination of these techniques can also be used, leading to higher removals, which may be necessary before the final disposal of the effluents or their reuse for irrigation or groundwater recharge.

Conclusion: Many antibiotics cannot be removed completely in wastewater treatment processes and would enter into the environment via effluent and sludge. The molecular structure of macrolides and their load-bearing capacity has led to the advantage of biological treatment over other treatments. However, the main part of the treatment has been done using biological treatment.

Citation: Abbasi Z, Ahmadi M. *Occurrence and Removal of Macrolides in Municipal Wastewater Treatment Plants: A Review*. J Environ Health Sustain Dev. 2021; 6(4): 1419-42.

Introduction

Pharmaceutical compounds which are widely used for different purposes today are detected in natural surface water, groundwater, and wastewater¹. Antibiotics, beta-blockers, anti-inflammatories, lipid regulators, beta-agonists, hormones, antineoplastic, and iodinated contrast media are some of the several usually administered

remedial and diagnosis groups of drugs^{2,3}. The wide use of antibiotics has contributed to spreading these compounds in the wastewater. Antibiotics are usually classified as bactericidal when they remove the infecting bacteria or as bacteriostatic when they inhibit the growth without killing bacteria. They are classified to different groups according to their chemical structure and mode of action, such as

aminoglycosides, β -lactams, tetracycline, and quinolones⁴⁻⁶. A trace volume of antibiotics has been known in natural water systems worldwide, frequently relating their occurrence to wastewaters and livestock operations^{4, 7}. Extensive use of these drugs may cause many biological hazards; since, in addition to their direct presence in the environment, they prevent the effective treatment of wastewater. Most antibiotics are poorly absorbed by humans or animals and consequently, after prescribing antibiotics, some of them are metabolized (usually 55-80%). A mixture of metabolites and conjugates of raw materials is excreted unaltered through urine and faeces, and along with sanitary wastewater, reaching municipal wastewater treatment plants⁸⁻¹⁰. Another route to enter the environment is to discharge expired drugs into toilets and household waste. However, the concentration of antibiotics residue in the environment is low, ordinarily at ng/L to μ g/L level in natural water¹¹ and wastewater^{12,13}, and μ g/kg to mg/kg level in soil¹⁴ and sludge¹⁵. The occurrence and removal of antibiotics in the environment, including wastewater, groundwater, and surface water have drawn great attention of researchers in recent years^{16, 17}. Critical and persistent effects of antibiotics on ecosystems, the resistance of bacteria to antibiotics, and increasing tolerance of antibiotics by humans and livestock have not been well known which are at the source of increasing global concern¹⁸. Municipal wastewater is an important source of organic contaminants in the aquatic environment¹⁹. Municipal wastewater treatment is the process of removing contaminants from effluents, especially domestic wastewater, which includes

chemical, physical, and biological processes^{20, 21}. This process removes these pollutants and provides treated wastewater that is safe for the environment. The wastewater characteristics play an important role in the selection of treatment types. Antibiotics are one of the most important drugs for controlling dangerous diseases, and high amounts of these compounds are released into municipal wastewater due to extreme waste²². This study focused on macrolide antibiotics, which are among the most famous antibacterial. Among several kinds of resistant antibiotics, macrolides recently came under special scrutiny. Macrolides are composed of a macrocyclic lactone of different ring sizes, to which one or more deoxy sugar or amino sugar residues are attached. Macrolides act as antibiotics by binding to bacterial 50S ribosomal subunits and interfering with protein synthesis. They bind at the nascent peptide exit tunnel and partially occlude it. Thus, macrolides have been viewed as 'tunnel plugs' that stop the synthesis of every protein. The persistence of macrolides in water is defined based on their half-life value. The half-life value for Azithromycin is < 5 h²³, Tylosin is 9.5–54 days, and for Erythromycin is < 17 days²⁴. The given half-life values refer to surface water. These values can be much higher (longer half-life) in the case of groundwater or soil/sediments due to the scarcity or lack of sunlight and aerobic conditions²⁵. The half-life of macrolides makes them stable in the environment. This matter disrupts the microbial ecology of surface water. The ecotoxicity of the macrolides is shown in Table 1. This Table shows macrolides high toxicity to aquatic organisms.

Table 1: Toxicity values for macrolides concerning aquatic organisms ²⁵

Compound	Organism	Ecotoxicity indicator, (mg/L)	Ref.
Azithromycin	<i>Daphnia magna</i> (crustacean)	120 (IC50)	26
	<i>Pseudokirchneriella subcapitata</i> (green algae)	0.5 (IC50)	27
	<i>Skeletonema marinoi</i> (diatom)	0.214 (IC50)	27
Clarithromycin	<i>Vibrio fischeri</i> (luminescent bacteria)	no effect	28
	<i>Daphnia magna</i> (crustacean)	25.72 (EC50)	28
	<i>Pseudokirchneriella subcapitata</i> (green algae)	0.002 (IC50)	28
Tylosin	<i>Selenastrum capricornutum</i> (green algae)	0.95 (EC50)	29
	<i>Lemna gibba</i> (duckweed)	0.3 (LOEC)	30
	<i>Pseudokirchneriella subcapitata</i> (green algae)	3.8 (EC50)	31
Erythromycin	<i>Vibrio fischeri</i> (luminescent bacteria)	no effect	28
	<i>Daphnia magna</i> (crustacean)	22.45 (EC50)	28
	<i>Pseudokirchneriella subcapitata</i> (green algae)	0.02 (IC50)	28

This review began with a summary of the treatment and removal of macrolides in municipal wastewater treatment plants from various countries in the world. Their main representatives, ERY, CLA, AZI, and ROX have been included in the EU Watch List of potentially hazardous compounds for the aquatic environment. The widespread occurrence of macrolide antibiotics in municipal wastewater, as well as their incomplete removal during wastewater treatment, has been frequently reported. This review examined conventional and advanced treatment methods, including anoxic, aerobic and anaerobic biological processes, activated carbon, ozonation, chlorination, and advanced oxidation processes. The review also contained an extensive list of tables showing the removal percentage of macrolides using different treatment methods.

Materials and Methods

Search strategy

Considering that English articles published during 2004-2020, which included occurrence and removal efficiency in different treatment plants in different countries, international databases were searched, including Thomson Reuters-Web of Science, Scopus, and Science Direct. Searching was done employing relevant keywords, such as macrolides occurrence in “municipal wastewater”, “macrolides removal”, “macrolides physicochemical properties”, and “wastewater treatment plants”. Prisma protocol principles were

used in the articles screening process. Finally, 266 articles were found; only 96 were cited in this review, as the most relevant and essential for this study.

Inclusion criteria of the study

Articles that met the following criteria were included in the study; 1- Studies conducted on the occurrence of macrolides in municipal wastewater 2- Studies conducted on the removal of macrolides in municipal wastewater, 3- Studies conducted on different strategies for removal of macrolides, 4- Original studies and 5- Existence of full text. The authors used the information of articles, including the city/country of municipal wastewater treatment plant, the abundance of macrolides in the wastewater, and the methods used to remove macrolides. According to the reviewed articles, the classification of different removal methods was shown.

Data extraction and analysis

The data structure included the number of macrolides in different wastewater, number of macrolides in influents and effluents, name of authors, municipal wastewater treatment plants of study, province, urban and country, year, and removal management method. Finally, the extracted data included treatment processes, removal efficiency, and location of municipal wastewater plant (city/country). The results were classified into eight groups, as follows: physical treatment, biological treatment, a combined of biological process techniques, advanced oxidation

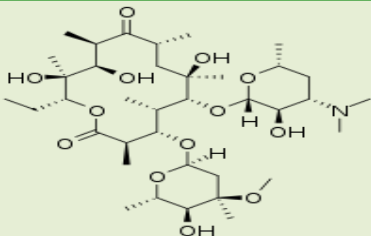
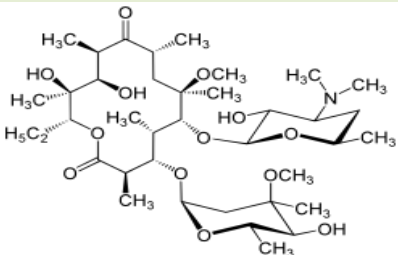
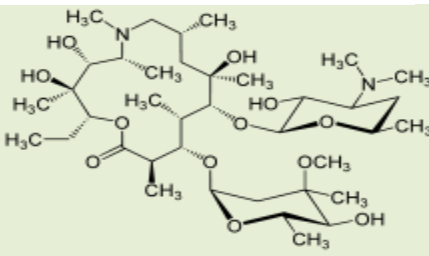
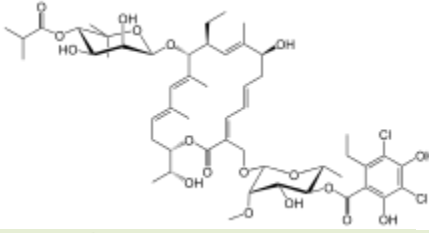
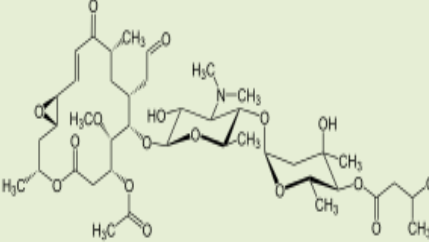
processes, physicochemical treatment, natural treatment, advanced treatment, and combination of treatment processes. The study examined these groups and their effects on the removal of macrolides reported in municipal wastewater.

