The occurrence of pharmaceutical waste in different parts of the world: A scoping review

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Pharmaceutical waste in our ecosystem is the huge burden for our future generations, especially in developing countries. It can be in every place even in drinking water after water treatment. It was observed the presence of over the counter drugs such as ibuprofen, naproxen, acetaminophen and antibiotic such as sulfamethoxazole, trimethoprim, erythromycin the most in the environment. Among all result, Carbamazepine which is known to treat epilepsy was found the most in the environment when the results were compiled from different parts of the world due to its low biodegradable properties. The current article is focused on the occurrence of pharmaceutical waste in the last eight years (January 2010- July 2018) published research work.

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Abstract:

Background: Pharmaceutical waste in our ecosystem is a massive burden for our future generations, especially in developing countries. It can be in every place even in drinking water after water treatment.
Objectives: The focus of the current article is the occurrences of pharmaceutical waste in the last eight years (January 2010- July 2018) of published research work. Two independent reviewers screened the articles for eligibility of studies included for scoping review.
Results: The presence of over the counter drugs was observed, such as ibuprofen, naproxen and acetaminophen, and antibiotics, such as sulfamethoxazole, trimethoprim and erythromycin, the most in the environment.
Conclusion: Among all the results, Carbamazepine, which is known to treat epilepsy, was found the most in the environment. The presence of Carbamazepine resulted due to its low biodegradable properties.

Keywords: Pharmaceutical Waste, Over the counter drugs, Antibiotics, Carbamazepine

Introduction:

The utilization of pharmaceuticals has amplified over the last ten years due to an increase in the volume or quantity of medicine consumed (OECD, 2012). The increase in consumption of pharmaceuticals has resulted in a massive problem in their disposal. Pharmaceutical waste is known to possess a real threat to the ecosystem, particularly for the marine environment. Fish have been found to be a real threat to the ecosystem due to pharmaceutical waste. There are around 37% of the sea foodborne illnesses found in the USA (Gheorghe, Petre, Lucaciu, Stoica & Nita-Lazar, 2016)(Diaz, 2004). Our objective was to complete a scoping review in context of availability of pharmaceutical waste around the world to synthesize list of drugs commonly available as pharmaceutical waste.

Methodology:

The framework for this review has used Arksey & O'Malley's (2005) scoping model followed by Levac, Colquhoun & O'Brien (2010); Colquhoun, et al. (2014) and Daudt, Van Mossel & Scott (2013). This review has been based more upon the narrative approach rather than a quantitative approach or meta-analytical synthesis. A large number of articles have been included under evidence using the search strategy where the authors focussed on in-depth information rather than details.

Aims:

The specific aims of this study consisted of collecting evidence of pharmaceutical waste from different parts of the world. The study focused on the identification of pharmaceutical waste in different sampling sites, along with their concentration ranges. The study discussed the identification methods used in different regions of the world (Table 1). The study also collected the evidence of the list of journals (Figure 2) and the number of published articles (Figure 3) over the specific range period. The methodological assessment of the included studies was also under the current aims and objectives of the study (Table 2). The pharmacological activities of the identified compounds were also identified and discussed under this review (Table 3).

Search Strategy:

A systematic literature review was performed according to the PRISMA Statement. Google Scholar was used as the search engine, using the search terms (allintitle: Pharmaceutical waste water AND Occurrence), (allintitle: Pharmaceutical residues AND wastewater), (allintitle: Pharmaceutically active AND wastewater), (allintitle: Pharmaceutical AND personal care products AND wastewater) and (allintitle: occurrence AND fate AND wastewater). The duration of the studies included was between 1st January 2010 till 31st July 2018.

Data extraction:

Records were identified (n=191) using the Google Scholar search engine. Irrelevant articles (n=75) were removed. The records were further screened for qualitative synthesis. A number of articles have been excluded consisting of wastewater treatments, screening articles, abstracts only, case studies, review articles, articles on method development and duration of study after July 2018. This led to the investigation of forty-four (n=44) articles for the qualitative synthesis. The identification of the data was performed manually using Microsoft word 2016. The results have been expressed in a Prisma flow diagram (Figure 1). The characteristics of each full-text article were extracted by two independent reviewers Mylene Sevilla Andal and Ana Marie Rubenicia from School of Pharmacy, Centro Escolar University, Manila, Philippines.

