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

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A R T I C L E I N F O

REVIEW ARTICLE

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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.

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## Introduction

Pharmaceutical compounds which are widely used for different purposes today are detected in natural surface water, groundwater, and wastewater [1]. 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 quinolones [4-6]. 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 plants [8-10]. 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 μg/L level in natural water [11] and wastewater [12,13], and μg/kg to mg/kg level in soil [14] and sludge [15]. 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 concern [18]. Municipal wastewater is an important source of organic contaminants in the aquatic environment [19]. 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 waste [22]. 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 h [23], Tylosin is 9.5–54 days, and for Erythromycin is < 17 days [24]. 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 conditions [25]. 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.



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**Table 1:** Toxicity values for macrolides concerning aquatic organisms [25]

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



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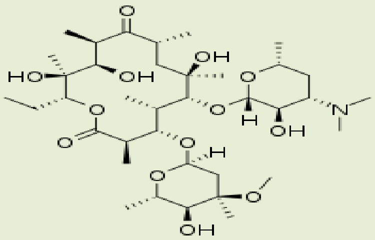
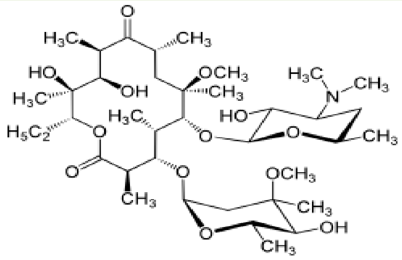
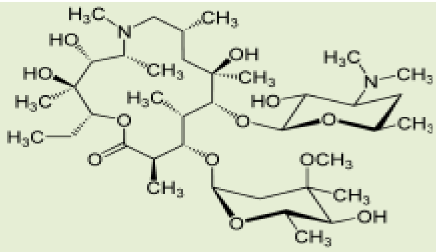
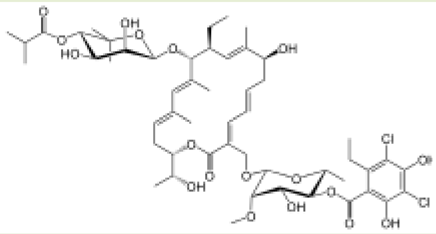
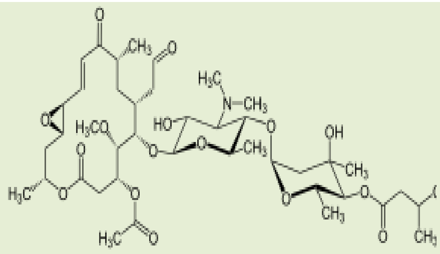
processes, physicochemical treatment, natural treatment, advanced treatment, and combination of treatment processes. The study examined these groups and their effects on the removal of macrolides reported in municipal wastewater.