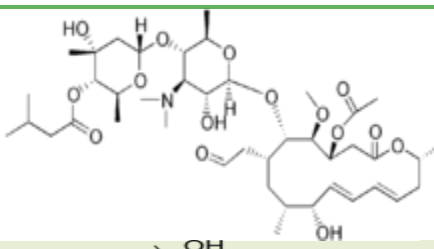
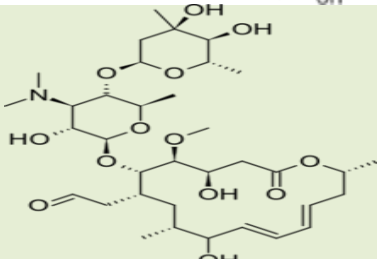
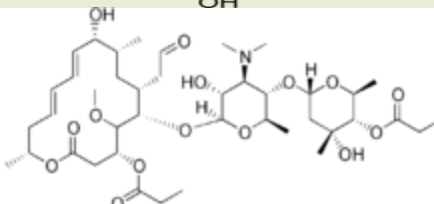
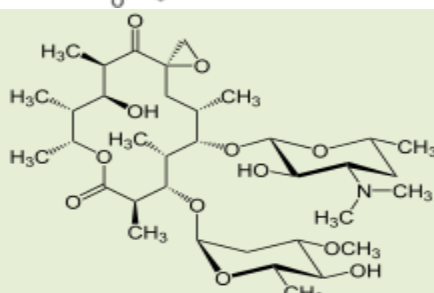
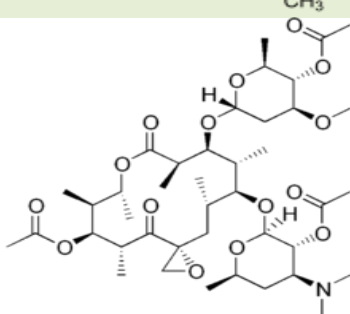
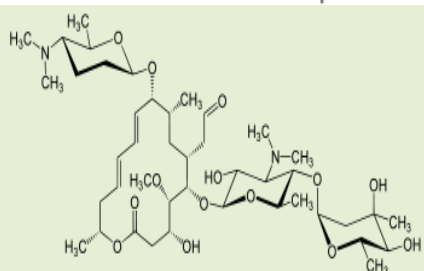
Molecular structure

Macrolides were introduced to the world in 1952 by Mc Guire et al. with the introduction of erythromycin derived from the fungus

Streptomyces Erythreus. Macrolides are characterized by a large highly substituted macrocyclic lactone ring which can vary from 12-16 atoms with one or more chains of deoxy sugars (mainly cladinose and desosamine) attached to a hydroxyl group. They contain a dimethylamino group which makes them basic. They are sparingly soluble in water but dissolve relatively well in polar organic solvents³²⁻³⁵ (Table 2).

Table 2: Macrolides, physicochemical properties, and structures³²⁻³⁵

Compound	Acronym	Structure	CAS number	Molecular weight (g/mol)
Erythromycin	ERY		114-07-8	733.93
Clarithromycin	CLA		81103-11-9	747.95
Azithromycin	AZI		83905-01-5	748.98
Fidaxomicin	FID		873857-62-6	1058.04
Carbomycin A	CAR		4564-87-8	841.97848

Compound	Acronym	Structure	CAS number	Molecular weight (g/mol)
Josamycin	JOS		16846-24-5	828.006
Kitasamycin	KIT		39405-35-1	701.84
Midecamycin	MID		35457-80-8	813.968
Oleandomycin	OLE		3922-90-5	687.858
Solithromycin	SOL		760981-83-7	845.01
Spiramycin	SPI		8025-81-8	843.053

Compound	Acronym	Structure	CAS number	Molecular weight (g/mol)
Troleandomycin	TRO		2751-09-9	813.968
Tylosin	TLY		1401-69-0	916.10
Roxithromycin	ROX		80214-83-1	837.047

Macrolides, environmental occurrence, and removal efficiency

There are three main stages of the wastewater treatment process, aptly identified as primary, secondary, and tertiary treatment. In some wastewater, more advanced treatment is required; this stage uses a combination of primary, secondary, and tertiary treatments¹⁷. In this review, the performance of currently applied methods for the removal of macrolides in municipal wastewaters was analyzed. In this review, the occurrence and removal of macrolide antibiotics were investigated at municipal wastewater in many countries. The most frequently detected macrolide antibiotics in the present study were AZI, ERY, CLA, ROX, and TLY. The concentrations of these compounds ranged from 28 to 5500 ng/L, 20 to 3900 ng/L, 25 to 6080 ng/L, 10 to 1500 ng/L, and 1 to 1500 ng/L, respectively. The other macrolide antibiotics have been reported in small amounts from municipal wastewater. Previous studies have revealed that several treatment techniques are available to remove macrolides in municipal wastewater treatment

plants, including coagulation, flocculation, sedimentation, filtration, biological treatments, such as activated sludge (AS); sequencing batch reactors (SBR); membrane bioreactor (MBR); physio-chemical treatment, such as UV irradiation; reverse osmosis (RO); chlorination; ultrasonication (US); an advanced oxidation processes (AOPs), such as ozonation; UV/TiO₂; UV/H₂O₂; and Fenton/photo-Fenton.^{22, 36-37}

Result

Physical treatment

When physical and mechanical properties are used to separate and remove external dissolved solids, it is called physical wastewater treatment. These processes include coagulation, flocculation, sedimentation, filtration, grain collection, grit chamber, sand filtration, etc. Most of these methods are performed before wastewater treatment, which is also called primary treatment. With physical treatment, the amount of macrolides removal has been rarely reported^{38, 39}. The range percentage removal of macrolides by the physical method was reported to be between 0 and 33%. The physical treatment method is not a good way

to remove the drug but to explain the reported 33% removal; it can be attributed to the structure of hydrophilic macrolides. This might be affected by the removal of the fine suspended particles adsorbing these hydrophilic compounds. The physical treatment is effective in combination with other treatments. The percentage removal of macrolides from Kloten-Opfikon in Switzerland using physical treatment has been reported 0-4% for ERY, 11%-14% for CLA, and 10%-33% for AZI⁴⁰. The GC method was applied for removing Clarithromycin from municipal wastewater in Guangdong, in China, with influent of 125 ng/L,

zero reported (Table 3). Nakada et al.³⁸ discussed macrolides removal in terms of chemical structure. They reported that removal of the CLA, ERY, ROX, and AZI during sand filtration was generally inefficient. They concluded that the reason for inefficient sand filtration is lack of hydrophobicity. Table 3 shows that physical treatment has not provided any notable removal for the investigated macrolides. The removal percentage range is 0 to 31%; it has been observed that clarification has a higher efficiency method in removing macrolides than other physical methods.

Table 3: Removal of macrolides in municipal wastewater treatment plants with physical processes

	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	SF	0	228	Tokyo/Japan	38
	S + GC + Sed	11-14	330-600	Kloten-Opfikon/Switzerland	40
	GC	0	125	Guangdong/China	39
	GC	5.67	50	Guangdong/China	39
ERY-H ₂ O	SF	0	150	Tokyo/Japan	38
	GC + Sed	0-4	60-190	Kloten-Opfikon/Switzerland	40
	GC + Sed	0	810 ± 11	Wan Chai/China	41
	GC	0	~900	Guangdong/China	39
	GC	13.8	~700	Guangdong/China	39
ROX	SF	5.36	27.2	Tokyo/Japan	38
	GC + Sed	3-9	10-40	Kloten-Opfikon/Switzerland	40
	GC	3.04	70	Guangdong/China	39
	GC	2.42	40	Guangdong/China	39
	Sed	31	108 ± 3.3	Dalian/China	42
AZI	SF	0	-	Tokyo/Japan	38
	S + GC + Sed	10-33	90-380	Kloten-Opfikon/Switzerland	40
	Sed	29.8	345 ± 21	Dalian/China	42

Biological treatments

The physical treatment will only be able to separate a part of the suspended solids (which can be separated) and finally a small amount of macrolides matter. Thus, to separate and remove soluble materials, as well as colloidal and non-sedimentary materials, another step of treatment is required. In secondary treatment, biological agents are often used to convert and decompose pollutants⁴³. Removal is usually performed by biological processes in which microorganisms utilize the organic impurities as food, reducing them into carbon dioxide, water, and energy for their growth and replication⁴⁴. Biological treatment methods have traditionally been used for the

management of pharmaceutical wastewater. Biological treatment processes are divided into three main groups, including aerobic, anaerobic, and anoxic processes. Aerobic applications include activated sludge, membrane batch reactors, and sequence batch reactors. Anaerobic methods include anaerobic sludge reactors, anaerobic film reactors, and anaerobic filters and anoxic method include the process by which nitrate NO₃ nitrogen is converted to molecular nitrogen gas in the absence of oxygen⁴⁵.

Aerobic treatment

Variations on aerobic treatment, including SBR, MBR, moving bed biofilm reactor (MBBR), and AS were shown to have added advantages for the

treatment of wastewater ⁴⁶. However, aerobic process was discussed in detail regarding the subject of this article.