Results and Discussion:

Identification of pharmaceutical waste was observed in different parts of the world which included the United States of America (USA), Ireland, Korea, China, Taiwan, Spain, Belgium, Portugal, Serbia, Sweden, Greece, South Africa, Pakistan, Nigeria, France, Singapore, the Hawaiian Islands, India, Colombia and

Thailand. China, the USA and Spain were focussed on for the identification of pharmaceutical waste from different sources. The results consisted of research publications from the last eight years (2010-2018).

Bartelt-Hunt et al. (2011) identified the pharmaceutical waste in the state of Nebraska, USA, from different locations, such as cattle and swine farms. It was also found that there were some variable pharmaceutical active ingredients at a particular site, and they were able to travel from wastewater lagoons to groundwater, such as Erythromycin and Monensin. The occurrence of Monensin was due to animal waste as this drug is used in the treatment of coccidiosis and growth development in animals (Bartelt-Hunt, Snow, Damon-Powell & Miesbach, 2011).

Pharmaceutical waste in public drinking water was indicated in California. Sulfamethoxazole and Carbamazepine were found to be the most common contaminants. Carbamazepine was found to be available from different sources due to its high bio-stability and lack of absorption and adsorption properties (Fram & Belitz, 2011)(Clara, Strenn & Kreuzinger, 2004). Acetaminophen and caffeine are the most frequently used pharmaceutically active ingredients in our daily lives but were found to be available only in lower concentrations in wastewater due to their physical properties. Sulfamethoxazole has similar properties as carbamazepine, and that is the reason it was the second most available contaminant (Benotti & Brownawell, 2009). It was also found to be as high as 1566 ng/L in the East Lansing Wastewater Treatment Facility in Michigan, USA (Gao, Ding, Li & Xagoraraki, 2012).

Pharmaceutical and personal care products (PPCPs) were identified in the surroundings of Liberty Bay and Puget Sound, Washington. Most of the PPCPs were present on the surface water grab samples. The surface water contamination from the herbicides transferred to the groundwater system directly without a proper sewage system. This PPCP contamination in the environment could result in one of the reasons for drug resistance and may affect human health. There is no available knowledge about the possible synergistic interaction of multiple drugs in the environment (Dougherty, Swarzenski, Dinicola & Reinhard, 2010). Identification of Pharmaceutical waste from the rural wastewater treatment plant of Illinois, USA, was a real concern. It was found that caffeine was the prominent contaminant inside the rural wastewater with a range from 0.048 to 58 μg/L. However, Carbamazepine still existed even after the treatment of the lagoon wastewater (Li, Zheng & Kelly, 2013). Alessio et al. (2018) stated that the occurrence of pharmaceutical waste depends upon the physical and chemical properties of the soil. Sulfamethoxazole (0-75%) was found even after treatment using Schofield Barracks Wastewater Treatment (D'Alessio, Onanong, Snow & Ray, 2018).

There were fourteen (14) active pharmaceutical compounds found from the East China swine wastewater treatment. Tetracycline, Oxytetracycline, Chlortetracycline, Doxycycline and Sulfadiazine were among those in the highest concentrations. The available concentrations in the aquatic environment could be harmful to the aquatic environment. The concentrations of veterinary antibiotics were found to be higher in the animal feed as compared to the wastewater produced by these farms (Chen, Zhang, Luo & Song, 2012). Pharmaceutical wastewater treatment plants could help remove the antibiotics, but studies have found that these treatment plants lack effectiveness in removing the waste (Hou, Wang, Mao & Luo, 2016). Chongqing is a major city in southwest China with twenty-one active pharmaceutical compounds having been identified in municipal wastewater treatment plants, which are potential risks for the environment (Yan et al., 2014).