### *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 solvents [32-35] (Table 2).

**Table 2:** Macrolides, physicochemical properties, and structures[32-35]

| 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 |



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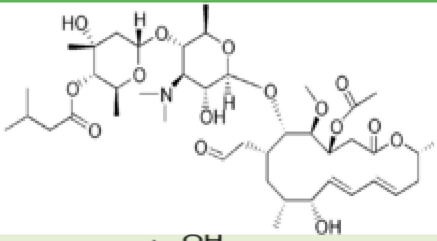
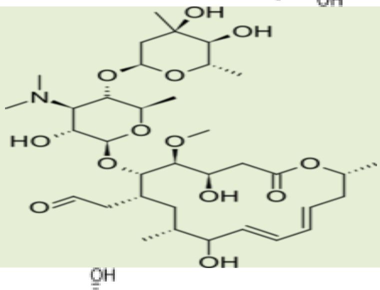
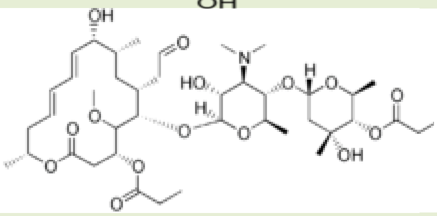
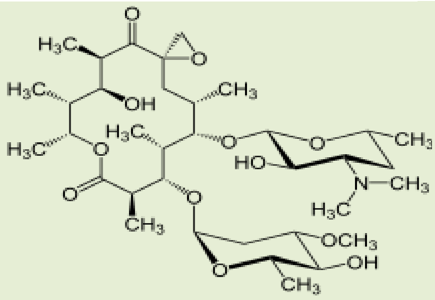
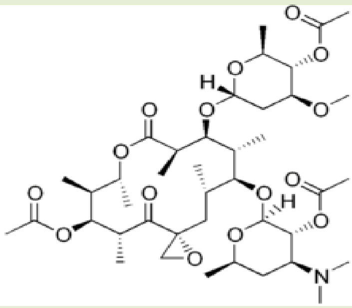
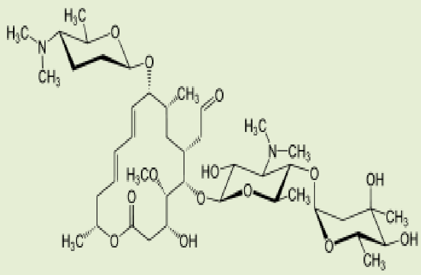
| Compound | Acronym | Structure | CAS number | Molecular weight (g/mol) |
|---|---|---|---|---|
| Josamycin | JOS |  | 16846-24-5 | 828.006 |
| Kitasamycin | KIT |  | 39405-35-1 | 701.84 |
| Midecamycin | MID |  | 35457-80-8 | 813.968 |
| Oleandomycin | OLE |  | 3922-90-5 | 687.858 |
| Solithromycin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



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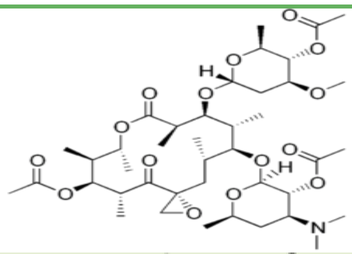
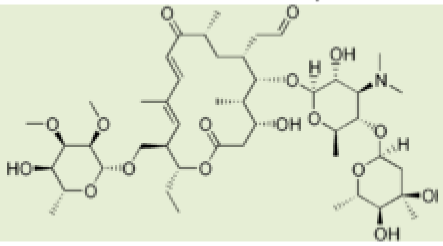
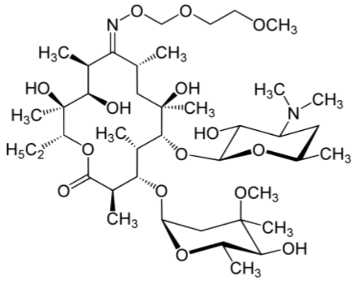
| Compound | Acronym | Structure | CAS number | Molecular weight (g/mol) |
|---|---|---|---|---|
| Troleandomycin | TRO |  | 2751-09-9 | 813.968 |
| Tylosin | TLY |  | 1401-69-0 | 916.10 |
| Roxithromycin | ROX |  | 80214-83-1 | 837.047 |

***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 treatments [17]. 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; $UV/TiO_2$; $UV/H_2O_2$; 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







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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 AZI [40]. 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-$H_2O$ | 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 pollutants[43]. 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 replication[44]. 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 $NO_3$ nitrogen is converted to molecular nitrogen gas in the absence of oxygen[45].

### *Aerobic treatment*

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



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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-$H_2O$, 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-$H_2O$, 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-$H_2O$ in two wastewater treatment plants (WWTPs) of Hong Kong. The mean removal efficiencies using activated sludge process for ROX and ERY-$H_2O$ 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].


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**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-$H_2O$ | 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 | STP1 Karnataka/ India | 54 |
| | EA | 0 | 59 | STP1 Karnataka/ India | 54 |
| | EA | 31 | 6 | STP1 Karnataka/ India | 54 |
| | EA | 0 | 28 | STP2 Karnataka/ India | 54 |
| | EA | 0 | 26 | STP2 Karnataka/ India | 54 |
| | EA | 100 | 7 | STP2 Karnataka/ India | 54 |
| 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 |
| | SBR | 24 | 290 | Gyeonggi/South Korea | 59 |
| AZI | 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 type [62]. 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-$H_2O$, ROX, and AZI in two municipal wastewater treatment plants located in Wuxi City, East China. The analysis showed that a maximum