Activated sludge modification process

The activated sludge process is used for the reduction of organic matter present in the wastewater. Conventional activated sludge (CAS) with a long hydraulic retention time (HRT) has historically been the method of selection for the treatment of wastewater. Extended activated sludge is another kind of activated sludge that has been widely used in many countries ³⁷. The SBR is an activated sludge method of treatment in which separate tanks for aeration and sedimentation are not required and there is no sludge return ⁴⁷. This system is ordinarily used to treat wastewater from small communities and can accept periodic loadings without becoming disturbed ⁴⁸. Macrolide antibiotics, including AZT, CLA, ROX, ERY, and ERY-H₂O, indicated different results suggesting a difference with the activated sludge process. High variability was observed in the removal efficiencies, Table 4 shows removal efficiency macrolides significantly ranged between 0 to 100 %. Earlier studies have reported that macrolide antibiotics are often moderately removed by activated sludge processes for municipal wastewater ^{40, 49-51}. Nakada et al. ³⁸ applied a combination of ozon and SF with activated sludge treatment and the removal efficiency was above 80%. They observed that by using activated sludge with a hydraulic retention time of 9 h, removal efficiencies of 0, 38.9%, 40.9%, and 18.6% were observed for AZI, ERY, CLA, and ROX, respectively. Göbel et al. ⁴⁰ investigated two conventional activated sludge (CAS) systems, including the CAS system at the municipal wastewater treatment plant Kloten-Opfikon, Switzerland (CAS-K) and CAS system at the municipal wastewater treatment plant Altenrhein, Switzerland (CAS-A). The results were discussed

based on temperature, hydraulic retention time, and solids retention time. In CAS-K, hydraulic retention time was ~15 h; solid retention time was 10–12 d, and wastewater temperature was 12–16°C. In CAS-A hydraulic retention time was ~31 h, solid retention time was 21–25 d, and wastewater temperature was 12–19°C. The removal efficiencies of AZI, ERY-H₂O, CLA, and ROX using CAS-K and CAS-A were reported 0 and 22%-55%; 0-6% and 0-7%; 0-9% and 4%-20%, and 0-38% and 5%-38%, respectively. Dong et al. ⁵² studied CW, SP, AS, and MP for occurrence and removal of 19 antibiotics (including four macrolides) in a county of eastern China. Their review analysis demonstrated that AS and CW outperformed the MP and SP processes and AS performed better than the CW process in terms of antibiotics removal. Bing and Zhang ⁵³ investigated the mass flows and the removal of ROX and ERY-H₂O in two wastewater treatment plants (WWTPs) of Hong Kong. The mean removal efficiencies using activated sludge process for ROX and ERY-H₂O were 46% and 15% in Shatin and 40% and 26% in Stanley. Valiparambil et al. ⁵⁴ investigated four STPs in South India. They studied the seasonal effects on the occurrence and removal efficiency during pre-monsoon, monsoon, and post-monsoon seasons. They found that effluents received in the monsoon season had the highest concentration range versus other seasons which may be due to the higher incidence of flu/infections. The performance of activated sludge systems depends on the type of macrolide and the location of the wastewater. Generally, higher rates of removal have been reported for CLA than for other macrolides. Efficiency of reported removals may depend on whether the effluents have been sampled after aeration and sludge separation or after sedimentation following activated sludge treatment ⁵⁴.

Table 4: Removal of macrolides in municipal wastewater treatment plants using activated sludge processes

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (city/country)	Ref.
CLA	CAS	40.9	228	Tokyo/Japan	38
	CAS	0-9	330–600	Kloten–Opfikon/Switzerland	40
	CAS	4-20	-	Altenrhein/Switzerland	40
	CAS	83.4 ± 25.7	173	Hikkaduwa/Sri Lanka	55
	CAS	87	230	Castellon/Spain	56
	CAS	90	-	Germany	57
	CAS	91	2200	Eastern China	52
	CAS	62	71	Zagreb/Croatia	58
	SBR	50	850	Gyeonggi/South Korea	59
ERY	CAS	38.9	150	Tokyo/Japan	38
	CAS	0-6	60–190	Kloten–Opfikon/Switzerland	40
	CAS	0-7	-	Altenrhein/Switzerland	40
ERY-H ₂ O	CAS	-	261	Hikkaduwa/Sri Lanka	55
	CAS	26	-	Stanley/Hong Kong	53
	CAS	15	-	Shatin/Hong Kong	53
	CAS	-	280	Eastern China	52
	CAS	15	36	Zagreb/Croatia	58
	SBR	24	290	Gyeonggi /South Korea	59
	EA	65	24	Karnataka/ India	54
	EA	0	59		
	EA	31	6		
	EA	0	28		
	EA	0	26		
	EA	100	7	STP2	
ROX	CAS	18.6	27.2	Tokyo/Japan	38
	CAS	0-38	10–40	Kloten–Opfikon/Switzerland	40
	CAS	5-38	-	Altenrhein, Switzerland	40
	CAS	69.8 ± 38.4	108	Hikkaduwa/Sri Lanka	55
	CAS	40	-	Stanley/Hong Kong	53
	CAS	46	-	Shatin/Hong Kong	53
	CAS	100	-	Germany	57
	CASS	50	500	Harbin/China	60
	CAS	-	280	Eastern China	52
AZI	SBR	24	290	Gyeonggi/South Korea	59
	CAS	0	-	Tokyo/Japan	38
	CAS	0	90–380	Kloten Opfikon/Switzerland	40
	CAS	22-55	-	Altenrhein/Switzerland	40
	CASS	0	28	Harbin/China	60
	CAST	0	28	Harbin/China	60
	CAS	78	1949	Singapore	61
	CAS	100	-	Germany	57
	CAS	19	350	Zagreb/Croatia	58
LIN	CAS	42.1	65.5	Singapore	61

Moving bed bioreactor (MBBR) treatment

MBBR technology is an advancement over the CAS technology and is a biological process of attached growth type⁶². This method consists of an activated sludge aeration system where the sludge is collected on recycled plastic carriers. These carriers have an internal large surface for optimal contact with water, air, and bacteria. MBBR

technology is more efficient than ASP and SBR and requires less area. The data of macrolides removal using MBBR are shown in Table 5. Xiangjuan Yuan et al.⁴¹ studied the occurrence, fate, and environmental impact of CLA, ERY-H₂O, ROX, and AZI in two municipal wastewater treatment plants located in Wuxi City, East China. The analysis showed that a maximum

concentration of CLA, ERY- H₂O, ROX, and AZI in influent was > 100, 10, > 103, and 232.5-876.9 ng/L, respectively. The removal percentage range

was 20% to 76.2%. The removal range of the macrolides was almost identical with MBBR treatment.

Table 5: Removal of macrolides in municipal wastewater treatment plants using MBBR process

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (city/country)	Ref.
CLA	MBBR	20	850	Gyeonggi/South Korea	59
	MBBR	59.9	> 100	Wuxi/china	41
ERY- H ₂ O	MBBR	60.8	10	Wuxi/china	41
ROX	MBBR	53.7	> 103	Wuxi/china	41
AZI	MBBR	76.2	232.5-876.9	Wuxi/china	41

MBR process

The MBR is a combined of conventional biological treatment processes with membrane filtration to provide an advanced level of organic and suspended solids removal and in some cases nutrient removal. The MBR is one of the most modern methods of wastewater treatment. Removal efficiencies of macrolides from the municipal wastewater using MBR are shown in Table 6. According to the results of the studied wastewater Gyeonggi-province, South Korea using MBR exhibited better performance over MBBR and SBR for most macrolides⁵⁹. Wang et

al.³⁶ investigated the use of MBR linked with RO and NF to remove drugs from municipal wastewater. In this study, MBR was operating with HRT of 3.2 h, mean pH 7.8, and from texture polyvinylidene fluoride and polyethylene terephthalate with an effective area of 0.8 m². The results showed that for macrolide antibiotics, MBR removal efficiency was 74% to 82% (Table 6). By comparing MBR and CAS methods (Table 3 and 5), it can be concluded that MBR has a better effect on most macrolides (CLA 91.4%, ERY- H₂O 90%, ROX 74%, AZI 91.4%, and LIN 62.1%) than CAS.

Table 6: Removal of macrolides in municipal wastewater treatment plants using MBR processes

	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	MBR	60	850	Gyeonggi/South Korea	59
	MBR	82	368	China	36
	MBR	71.3	1497	Singapore	61
	Aerobic	16.8	125	Guangdong/China	39
	MBR	52	2020	Castell- Platjad' Aro/Spain	63
	FBR	5.6-14		Altenrhein/Switzerland	40
	MBR	71.87-74.06	6080	Croatia	64
ERY- H ₂ O	MBR	77	20	China	36
	MBR	0.71	-	Zagreb, Croatia	65
	MBR	40	44	Jeolla/South Korea	66
	MBR	42	44	Jeolla/South Korea	66
	MBR	64.8	652	Singapore	61
	Aerobic	13.7	~900	Guangdong/China	39
	Aerobic	21	221	Beijing/China	67
	MBR	81	49	Castell-Platja d' Aro/Spain	63
ROX	MBR	59	290	Gyeonggi/South Korea	59
	MBR	74	79	China	36
	MBR	0.36	-	Zagreb/Croatia	65
	FBR	35±6	-	Altenrhein/Switzerland	40
	Aerobic	9.91	70	Guangdong/China	39
	Aerobic	29	129	Beijing/China	67
AZI	MBR	80	1410	China	36
	MBR	91.4	1949	Singapore	61
	MBR	77	118	Castell-Platja d' Aro/Spain	63

	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
	MBR	23.25-52.62	-	Croatia	64
	FBR	30±6	-	Altenrhein/Switzerland	40
TYL	Aerobic	2	6.42	Beijing/China	67
SPI	Aerobic	0	7.46	Beijing/China	67
JOS	Aerobic	0	0.86	Beijing/China	67
LIN	MBR	62.1	65.5	Singapore	61