Bohai Bay is an innermost gulf in the northeast part of China. Zou et al. (2011) identified twenty-one active pharmaceutical ingredients, with Sulfamethoxazole, Ofloxacin, Norfloxacin and Erythromycin possessing high detection levels. The high concentrations of pharmaceutically active ingredients were due to increased human activities, especially in the northern region (Zou et al., 2011). Pharmaceutical waste was also identified in the Huangpu River, Shanghai, China, from the surface water with around twenty-two antibiotics present in moderate levels (Jiang, Hu, Yin, Zhang & Yu, 2011). Table 1 lists different pharmaceutical compounds identified from various waste related artcles published from January 2010 to June 2018.

Carbamazepine is the most common antiepileptic drug found during the last eight years, which cannot be removed easily even with wastewater treatment (Deziel, 2014)(Kasprzyk-Hordern, Dinsdale & Guwy, 2009). Ibuprofen, which is used to treat pain and inflammation, was the most often present after carbamazepine as one of the most significant threats (Rainsford, 2009). Sulfamethoxazole is used to treat urinary tract infections and has less biodegradable properties (Guneysel, Onur, Erdede & Denizbasi, 2009). Many studies are on-going to find a way to enhance its degradation using Ammonia-oxidizing bacteria (Kassotaki, Buttiglieri, Ferrando-Climent, Rodriguez-Roda & Pijuan, 2016).

The list of other frequently used antibiotics included Erythromycin, Sulfamethazine, Ciprofloxacin, Sulfadiazine, Ofloxacin, Oxytetracycline, Tylosin, Tetracycline, Roxithromycin, Clarithromycin, Chlortetracycline, Enrofloxacin, Chloramphenicol, Sulfamerazine, Sulfathiazole, Lincomycin and Doxycycline. Some of these antibiotics were also indicated in the treatment of infections occurring in animals. So animal waste is another reason for the contamination in the pharmaceutical waste. Non-steroidal anti-inflammatory drugs are another class of compounds that has frequently been found to be present inside the pharmaceutical waste. These include Naproxen, Diclofenac, Ketoprofen, Mefenamic acid

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and Indomethacin. These pharmaceutical waste compounds indicate the very frequent use of over the counter medicine.

The identification of pharmaceutical waste from the environment has also given some indication of common diseases, human behavior, excessive use of antibiotics and over the counter drugs and specific diseases, such as hypertension, that indicate the daily life stress for every ordinary person. Table 2 lists the generic names of several Pharmaceutical waste compounds that have appeared during the past eight years. It also briefs about their classification, chemical formulas, and uses.

Figure 1: Prisma Flow diagram

Table 1: List of Pharmaceutical compound identified from different kind of waste Published from 2010 till June 2018.

Figure 2: List of Journal along with several articles published between January 2010 till July 2018.

Figure 3: Number of article included in the study published between January 2010-July 2018

Table 2: Methodological assessment of Articles included

Conclusion:

The presence of over the counter drugs and antibiotics in the pharmaceutical waste was found to be the highest of all the identified compounds. The excess use of antibiotics shows the reason for the antibiotic resistance in the world. There has also been an identification of CNS stimulants, such as caffeine and anti-depressant drugs, such as Diazepam, all around the World, which shows that ordinary people in the world are suffering from anxiety, depression and restlessness even in developed countries. Furthermore, the presence of antihypertensive, lipid-lowering and anti-ulcer drugs, such as gemfibrozil, cimetidine, famotidine and atenolol, in pharmaceutical waste indicates the lifestyle and eating habits of people in developed countries. The identification of Clofibric acid, a metabolite, in the pharmaceutical waste indicates the presence of the cholesterol-lowering pharmaceutical drug clofibrate, which is also related to eating habits.

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Table 1 (on next page)

List of Pharmaceutical compound identified from different kind of waste Published from 2010 till June 2018.

Table 1: List of Pharmaceutical compound identified from different kind of waste Published from 2010 till June 2018.