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concentration of CLA, ERY- $H_2O$, 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- $H_2O$ | 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 macrolides [59]. 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 $m^2$. 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- $H_2O$ 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- H2O | 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 |
| | MBR | 59 | 290 | Gyeonggi/South Korea | 59 |
| ROX | 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 filters [68]. 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-$H_2O$ 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-$H_2O$ | 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 effluent [70]. 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 Li [67] 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 × $10^5$ $m^3$/d, 44.7 × $10^5$ kg/d, and 3, respectively. Wenhui Li [67] 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



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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 $A_2O$ treatment. Aerobic tanks may be coupled with anoxic or anaerobic tanks to give biological nutrient removal. The $A_2O$ 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 $A_2O$ 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 $A_2O$ treatment process. The results indicated that the mean concentrations of anaerobic sludge, anoxic sludge, oxic sludge, and return sludge for ERY-$H_2O$ 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 | $A_2O$ | 15 | 850 | Gyeonggi/South Korea | 59 |
| | $A_2O$ | 51 | 35.8 | Harbin/China | 60 |
| | AO | 8.7 | 35.8 | Harbin/China | 60 |
| | $A_2O$ | 55 | ~1750 | Kyoto/Japan | 72 |
| | $A_2O$ | 56 | ~650 | Beijing/China | 72 |
| | $A_2O$ | 95 | 550 | China | 71 |
| | AO | 85 | ~5000 | Shiga/Japan | 72 |
| | $A_2O$ | 3.6 | > 100 | Wuxi/china | 41 |
| ERY-$H_2O$ | $A_2O$ | 80 | 500 | China | 71 |
| | $A_2O$ | 13 | 10 | Wuxi/china | 41 |
| | $A_2O$ | 53.58 | 66.3-159.5 | Tehran/Iran | 73 |
| | $A_2O$ | 67.8 | 159.5 | Tehran/Iran | 74 |
| ROX | $A_2O$ | 7 | 290 | Gyeonggi/South Korea | 59 |
| | $A_2O$ | 25 | ~100 | Kyoto/Japan | 72 |
| | $A_2O$ | 13.6 | > 103 | Wuxi/China | 41 |
| | AO | 69 | 500 | Harbin/China | 60 |
| | $A_2O$ | 72 | 500 | China | 71 |
| | AO | 73 | ~213 | Shiga/Japan | 72 |
| | $A_2O$ | 0 | 500 | Harbin/China | 60 |
| | $A_2O$ | 27 | ~800 | Beijing/China | 72 |


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| Macrolides | Treatment processes | Removal (%) | Influent (ng/L) | Location (City/Country) | Ref. |
|---|---|---|---|---|---|
| AZI | $A_2O$ | 60 | 28 | Harbin/China | 60 |
| | AO | 0 | 28 | Harbin/China | 60 |
| | $A_2O$ | 40 | ~250 | Kyoto/Japan | 72 |
| | $A_2O$ | 13 | ~280 | Beijing/China | 72 |
| | AO | 95 | ~5500 | Shiga/Japan | 72 |
| | $A_2O$ | 17.5 | 232.5-876.9 | Wuxi/China | 41 |
| | $A_2O$ | 66.6 | 43.3 | Tehran/Iran | 73 |

***Advanced Oxidation Processes (AOP$_s$)***

AOPs include photo Fenton ($UV/H_2O_2/Fe^{2+}$), $UV/H_2O_2$, solar photo Fenton, UV- Photolysis, Oz, US, Oxidation, and Fenton Processes ($H_2O_2/Fe^{2+}$). 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 investigated[67] 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 $TiO_2$ 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 enhancement[76].

**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 |
| | Oz | 63 | 2600 | Gwinnett/USA | 77 |
| ROX | 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 |



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***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 ERY[66]. 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 itself [63].