Anaerobic treatment

Anaerobic treatment processes consist of several methods in which microorganisms break down organic components of the wastewater in the lack of oxygen. Configurations of anaerobic reactors include up-flow anaerobic reactors, anaerobic film reactors, and up-flow anaerobic filters⁶⁸. The performance of an anaerobic condition was evaluated for the removal of macrolides from municipal wastewater^{39, 67, 69}. Kasturi Dutta et al.⁶⁹ investigated a two-stage AFMBR and AFBR followed by AFMBR and used GAC as a carrier medium in both stages. They found that the two-stage AFMBR was able to treat municipal wastewater at a minimum HRT of 1.28 h. Using

AFBR, the effluent was obtained by 132 ± 19.1 ng/L and 140 ± 4.9 ng/L for ERY-H₂O and CLA, respectively, and using AFMBR, it was obtained 43.9 ± 2.1 ng/L and 35.5 ± 2.1 ng/L for these two macrolides, respectively. Li et al.⁶⁷ investigated the occurrences and fates of five macrolides in a wastewater reclamation plant in Beijing, China. The concentrations of TYL, SPI, and JOS in the influent were low, obtained 6.42 ng/L, 7.46, and 0.86 ng/L for TYL, SPI, and JOS, respectively. This study indicated that macrolides were mainly removed from the wastewater with anaerobic treatment. The removal percentage range of TYL, SPI, and JOS were reported to be between 23% and 68% (Table 7).

Table 7: Removal of macrolides in municipal wastewater treatment plants with anaerobic processes

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (city/country)	Ref.
CLA	AFBR	56.9	324 ± 6.4	Taiwan	69
	AFMBR	74.6	324 ± 6.4	Taiwan	69
	Anaerobic	2.99	125	Guangdong/China	39
ERY	Anaerobic	6.45	~900	Guangdong/China	39
	Anaerobic	31	221	Beijing/China	67
ERY-H ₂ O	AFBR	56.9	319 ± 42.4	Taiwan	69
	AFMBR	74.6	319 ± 42.4	Taiwan	69
ROX	Anaerobic	17.6	70	Guangdong/China	39
	Anaerobic	39	129	Beijing/China	67
TYL	Anaerobic	68	6.42	Beijing/China	67
SPI	Anaerobic	55	7.46	Beijing/China	67
JOS	Anaerobic	23	0.86	Beijing/China	67

Anoxic treatment

Anoxic treatment is the chemical and biological treatment of wastewater that decreases nitrate, phosphorus, and other residual organics and solids in wastewater effluent⁷⁰. Zhou et al.³⁹ chose a municipal wastewater treatment plant in Guangdong Province in China. They reported that using anoxic treatment the removal percentage of macrolides for CLA, ERY, and ROX was obtained 49.2%, 10.2%, and 11.1%, respectively.

Wenhui Li⁶⁷ investigated wastewater reclamation plants in Beijing-China. The anoxic treatment parameters in the studied wastewater plant: water flow, sludge flow, and hydraulic residence time were 10×10^5 m³/d, 44.7×10^5 kg/d, and 3, respectively. Wenhui Li⁶⁷ reported that mean influent concentrations of JOS, TYL, ROX, and ERY were 0.86 ng/L, 6.42 ng/L, 129, and 221 ng/L, respectively. The mean concentrations of JOS, TYL, ROX, and ERY after anoxic treatment

were obtained 0.13 ng/L, 2.11 ng/L, 100 ng/L, and 172 ng/L, respectively. The removal efficiency of different macrolides ranged from 0 (ROX, ERY and TYL) to 62% (JOS). The three

macrolides, SPI, JOS, and TYL, detected with low frequencies and at relatively low concentrations, were removed effectively during the Anoxic treatment (Table 8).

Table 8: Removal of macrolides in municipal wastewater treatment plants using anoxic process

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	Anoxic	42.9	125	Guangdong/China	39
ERY	Anoxic	10.2	~900	Guangdong/China	39
	Anoxic	0	221	Beijing/China	67
ROX	Anoxic	11.1	70	Guangdong/China	39
	Anoxic	0	129	Beijing/China	67
TYL	Anoxic	0	6.42	Beijing/China	67
SPI	Anoxic	4	7.46	Beijing/China	67
JOS	Anoxic	62	0.86	Beijing/China	67

Biological combined processes

This section describes a combination of different biological processes utilized for the treatment of several macrolides' antibiotics. Table 9 reveals removal efficiency using AO and A₂O treatment. Aerobic tanks may be coupled with anoxic or anaerobic tanks to give biological nutrient removal. The A₂O process is a patented two-stage biological process. In the first stage, under anaerobic conditions, a three-series chamber anaerobic baffled reactor (ABR) was used, while in the second stage, an AS with a settler was utilized. Park et al.⁵⁹ evaluated the removal efficiency of CLA and ROX

in a municipal WWTP in South Korea using the A₂O process. The removal efficiency of 15% (CLA) and 7% (ROX) indicated low removal efficiency of this treatment. Xiangjuan Yuan et al.⁷¹ presented the concentrations of macrolides in various sludge samples along with the A₂O treatment process. The results indicated that the mean concentrations of anaerobic sludge, anoxic sludge, oxic sludge, and return sludge for ERY-H₂O were 4.06, 9.75, 6.45, and 3.30 µg/kg; for CLA were 8.85, 28.31, 7.76, and 7.19 µg/kg; for ROX were 13.06, 23.57, 12.17 µg/kg, and 11.21 µg/kg; and for TYL were 0.25, 0.28, 0.28, and 0.28 µg/kg, respectively.

Table 9: Removal of macrolides in municipal wastewater treatment plants using combined biological processes

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	A ₂ O	15	850	Gyeonggi/South Korea	59
	A ₂ O	51	35.8	Harbin/China	60
	AO	8.7	35.8	Harbin/China	60
	A ₂ O	55	~1750	Kyoto/Japan	72
	A ₂ O	56	~650	Beijing/China	72
	A ₂ O	95	550	China	71
	AO	85	~5000	Shiga/Japan	72
	A ₂ O	3.6	> 100	Wuxi/china	41
ERY-H ₂ O	A ₂ O	80	500	China	71
	A ₂ O	13	10	Wuxi/china	41
	A ₂ O	53.58	66.3-159.5	Tehran/Iran	73
	A ₂ O	67.8	159.5	Tehran/Iran	74
ROX	A ₂ O	7	290	Gyeonggi/South Korea	59
	A ₂ O	25	~100	Kyoto/Japan	72
	A ₂ O	13.6	> 103	Wuxi/China	41
	AO	69	500	Harbin/China	60
	A ₂ O	72	500	China	71
	AO	73	~213	Shiga/Japan	72
	A ₂ O	0	500	Harbin/China	60
	A ₂ O	27	~800	Beijing/China	72

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
AZI	A ₂ O	60	28	Harbin/China	60
	AO	0	28	Harbin/China	60
	A ₂ O	40	~250	Kyoto/Japan	72
	A ₂ O	13	~280	Beijing/China	72
	AO	95	~5500	Shiga/Japan	72
	A ₂ O	17.5	232.5-876.9	Wuxi/China	41
	A ₂ O	66.6	43.3	Tehran/Iran	73

Advanced Oxidation Processes (AOPs)

AOPs include photo Fenton (UV/H₂O₂/Fe²⁺), UV/H₂O₂, solar photo Fenton, UV- Photolysis, Oz, US, Oxidation, and Fenton Processes (H₂O₂/Fe²⁺). Many researchers have used advanced oxidation methods to investigate the removal of macrolides in municipal wastewater^{38, 39, 67, 72, 75}. Table 10 presents the removal efficiency of macrolides in municipal wastewater by AOPs. Sousa et al.⁷⁵ reported full removal of 19% out of 22% pharmaceuticals with ca. 32 kJ/L solar UV energy. The Beijing wastewater in China was investigated⁶⁷ using CAS system, coupled with subsequent

ultrafiltration and ozone oxidation system. They observed that removal contribution of ozone oxidation system for JOC, TYL, ROX, and ERY was 27%, 27%, 100%, and 83%, respectively. Among various technologies that have been developed and applied to remove macrolides, Oz and photocatalysis with TiO₂ have both shown encouraging results. The Oz has shown good removal efficiencies on a wide range of different macrolides, both at the laboratory and full scales. In order to achieve the desired removal of macrolides, the technology can be improved with additional features, such as photocatalytic enhancement⁷⁶.