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentration range**	**Identification Method**	**Referenc**
Estrone, testosterone, 4-androstenedione, androsterone, sulfamerazine, sulfamethazine, erythromycin, monensin, tiamulin, sulfathiazole, Lincomycin; ractopamine; sulfamethazine, sulfadimethoxine	Nebraska, U.S.A	Groundwater contamination by wastewater or other high nitrogen sources. Two swine facilities and two beef cattle facilities in the state of Nebraska were selected for sampling	30 to 3600 ng/L	LC/MS/MS	(Bartelt-Hunt et a 2011)
Carbamazepine, clotrimazole, propranolol, nimesulide, furosemide, mefenamic acid, diclofenac, metoprolol, and gemfibrozil	Dublin, Ireland	Wastewater treatment plant (WWTP)	0.001-300 µg/l	LC-ESI-MS/MS	(Lacey, Basha, Morrisse & Tobin, 2012)
Acetaminophen. caffeine, carbamazepine, codeine, p-xanthine, sulfamethoxazole, and trimethoprim	California, U.S.A	1231 sites in California between May 2004 and March 2010 from groundwater samples collected	0.04-0.42 µg/l	Mass spectrometric detection	(Fram & Belitz, 2011)
Acetaminophen, Caffeine, Carbamazepine, Sulfamethoxazole, Sulfathiazole, Sulfamethazine, Trimethoprim, Lincomycin, Ciprofloxacin, Enrofloxacin, Chlortetracycline, Oxytetracycline, Acetylsalicylic acid, Diclofenac, Ibuprofen, Mefenamic acid, Naproxen, Florfenicol, Erythromycin, Tylosin, Cefradine, Cefadroxil Penicillin G, Vancomycin	Major river basins of Korea	Livestock, hospital, pharmaceutical manufacture wastewater treatment plants	0.004-384 µg/l	(LC/MS/MS). separated and quantified using a 1200 HPLC coupled to a 6410 QQQ	(Sim et a 2011)
Tetracycline, oxytetracycline, chlortetracycline, doxycycline, and sulfadiazine	East China	Wastewater treatment systems at two intensively reared swine farms	685.6×10^3 ng/L	Ultra-performance liquid chromatography (UPLC) MS/MS	(Chen et al., 2012

Pharmaceutical Compounds identified	Country	Sampling sites & method	Concentration range	Identification Method	Referen
Clofibric acid, Diclofenac, Ibuprofen, Ketoprofen	Northern Taiwan,	stations D1-D12, Bali sewage treatment plant	68-143000 ng/l	(LC/MS/MS). quadrupole mass spectrometer equipped with electrospray ionization (ESI) interface	(Fang, N Chin, & Feng, 2012)
Bezafibrate, clofibric acid, diclofenac, gemfibrozil, ibuprofen, triclosan, Bisphenol A, Butylparaben, Chloramphenicol, Ethylparaben, Flufenamic acid, Indomethacin, Methylparaben, Naproxen, Propylparaben, Salicylic acid, Thiamphenicol, Triclocarban, Triclosan, Warfarin	Turia River Basin (Valencia, Spain)	wastewater, surface water, drinking water	1- 4374 ng/l 1- 318 ng/g	(LC-MS/MS) tandem mass spectrometry method	(Carmo Andreu, Picó, 20
flubendazole, pipamperone, rabeprazole, domperidone, ketoconazole, itraconazole, cinnarizine, miconazole, and propiconazole	Belgium	Surface water samples were grab samples, taken from different locations in Belgium (1-16 Locations).	0.4-297.0 ng/l	multiple reaction monitoring (MRM) using electrospray ionization mass spectrometry (ESI-MS)	(Van De Steene, Stove, & Lamber 2010)
Paracetamol/acetaminophen, Carbamazepine, Amitriptyline, Doxepin, Imipramine, Fluoxetine, Alprazolam, Bromazepam, Diazepam, Nordiazepam, Diclofenac, Ibuprofen, Ketoprofen, Naproxen, Clenbuterol, Salbutamol, Theophylline, Gemfibrozil, Caffeine	Southern Portugal	Arade River estuary (upriver site and down river)	0- 804 ± 209 ng/L)	Agilent 6410 QQQ triple quadrupole mass spectrometer	(Gonzal Rey et a 2015)