**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 |
| | UF | 0 | 221 | Beijing/China | 67 |
| | RO | 19 | 49 | Castell-Platja d'Aro/Spain | 63 |
| ROX | 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 $N_4$–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 degradation [82]. 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 | | | |
| | CW2 | Typha-FW-SF | 32 | 250 ± 84 | Leon/Spain | 80 |
| | 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 | | | |
| | CW2 | Typha-FW-SF | 0 | | | |
| | CW3 | Typha-FW-SSF | 0 | | | |
| | CW4 | Unplanted-FW-SSF | 0 | 56 ± 26 | Leon/Spain | 80 |
| | 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-$H_2O$ (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.



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**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-$H_2O$ | 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 wastewater[87-90]. 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 $O_3$, CMF, and BAC processes which were effective in removing almost all kinds of pollutants[55]. Other studies indicated removal rates of above 95% for most of the macrolides using MBR with RO/NF [36]. Table 14 presents several combined methods for removing macrolides from municipal wastewater plants in different countries.



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**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 | - | Eastern United States | 88 |
| | ST+ MBBR +TR + SF | | 91 | | | |
| | ST+ Sed+ Oz/ BAF/ GAC+UV | | 99 | | | |
| | PT+ SBR+ UV | | 96 | | | |
| | 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+$A_2O$+OD+MBR | | 52 | ~25 | 12 WWTPs/China | 89 |
| | GC + $A_2O$+ OD+ CAS+ MBR+ UV+ RFDF+ $ClO_2$+ UF+ Oz+ CS | | 75 | 550.3 | 14 WWTPs/China | 90 |
| | NF/RO | NF90 | > 99.9 | 6080 | Croatia | 64 |
| | | RO XLE | > 99.9 | | | |
| | | NF270 | 75.88 | | | |
| | MBR+RO | | 100 | - | Zagreb/Croatia | 65 |
| ERY | 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 | - | Eastern United States | 88 |
| | ST+ MBBR+ TS+ SF | | 97 | | | |
| | 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 + $A_2O$ + 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 + $A_2O$/MBBR+ OD +$A_2O$/CAS+CAS/MBR+ UV+ RFDF + $ClO_2$ + UF + $O_3$ + CS | | 78 | 1151.6 | 14 WWTPs/China | 90 |
| | Primary +AS | | 39 | 200 | China | 50 |
| | PT + CAS | | 39.11 | 254.24 ± 15.36 | Southwest/china | 51 |
| ROX | | | | | | |
| | 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 |


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| Macrolides | Treatment processes | Removal (%) | Influent (ng/L) | Location (City/Country) | Ref. |
|---|---|---|---|---|---|
| | SBR+ $A_2O$ + OD+ $A_2O$ /MBR | 48 | ~80 | 12 WWTPs/China | 89 |
| | AS+ OD+ AL | 67 | 1500 | Wisconsin/USA | 93 |
| | GC+ $A_2O$ /MBBR+ OD+ $A_2O$ /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<br>$O_3$+CMF | 99<br>99 | 40 | Jindawanxiang/North China | 91 |
| | MBR-RO<br>MBR-NF | 98<br>97 | 1410 | China | 36 |
| | ST + GAC + UV<br>ST + MBBR+ TS + SF<br>ST + Sed+ $O_3$, BAF+ GAC + UV<br>PT + SBR+ UV<br>AABR + MBR+ UV<br>PT + SBR + CLO<br>PT +AS + NAS + CLO | 100<br>96<br>100<br>0<br>0<br>60<br>45 | - | Eastern United States | 88 |
| | PT + CAS | 50.55 | 362.5 ± 21.7 | Southwest/China | 51 |
| | SBR + $A_2O$ +OD+ $A_2O$ /MBR | 45 | ~450 | 12 WWTPs/China | 89 |
| | GC + $A_2O$ /MBBR + OD + $A_2O$ /CAS + CAS/MBR + UV + RFDF + $ClO_2$ + UF + $O_3$ + CS | 51 | 1687.2 | 14 WWTPs/China | 90 |
| | NF/RO NF90<br>RO XLE<br>NF270 | > 99.9<br>> 99.9<br>80.08 | - | Croatia | 64 |
| 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<br>RE-SST<br>RE-FE | 0.3<br>24.7<br>24.7 | 380 | Al Ain /United Arab Emirates | 96 |

## 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


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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 radiation [85].

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- $O_3$/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 China[36]. 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.

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## Conflict of interest

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