Table 10: Removal of macrolides in municipal wastewater treatment plants using AOPs processes

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	Oz	84.6	228	Tokyo/Japan	38
	OD	77	~950	Beijing/China	72
	Photocatalysis	40	24-676	Portugal	76
	Photocatalytic + Oz	> 94	24-676	Portugal	76
	OD	70.1	50	Guangdong/China	39
	OD	1.1	>100	Wuxi/china	41
ERY	Oz	88.7	150	Tokyo/Japan	38
	Photocatalysis	35	-	Portugal	76
	Photocatalytic + Oz	100	-	Portugal	76
	OD	0	60	Wuxi/china	41
	OD	55.3	~700	Guangdong/China	39
	Oz	83	221	Beijing/China	67
ROX	Oz	63	2600	Gwinnett/USA	77
	Oz	90.9	27.2	Tokyo/Japan	38
	OD	43	~775	Beijing/China	72
	OD	52.1	40	Guangdong/China	39
	OD	0	>103	Wuxi/china	41
	Oz	92.3	129	Beijing/China	67
AZI	Oz	92.6	-	Tokyo/Japan	38
	OD	10	~60	Beijing/China	72
	Photocatalysis	100	631	Portugal	75
	Photocatalysis	50	-	Portugal	76
	Photocatalytic + Oz	> 95	-	Portugal	76
	OD	7.1	232.5-876.9	Wuxi/China	41
TYL	Oz	27	6.42	Beijing/China	67
SPI	Oz	48	7.46	Beijing/China	67
JOS	Oz	27	0.86	Beijing/China	67

Physio-chemical treatment

Physicochemical treatments are very important within the wastewater treatment systems and before any biological and advanced treatment technologies. This treatment of wastewater focuses primarily on the separation of colloidal particles^{78, 79}. Physiochemical treatment options for this review were divided into four main topics, including membrane processes, reverse osmosis, and activated carbon. The removal of macrolides with RO, MF, and UF during the drinking water and wastewater treatment processes at full- and pilot-scale have also been investigated^{50, 63, 65-67}. Macrolide antibiotics can be removed by

physicochemical treatment (Table 11). Membrane filtration processes using RO and NF showed excellent removal (> 95%) for ERY⁶⁶. The removal of ERY in wastewater by RO and NF was <1.0. Li et al.⁶⁷ studied Beijing municipal wastewater in China. Based on their study concentrations of TLY, ROX, ERY, and JOS after UF treatment were 0.23, 1.7, 143, and 186 ng/L, respectively. The removal efficiency of individual macrolide ranged from 0 (ERY) to 23% (ROX). Removal of macrolides by physio-chemical treatment is defined by multiple synergies of electrostatic and other physical forces acting between a special solute, the solution, and the membrane itself⁶³.

Table 11: Removal of macrolides in municipal wastewater treatment plants using UF, NF or RO processes

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	RO	100	-	Zagreb/Croatia	65
	NF	97	-	Wuxi/China	65
	RO	48	2020	Castell-Platjad' Aro/Spain	63
	RO	100	-	Zagreb/Croatia	65
	NF	< 1.0	44	Jeolla/South Korea	66
	RO	< 1.0	44	Jeolla/South Korea	66
ROX	UF	0	221	Beijing/China	67
	RO	19	49	Castell-Platja d' Aro/Spain	63
	RO	100	-	Zagreb/Croatia	65
	UF	23	129	Beijing/China	67
AZI	RO	100	-	Zagreb/Croatia	65
	RO	23	118	Castell-Platja d' Aro/Spain	63
TYL	UF	2	6.42	Beijing/China	67
SPI	UF	0	7.46	Beijing/China	67
JOS	UF	6	0.86	Beijing/China	67

Natural wastewater treatment

Natural treatment systems, such as CW and SP are used for wastewater treatment. This treatment is an alternative wastewater treatment system that reproduces the processes of removing contaminants which occur in natural wetlands and ponds. Removal efficiencies of the natural wastewater treatment related to macrolides are presented in Table 12. Studies have shown that natural treatment of antibiotics has shown a strong dependency on the specific wastewater treatment process and was higher in summer than in winter. It indicates the vital role of biological degradation, removal efficiency, and associated ecological risk assessment^{52, 80, 81}. The results showed that the removal efficiencies of AZI, CIP, and SMZ were

78.8%, 23%, and 17.6% in winter and 80.9%, 1.5%, and -30.6 in summer, respectively (Tezmant WWTP-Egypt). The reason for the negative removal percentage of SMZ in summer was transmutation of N₄-acetyl sulfamethoxazole (SMZ metabolite, 43% in the excreted urine) to the parent compound of sulfamethoxazole.

Among the numerous important factors, temperature may play an important role in the removal of antibiotics in WWTFs, which is closely related to microbial activity and growth rate. However, studies have shown inconsistent results. In brief, higher and more stable removals of the macrolides have been achieved in summer in both AS and CW processes. Considering the significant change in the influent concentrations of ROX, its

removals by CW in summer ranged from 60% to 98%, while some negative removals have been observed in winter. The removal of micropollutants by CW is a result of complex Physico-chemical and microbial interactions, including substrate sorption, plant uptake, and biological degradation⁸². Apart from the poor

biological degradation activity in winter, both desorption of substrate-bound compounds and the potential cleavage of conjugates in winter can cause negative removals^{83, 84}. Therefore, better removals have been achieved in the AS process in summer and winter seasons and the CW process in summer.

Table 12: Removal of macrolides in municipal wastewater treatment plants using natural processes

Macrolides	Treatment processes		Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	CW1	Typha-FM-SF	22	250 ± 84	Leon/Spain	80
	CW2	Typha-FW-SF	32			
	CW3	Typha-FW-SSF	39			
	CW4	Unplanted-FW-SSF	50			
	CW5	Phragmites-FM-SF	11			
	CW6	Phragmites-SSF	31			
	CW7	Unplanted-SSF	32			
	CW		81	650	Eastern China	52
	SP		78	700	Eastern China	52
ERY-H2O	CW1	Typha-FM-SF	0	56 ± 26	Leon/Spain	80
	CW2	Typha-FW-SF	0			
	CW3	Typha-FW-SSF	0			
	CW4	Unplanted-FW-SSF	0			
	CW5	Phragmites-FM-SF	0			
	CW6	Phragmites-SSF	64			
	CW7	Unplanted-SSF	0			
ERY	CW			340	Eastern China	52
	SP			190	Eastern China	52
ROX	CW			250	Eastern China	52
	SP			280	Eastern China	52

Advanced treatment

Advanced wastewater treatment is any process that decreases the level of pollutants in wastewater that is available through conventional secondary or biological treatment. Table 13 shows the removal of macrolides in municipal wastewater using advanced treatment. According to research studies, chlorination treatment has shown the highest efficiency^{41, 85}. On the other hand, studies have shown different results for UV

treatment to remove macrolides in municipal wastewater. The removals by UV treatment for CLA (63%), ERY-H₂O (52.5%), TLY (60%), ROX (20.8%), and AZI (29.7%) were reported with high efficiency^{53, 68, 86}. UV treatment showed low efficiency for OLE in municipal wastewater^{85, 86}. It seems that the removal efficiency of UV treatment depends on the structure of the macrolide and the amount of them in municipal wastewater.

Table 13: Removal of macrolides in municipal wastewater treatment plants using advanced processes

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	pre-UV	63	319	Varese/Italy	85
	post-UV	0			
	UV	86.9	> 100	Wuxi/China	41
	UV	9	775	Japan	86
ERY-H ₂ O	CLO	63.7	-	Stanley/Hong Kong	53
	pre-UV	0	12	Varese/Italy	85
	post-UV	0			
	DI	24	-	Stanley/Hong Kong	53
	UV	52.5	60	Wuxi/China	41
	UV	9	275	Japan	86
ROX	CLO	55.3	-	Stanley/Hong Kong	53
	DI	18	-	Stanley/Hong Kong	53
	UV	15	40	Guangdong/China	39
	UV	20.8	> 103	Wuxi/China	41
AZI	UV	29.7	232.5-876.9	Wuxi/China	41
	UV	5	102	Japan	86
TYL	UV	60	4.0 ± 3.0	Milan/Italy	85
SPI	pre-UV	25	603	Varese/Italy	85
SPI	post-UV	17	603	Varese/Italy	85
LIN	pre-UV	37	9.7	Varese/Italy	85
	post-UV	0			
OLE	pre-UV	0	2.2	Varese/Italy	85
	post-UV	0			

Combined processes of treatment

One of the great challenges of researchers is to use solutions to improve the performance of wastewater treatment plants to remove residual pharmaceuticals in the wastewater, especially antibiotics. The presence of antibiotics in wastewater over time causes microorganisms to become resistant to these drugs. The most important step in the development of a wastewater treatment plant is to choose a process that, in addition to having economic and proper efficiency is appropriate with the environmental and climatic conditions. The results indicated that in combined processes a high efficiency of removal was obtained; therefore, researchers use a combination of various treatments. Many studies have used primary, secondary, and tertiary processes to remove macrolides from municipal wastewater⁸⁷⁻⁹⁰.

In the first stage, under anaerobic conditions, a three-series chamber ABR was used, while in the second stage, an aerobic activated sludge with a settler was applied. Lin et al.⁸⁷ demonstrated that there were many pharmaceuticals in influents of WWTPs, and the ST processes applied by the WWTPs are variably and inadequately effective in removing numerous pharmaceutical contaminants from influent wastewater. Researchers have shown that synergistic effects were in the in situ O₃, CMF, and BAC processes which were effective in removing almost all kinds of pollutants⁵⁵. Other studies indicated removal rates of above 95% for most of the macrolides using MBR with RO/NF³⁶. Table 14 presents several combined methods for removing macrolides from municipal wastewater plants in different countries.

Table 14: Removal of macrolides in municipal wastewater treatment plants using combined processes

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
CLA	O ₃ +CMF		173	Hikkaduwa/Sri Lanka	55
	S+ Sed+ G+ AS	44.5	~2200	4 WWTPs in Taipei/Taiwan	87
	MBR+ RO	100	368	China	36
	MBR+ NF	100			
	ST+ GAC+ UV	98			
	ST+ MBBR +TR + SF	91			
	ST+ Sed+ Oz/ BAF/ GAC+UV	99			
	PT+ SBR+ UV	96	-	Eastern United States	88
	AABR+ MBR+UV	100			
	PT +SBR+ CLO	18			
	PT+ AS+NAS+ CLO	24			
	SC + NaClO	0	50	Guangdong/China	39
	SC+ UV	15			
	RFDFs	66.2	>100	Wuxi/china	41
	RFDFs	85.2			
	SBR+A ₂ O+OD+MBR	52	~25	12 WWTPs/China	89
	GC + A ₂ O+ OD+ CAS+ MBR+ UV+ RFDF+ ClO ₂ + UF+ Oz+ CS	75	550.3	14 WWTPs/China	90
ERY	NF90	> 99.9			
	RO XLE	> 99.9	6080	Croatia	64
	NF270	75.88			
	MBR+RO	100	-	Zagreb/Croatia	65
	Pre- O ₃ + CMF+ BAC	97	390	Jindawanxiang/North China	91
	MBR+RO	100	20	China	36
	MBR-NF	98			
	S+Sed+ G+AS	43.8–100	~3000	4 WWTPs in Taipei/Taiwan	87
	ST+ GAC+UV	97			
	ST+ MBBR+ TS+ SF	97	-	Eastern United States	88
	ST + Sed+ Oz+ BAF, GAC + UV	98			
	PT+ SBR + UV	0			
	AABR+ GAC+UV	0			
	PT + SBR+ CLO	0			
	PT+ AS+ NAS+ CLO	0			
	PT + AS	39.11	254.24 ± 15.36	Southwest/China	51
	SBR + A ₂ O + OD + MBR	53	~250	12 WWTPs/China	89
	PT + AS + Anaerobic	0	470 ± 2.5	Tai Po/China	92
	PT+ BT	19	740 ± 14	Shatin/China	92
		9	590 ± 0.7	Stonecutter's island/China	92
	AS + OD + AL	43.8-100	3900	Wisconsin/USA	93
	CAS + MF	10	2600	Gwinnett/USA	77
	BT+ phosphorus precipitation	-	200	Nancy/France	94
	GC + A ₂ O/MBBR+ OD +A ₂ O/CAS+CAS/MBR+ UV+ RFDF + ClO ₂ + UF + O ₃ + CS	78	1151.6	14 WWTPs/China	90
	Primary +AS	39	200	China	50
ROX	PT + CAS	39.11	254.24 ± 15.36	Southwest/china	51
	Pre- O ₃ + CMF + BAC	96	-	Altenrhein, Switzerland	40
	O ₃ +CMF	95	175	Jindawanxiang/North China	91
	MBR-RO	100	79	China	36
	MBR-NF	97			
	PT + CAS	11.7	404.0 ± 34.2	Southwest/China	51

Macrolides	Treatment processes	Removal (%)	Influent (ng/L)	Location (City/Country)	Ref.
	SBR+ A ₂ O + OD+ A ₂ O /MBR	48	~80	12 WWTPs/China	89
	AS+ OD+ AL	67	1500	Wisconsin/USA	93
	GC+ A ₂ O /MBBR+ OD+ A ₂ O /CAS+ CAS/MBR+ UV+ RFDF+ ClO ₂ + UF+ O ₃ + CS	67	1035.7	14 WWTPs/China	90
	MF/RO		10	Brisbane/Australia	13
AZI	Pre- O ₃ + CMF+ BAC	99	40	Jindawanxiang/North China	91
	O ₃ +CMF	99			
	MBR-RO	98	1410	China	36
	MBR-NF	97			
	ST + GAC + UV	100	-	Eastern United States	88
	ST + MBBR+ TS + SF	96			
	ST + Sed+ O ₃ , BAF+ GAC + UV	100			
	PT + SBR+ UV	0			
	AABR + MBR+ UV	0			
	PT + SBR + CLO	60			
	PT +AS + NAS + CLO	45			
	PT + CAS	50.55	362.5 ± 21.7	Southwest/China	51
	SBR + A ₂ O +OD+ A ₂ O /MBR	45	~450	12 WWTPs/China	89
	GC + A ₂ O /MBBR + OD + A ₂ O /CAS + CAS/MBR + UV + RFDF + ClO ₂ + UF + O ₃ + CS	51	1687.2	14 WWTPs/China	90
	NF90	> 99.9	-	Croatia	64
	RO XLE	> 99.9			
	NF270	80.08			
TYL	AS + OD + AL	50	1500	Wisconsin/USA	93
	MF/RO		1	Brisbane/Australia	13
	PT + AS	100	65	China	50
SPI	AS+ AOPs	91	Up to 30000	Campania/Italy	95
	RE-PST	0.3			
	RE-SST	24.7	380	Al Ain /United Arab Emirates	96
	RE-FE	24.7			

Discussion

This review highlighted the occurrence of macrolides in municipal wastewater influent and the removal efficiency by various processes. Municipal wastewater is the remnants and discharges of mainly local, urban, or industrial liquids. The method of collection and disposal in each area depends on local information of the environment^{8, 17}. The negative effects of medicines, especially antibiotic macrolides, on natural ecosystems and their entry into the environmental cycle are a major challenge that has occupied the purposes of many scientists. Meantime, municipal wastewater treatment plant outlets are the most important sources of medicine contaminants entering the environment. Therefore, it is important to study the concentration of

macrolides in these units and the rate of their removal during various treatment processes. The performance of wastewater treatment systems for these materials has been reported from high removal to negative removal. This review investigated scientists' studies on the removal of macrolides from municipal wastewater in different countries, including China, Japan, Germany, Iran, Italy, South Korea, France, Spain, Croatia, Singapore, USA, Australia, Taiwan, Sri Lanka, United Arab Emirates, and Switzerland. A variety of technologies have been used to determine the removal of macrolides from municipal wastewater at the whole or pilot scale. In most studies, different concentrations of ROX, ERY, AZI, and CLA macrolides have been reported in municipal wastewater, showing a more prominent application

of these macrolides among humans. Based on the occurrence, the concentration of other macrolides has been reported to be low or undetectable. The OLE macrolide was reported in Varese municipal wastewater in Italy, which has not shown any degradation by UV radiation, indicating the stability of the structure OLE against ultraviolet radiation⁸⁵.

Among the multiple treatment techniques, the combined processes of treatment technologies, such as AABR with membrane bioreactor/UV, NF/RO, sedimentation with Oz/BAF/GAC and UV, Pre- O₃/CMF with BAC, ST with tertiary treatment (Flocculation+ Sed, Oz, BAF, GAC, and UV), primary and secondary effluent of activated sludge processes completely remove macrolides from wastewater^{40, 50, 88, 91}. MBRs have shown good removal efficiencies on a wide range of different compounds. MBR-RO and MBR-NF have been widely used in the removal of all macrolides in municipal wastewaters and have shown high efficiency. The highest removal percentage was reported by the combination of MBR-RO in China³⁶. The combination of processes is effective in removing macrolides in municipal wastewater. Research has shown that these processes have the highest efficiency in removing CLA, ERY-H₂O, ROX, and AZI.

Despite the activity in this field of research, there are still many gaps between using effective and economical solutions to remove this group of antibiotics in municipal wastewater. However, it seems that due to using different patterns among different countries, finding economic and cost-effective solutions with high efficiency to remove these antibiotics depends on the conditions under which they are implemented, and each region should find the best process according to its capacity.

Conclusion

Different studies have shown that the removal efficiency of macrolides during wastewater treatment processes varies and is essentially dependent on a combination of macrolides physicochemical properties, location of municipal

wastewater, and the operating conditions of the treatment systems. The molecular structure of macrolides, on the one hand, and its load-bearing capacity, on the other, has led to the advantage of biological treatment over other treatments for their municipal wastewater treatment. Studies have shown that the removal of the CLA, ERY, ROX, and AZI during sand filtration has been generally inefficient. The removal percentage range of macrolides by the physical method was reported to be 0-33%. Also, removal efficiency of above 80% has been reported using a combination of Oz and SF with activated sludge treatment, and removal efficiency of 100% using MBR-RO. Predict the behavior of macrolides during the purification process is a challenging issue; therefore, different removal efficiencies have been reported in various studies.

Acknowledgements

The authors would like to thank Ahvaz Jundishapur University of Medical Sciences for supporting the current study.

Funding

This study was done without receiving funding.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

This is an Open-Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt, and build upon this work for commercial use.

References

1. Hamscher G, Beate P, Heinz N. A survey of the occurrence of various sulfonamides and tetracyclines in water and sediment samples originating from aquaculture systems in Northern Germany in summer 2005. *Archiv Fur Lebensmittelhygiene*. 2006;54(7):97-101.
2. Schwartz T, Wolfgang K, Bernd J, et al. Detection of antibiotic-resistant bacteria and their resistance genes in wastewater, surface water, and drinking

- water biofilms. *FEMS Microbiol Ecol.* 2003;43(3): 325-35.
3. Conkle J, Charisma L, John R, et al. Competitive sorption and desorption behavior for three fluoroquinolone antibiotics in a wastewater treatment wetland soil. *Chemosphere.* 2010;80(11):1353-9.
 4. Kolpin D, Edward T, Micheal T, et al. Pharmaceuticals, hormones and other organic wastewater contaminants in US streams, 1999-2000: a national reconnaissance. *Environ Sci Technol.* 2002;36(6):1202-11.
 5. Allen H, Luke A, Jitsupang R, et al. Functional metagenomics reveals diverse β -lactamases in a remote Alaskan soil. *ISME J.* 2009;3:243-51.
 6. Angela B, Daniel D, Diana S. Occurrence of sulfonamide antimicrobials in private water wells in Washington County, Idaho, USA. *Chemosphere.* 2006;64(11):1963-71.
 7. Ternes T. Occurrence of drugs in German sewage treatment plants and rivers. *Water Res.* 1998;32(11):3245-60.
 8. Eckenfelder WW. Industrial water pollution control. New York: Amazon; 2000.
 9. Kummerer K. Antibiotics in the aquatic environment-a review-Part I. *Chemosphere.* 2009;75(4):417-34.
 10. Tvrtko S, Senka T, Roko Z, et al. Assessment of toxicological profiles of the municipal wastewater effluents using chemical analyses and bioassays. *Ecotoxicol Environ Saf.* 2011;74(4):844-51.
 11. Diaz-Cruz M, Garcia-Galan M, Barcelo D. Highly sensitive simultaneous determination of sulfonamide antibiotics and one metabolite in environmental waters by liquid chromatography quadrupole linear ion trap-mass spectrometry. *Chromatogr A.* 2008;1193(2):50-9.
 12. Mirnasab MA, Hashemi H, Samaei MR, et al. Advanced removal of water NOM by pre-ozonation, Enhanced coagulation and bio-augmented granular activated carbon. *Int J Environ Sci Technol.* 2021;18:3143-52.
 13. Watkinson J, Murby E, Costanzo S. Removal of antibiotics in conventional and advanced wastewater treatment: Implications for environmental discharge and wastewater recycling. *Water Res.* 2007;41(18):4164-76.
 14. Hamscher G, Sczesny S, Hoper H, et al. Determination of persistent tetracycline residues in soil fertilized with liquid manure by high-performance liquid chromatography with electrospray ionization tandem mass spectrometry. *Anal Chem.* 2002;74(7):1509-18.
 15. Golet E, Irene X, Hansruedi S, et al. Environmental exposure assessment of fluoroquinolone antibacterial agents from sewage to soil. *Environ Sci Technol.* 2003;37(15):3243-9.
 16. Xiao Y, Chang H, Jia A, et al. Trace analysis of quinolone and fluoroquinolone antibiotics from wastewaters by liquid chromatography-electrospray tandem mass spectrometry. *J Chromatogr A.* 2008;1214(1-2):100-8.
 17. Kummerer K. Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks, Berlin: Springer-Verlag; 2001.
 18. Sun W, Xun Q, Jie G, et al. Mechanism and effect of temperature on variations in antibiotic resistance genes during anaerobic digestion of dairy manure. *Scientific Reports.* 2016;6:30237.
 19. Zhang Q, Yang W, Ngo H, et al. Current status of urban wastewater treatment plants in China. *Environ Int.* 2016;92-93:11-22.
 20. Hashemi H, Hajizadeh Y, Amin M, et al. Macro pollutants removal from compost leachate using membrane separation process. *Desalination Water Treat.* 2015;16: 7149-54.
 21. Kastelan-Macan M, Marijan A, Horvat M, et al. Water resources and waste water management in Bosnia and Herzegovina, Croatia and the State Union of Serbia and Montenegro. *Water policy.* 2007;9(3):319-43.
 22. Manvendra P, Rahul K, Kamal K, et al. Pharmaceuticals of emerging concern in aquatic systems: Chemistry, Occurrence, Effects, and Removal Methods. *Chem Rev.* 2019;119(6): 3510-673.
 23. Tong L, Eichhorn P, Pérez S, et al. Photodegradation of azithromycin in various aqueous systems under simulated and natural solar radiation: kinetics and identification of photoproducts. *Chemosphere.* 2011;83:340-8.

24. Sarmah AK, Meyer MT, Boxall AB. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. *Chemosphere*. 2006;65:725–59.
25. Ewa F, Joanna K, Adam S, et al. antimicrobial pharmaceuticals in the aquatic environment-occurrence and environmental implications. *Eur J Pharmacol*. 2020;866:172813.
26. Vestel J, Caldwell DJ, Constantine L, et al. Use of acute and chronic ecotoxicity data in environmental risk assessment of pharmaceuticals. *Environ Toxicol Chem*. 2016; 35:1201–12.
27. Minguez L, Pedelucq J, Farcy E, et al. Toxicities of 48 pharmaceuticals and their freshwater and marine environmental assessment in northwestern France. *Environ Sci Pollut Res*. 2016;23:4992–5001.
28. Isidori M, Lavorgna M, Nardelli A, et al. Toxic and genotoxic evaluation of six antibiotics on non-target organisms. *Sci Total Environ*. 2005; 346:87–98.
29. De Liguoro M, Cibir V, Capolongo F, et al. Use of oxytetracycline and tylosin in intensive calf farming: evaluation of transfer to manure and soil. *Chemosphere*. 2003;52:203–12.
30. Brain RA, Johnson DJ, Richards SM, et al. Effects of 25 pharmaceutical compounds to *Lemna gibba* using a seven-day static-renewal test. *Environ Toxicol Chem*. 2004;23:371–82.
31. Guo J, Selby K, Boxall A. Comparing the sensitivity of chlorophytes, cyanobacteria, and diatoms to major-use antibiotics. *Environ Toxicol Chem*. 2016;35:2587–96.
32. Herbert H. Introduction to the macrolide antibiotics. Springer; 2002.
33. Bekele L, Getachew G. Application of different analytical techniques and microbiological assays for the analysis of macrolide antibiotics from pharmaceutical dosage forms and biological matrices. *ISRN Analytical Chemistry*. 2012;12:1-17.
34. Wegst-Uhrich SR, Divina N, Zimmermann L, et al. Assessing antibiotic sorption in soil: a literature review and new case studies on sulfonamides and macrolides. *Chem Cent J*. 2014;8(5):5.
35. Biljana A, Jill B, Ana C, et al. 16-Membered Macrolide Antibiotics: a Review. *Int J Antimicrob Agents*. 2018;51(3):283-98.
36. Yonggang W, Xu W, Mingwei L, et al. Removal of Pharmaceutical and Personal Care Products (PPCPs) from Municipal Waste Water with Integrated Membrane Systems, MBR-RO/NF. *Int J Environ Res Public Health*. 2018;15(2):269.
37. Hamed M, Sabzali A, Gholami M, et al. Comparative study of SBR and extended aeration activated sludge processes in the treatment of high-strength wastewaters. *Desalination*. 2012;287:109–115.
38. Norihide N, Hiroyuki S, Ayako M, et al. Removal of selected pharmaceuticals and personal care products (PPCPs) and endocrine-disrupting chemicals (EDCs) during sand filtration and ozonation at a municipal sewage treatment plant. *Water Research*. 2007;41(19):4373-82.
39. Li-Jun Z, Guang-Guo Y, Shan L, et al. Occurrence and fate of eleven classes of antibiotics in two typical wastewater treatment plants in South China. *Sci Total Environ*. 2013;(452–453):365–76.
40. Anke Göbel, Christa M, Adriano J, et al. Fate of sulfonamides, macrolides, and trimethoprim in different wastewater treatment technologies. *Sci Total Environ*. 2007;372(2-3):361–71.
41. Xiangjuan Y, Zhimin Q, Weiwei B, et al. Distribution, mass load and environmental impact of multiple-class pharmaceuticals in conventional and upgraded municipal wastewater treatment plants in East China. *Environ Sci Process Impacts*. 2015;17:596-605.
42. Hanmin Z, Pengxiao L, Yujie F, et al. Fate of antibiotics during wastewater treatment and antibiotic distribution in the effluent-receiving waters of the Yellow Sea, northern China. *Mar Pollut Bull*. 2013;73(1):282–90.
43. Pawel K, Maria C, Popi K, et al. Performance of secondary wastewater treatment methods for the removal of contaminants of emerging concern implicated in crop uptake and antibiotic resistance

- spread: A review. *Sci Total Environ*. 2019;648:1052–81.
44. Nilesh TN. *Industrial Wastewater Treatment, Recycling, and Reuse*. Elsevier Ltd. 2014.
 45. Mittal A. *Biological wastewater treatment*. *Water Today*. 2011;23:32–44.
 46. Sarin V. *Wastewater Treatment Using Membrane Bio Reactor*. PhD Thesis, IIT. 2013.
 47. Judd S, the MBR Book–Principles and Application of Membrane Bioreactors. In: *Principles and Application of Membrane Bioreactors in Water and Wastewater*. Elsevier. 2011.
 48. Meghdad P, Samira K, Mehdi K. A comparison between extended aeration sludge and conventional activated sludge treatment for removal of linear alkylbenzene sulfonates (Case study: Kermanshah and Paveh WWTP). *Desalination Water Treat*. 2014;52:4673–80.
 49. Eyal S, Indal D, Yelena G, et al. The use of RO to remove emerging micropollutants following CAS/UF or MBR treatment of municipal wastewater. *Desalination*. 2011;273(1):142–7.
 50. Xiaosong C, Michael T, Xiaoyun L, et al. Determination of antibiotics in sewage from hospitals, nursery and slaughter house, wastewater treatment plant and source water in Chongqing region of Three Gorge Reservoir in China. *Environmental Pollution*. 2010;158(5): 1444–50.
 51. Qing Y, Xu G, Lei H, et al. Occurrence and fate of pharmaceutically active compounds in the largest municipal wastewater treatment plant in Southwest China: Mass balance analysis and consumption back-calculated model. *Chemosphere*. 2014;99:160–70.
 52. Huiyu D, Xianguan Y, Weidong W, et al. Occurrence and removal of antibiotics in ecological and conventional wastewater treatment processes: A field study. *Journal of Environmental Management*. 2016;178:11–9.
 53. Bing L, Tong Z. Mass flows and removal of antibiotics in two municipal wastewater treatment plants. *Chemosphere*. 2011;83(9):1284–9.
 54. Valiparambil P, Prabhasankar D, Joshua D, et al. Removal rates of antibiotics in four sewage treatment plants in South India. *Environ Sci Pollut Res*. 2016;23(9):8679–85.
 55. Dilanka ND, Xin L, Guangcai Z, et al. Antibiotics in two municipal sewage treatment plants in Sri Lanka: Occurrence, consumption and removal efficiency. *Emerg Contam*. 2019;5: 272–8.
 56. Emma G, Juan S, Roque S, et al. Occurrence and removal of pharmaceuticals in wastewater treatment plants at the Spanish Mediterranean area of Valencia. *Chemosphere*. 2012;87(5):453–62.
 57. Conrad M, Norbert G, Sara S, et al. Mass flow of antibiotics in a wastewater treatment plant focusing on removal variations due to operational parameters. *Sci Total Environ*. 2015;538:779–88.
 58. Ivan S, Senka T, Marijan A. Occurrence and fate of dissolved and particulate antimicrobials in municipal wastewater treatment. *Water Res*. 2013;47(2):705–14.
 59. Junwon P, Changsoo K, Youngmin H, et al. Distribution and removal of pharmaceuticals in liquid and solid phases in the unit processes of sewage treatment plants. *Int J Environ Res Public Health*. 2020;17:687.
 60. Weihua W, Wanfeng Z, Hong L, et al. Occurrence and fate of typical antibiotics in wastewater treatment plants in Harbin, North-east China. *Front Environ Sci Eng*. 2019;13(3):34.
 61. Ngoc HT, Hongjie C, Martin R, et al. Occurrence and removal of multiple classes of antibiotics and antimicrobial agents in biological wastewater treatment processes. *Water Research*. 2016;104:461–72.
 62. Toshiba Water Solutions Private Limited. *Sequencing Batch Reactors*. Place: Haryana, INDIA. Available from: <https://www.toshiba-water.com/sequencing-batch-reactors.html>. [Cited 11 September 2021]
 63. Davor D, Mertixell G, Sara R, et al. Removal of emerging contaminants from municipal wastewater with an integrated membrane system, MBR–RO. *J Hazard Mater*. 2012;239–240:64–9.
 64. Racar M, Dolar D, Karadakic K, et al. Challenges of municipal wastewater reclamation for irrigation by MBR and NF/RO: Physico-chemical and microbiological parameters, and

- emerging contaminants. *Sci Total Environ.* 2020;20:31472-8.
65. Ivan S, Martin M, Helena K, et al. Removal of antimicrobials using advanced wastewater treatment. *J Hazard Mater.* 2011;192(1):319-28.
 66. Sang D, Jaeweon C, In SK, et al. Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters. *Water Research.* 2007;41(5):1013-1021.
 67. Wenhui L, Yali S, Lihong G, et al. Occurrence and removal of antibiotics in a municipal wastewater reclamation plant in Beijing, China. *Chemosphere.* 2013;92(4):435-44.
 68. Tommaso G, Wan-Ting C, Peng L. et al. Chemical characterization and anaerobic biodegradability of hydrothermal liquefaction aqueous products from mixed-culture wastewater algae. *Bioresour Technol.* 2015;178:139-46.
 69. Kasturi D, Ming-Yi L, Webber W, et al. Removal of pharmaceuticals and organic matter from municipal wastewater using two-stage anaerobic fluidized membrane bioreactor. *Bioresour Technol.* 2014;165:42-9.
 70. Yorkor B, Momoh Y. A review of anoxic wastewater treatment: an overlooked aspect in wastewater treatment in Nigeria. *American Journal of Water Resources.* 2019;7(4):136-45.
 71. Xiangjuan Y, Zhimin Q, Weiwei B, et al. Rapid detection of multiple class pharmaceuticals in both municipal wastewater and sludge with ultra-high performance liquid chromatography tandem mass spectrometry. *Journal of Environmental Sciences.* 2014;26(9):1949-59.
 72. Ghosh G, Hanamoto S, Yamashita N, et al. Antibiotics removal in biological sewage treatment plants. *Pollution.* 2016;2(2):131-9.
 73. Mirzaei R, Mesdaghinina A, Hoseini S, et al. Antibiotics in urban wastewater and rivers of Tehran, Iran: Consumption, mass load, occurrence, and ecological risk. *Chemosphere.* 2018;18(221):32529-3.
 74. Mirzaei R, Yunesian M, Nasserli S, et al. Occurrence and fate of most prescribed antibiotics in different water environments of Tehran, Iran. *Sci Total Environ.* 2018;619-620: 446-59.
 75. Sousa MA, Goncalves C, Vilar JP, et al. Suspended TiO₂-assisted photocatalytic degradation of emerging contaminants in a municipal WWTP effluent using a solar pilot plant with CPCs. *Chem Eng J.* 2012;198-199:301-9.
 76. Nuno M, Jose S, Goncalo M, et al. Photocatalytic ozonation of urban wastewater and surface water using immobilized TiO₂ with LEDs: Micropollutants, antibiotic resistance genes and estrogenic activity. *Water Research.* 2016;94:10-22.
 77. Xin Y, Riley F, Howard SW, et al. Occurrence and removal of pharmaceuticals and personal care products (PPCPs) in an advanced wastewater reclamation plant. *water research.* 2011;45(16): 5218-28.
 78. Deegan AM. Pharmaceuticals in industrial wastewater and their removal using photo-Fenton 's oxidation, Dublin City University: Ireland. 2011.
 79. Van Nieuwenhuijzen AF, Van der Graff J, Kampschreur M, et al. Particle related fractionation and characterization of municipal wastewater. *Water Sci Technol.* 2004;50(12): 125-32.
 80. María H, Guido F, Michael P, et al. Removal of antibiotics from urban wastewater by constructed wetland optimization. *Chemosphere.* 2011;83(5): 713-9.
 81. Heba AY, Hamada MM, Maha M, et al. Seasonal occurrence, removal efficiency and associated ecological risk assessment of three antibiotics in a municipal wastewater treatment plant in Egypt. *Environmental Nanotechnology. Remote Monitoring and Management.* 2019;12: 100239.
 82. Hussain SA, Prasher SO, Patel RM. Removal of ionophoric antibiotics in free water surface constructed wetlands. *Ecol Eng.* 2011;41: 13-21.
 83. Clara MB, Strenn O, Gans E, et al. Removal of selected pharmaceuticals, fragrances and endocrine disrupting compounds in a membrane bioreactor and conventional wastewater treatment plants. *Water Res.* 2005;39:4797-807.

84. Lindberg RH, Wennberg P, Johansson MI. Screening of human antibiotic substances and determination of weekly mass flows in five sewage treatment plants in Sweden. *Environ Sci Technol*. 2005;39:3421-9.
85. Ettore Z, Sara C, Renzo B, et al. Source, occurrence and fate of antibiotics in the Italian aquatic environment. *J Hazard Mater*. 2010;179(1-3):1042-8.
86. Ilho K, Naoyuki Y, Hiroaki T. Performance of UV and UV/H₂O₂ processes for the removal of pharmaceuticals detected in secondary effluent of a sewage treatment plant in Japan. *J Hazard Mater*. 2009;166(2-3):1134-40.
87. Angela Yu-Chen L, Tsung-Hsien Y, Shik K. Removal of pharmaceuticals in secondary wastewater treatment processes in Taiwan. *J Hazard Mater*. 2009;167(1-3):1163-9.
88. Luisa F, Rachel AM, Irvin JH, et al. Assessing pharmaceutical removal and reduction in toxicity provided by advanced wastewater treatment systems. *Environ Sci Water Res Technol*. 2020;6(1):62.
89. Hou-Qi L, James CWL, Wen-Wei L, et al. Spatial distribution and removal performance of pharmaceuticals in municipal wastewater treatment plants in China. *Sci Total Environ*. 2017;586:1162-9.
90. Weiwei B, Bing Z, Xiangjuan Y, et al. Occurrence, removal and risk of organic micropollutants in wastewater treatment plants across China: Comparison of wastewater treatment processes. *Water Research*. 2018;130:38-46.
91. Kai Z, Zheng-Hua Z, Hao W, et al. Synergistic effects of combining ozonation, ceramic membrane filtration and biologically active carbon filtration for wastewater reclamation. *J Hazard Mater*. 2020;382:121091.
92. Gulkowska A, Leung HW, So MK, et al. Removal of antibiotics from wastewater by sewage treatment facilities in Hong Kong and Shenzhen, China. *Water Research*. 2008;42(1-2):395-403.
93. Karthikeyan KG, Meyer MT. Occurrence of antibiotics in wastewater treatment facilities in Wisconsin, USA. *Sci Total Environ*. 2006;361:196-207.
94. Laure P, Jean-Francois M, Marie-Noelle P, et al. Occurrence of eight household micropollutants in urban wastewater and their fate in a wastewater treatment plant. Statistical evaluation. *Sci Total Environ*. 2014;481:459-68.
95. Lofrano G, Libralato G, Casaburi A, et al. Municipal wastewater spiramycin removal by conventional treatments and heterogeneous photocatalysis. *Sci Total Environ*. 2018;624:461-9.
96. Maraqa MA, Meetani M, Alhalabi AM. Effectiveness of conventional wastewater treatment processes in removing pharmaceutically active compounds. 5th International Conference on Advances in Environment Research. 13-15 August 2019.