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Pharmaceutical Compounds identified	Country	Sampling sites & method	Concentration range	Identification Method	Referer
Ketoprofen, Naproxen, Ibuprofen, Diclofenac, Indomethacin, Acetaminophen, Salicylic acid, Phenazone, Propyphenazone Piroxicam, Tenoxicam, Meloxicam, Oxycodone, Codeine, Bezafibrate, Gemfibrozil, Pravastatin, Fluvastatin, Atorvastatin, Carbamazepine, 2- Hydroxycarbamazepinea, 10,11-Epoxycarbamazepinea, Acridonea, Olanzapine, Sertraline, Citalopram, Venlafaxine, Trazodone, Fluoxetine, Norfluoxetinea, Paroxetine, Diazepam, Diazepam, Lorazepam Alprazolam, Loratadine, Desloratadinea, Ranitidine, Famotidine, Cimetidine, Atenolol, Sotalol, Propranolol, Metoprolol, Nadolol, Carazolol, Hydrochlorothiazide, Furosemide, Torasemide, Glibenclamide, Amlodipine, Losartan, Irbesartan, Valsartan, Clopidogrel, Tamsulosin, Salbutamol, Warfarin, Iopromide Albendazole, Thiabendazole, Levamisole, Dexamethasone Dexamethasone, Xylazine, Azaperone, Azaperola Erythromycin, Azithromycin, Clarithromycin, Tetracyclin Sulfamethoxazole, Trimethoprim, Ofloxacin, Ciprofloxacin Metronidazole, Metronidazole-OHa Dimetridazole, Ronidazole Cefalexin, Diltiazem, Verapamil, Norverapamil	Northern Serbia	waste, surface, underground, and drinking water samples (25 locations)	Up to 20.1 µg/l,	mass spectrometry with hybrid triple quadrupole–linear ion trap (UPLC–QqLIT–MS/MS)	(Petrovi Škrbić, Živanče Ferrand Climent Barcelo 2014)
Caffeine, Ibuprofen, Ketoprofen, Gemfibrozil Propranolol, Trimethoprim, Carbamazepine	Liberty Bay, Puget Sound, Washington	Two liters of surface water were sampled at seven creeks (Sites 1 and 2, 3, 4, 6, 7, 8, and 9), and 1 L of groundwater was sampled at three shallow groundwater wells (Sites 5, 10, and 11)	0.7–12.3 ng L^{-1}	LC (LC-10AD VP), quadrupole mass spectrometer (API3000)	(Dough et al., 20

Pharmaceutical Compounds identified	Country	Sampling sites & method	Concentration range	Identification Method	Referer

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Ketoprofen, Naproxen, Diclofenac, Indomethacin, Mefenamic acid, Bezafibrate, Fenofibrate, Gemfibrozil, Atorvastatin, Pravastatin, Mevastatin, Diazepam, Lorazepam, Carbamazepine, Clarithromycin, Cimetidine, Ranitidine, Famotidine, Sulfamethazine, Trimethoprim, Metronidazole, Chloramphenicol, Atenolol, Sotalol, Metoprolol, Timolol, Nadolol, Salbutamol, Enalapril, Glibenclamide, Furosemide, Hydrochlorthiazide	Catalonia (Spain)	influent and effluent wastewater, and sewage sludge	1.2-10150 ng/L	HPLC-QLIT-MS/MS	(Jelic et 2011)
Caffeine, Carbamazepine, Naproxen, Ibuprofen, Gemfibrozil Trimethoprim, Triclocarban, Sulfamethoxazole, Diphenhydramine, Erythromycin, Fluoxetine, Sulfamethazine, Ethynylestradiol, Estrone, 17-α-Estrodiol, 17-β-Estrodiol, Estriol, Estone-3-sulfate, 17-α-estradiol-3-sulfate, 17-β-estradiol-3-sulfate	Illinois, USA	the 1st and 2nd aerated lagoons, and effluent of the treatment plant of rural wastewater	0.010-75 ng/L	tandem triple quadrupole MS/MS equipped with an electrospray ionization (ESI) source	(Li et al 2013)
Ciprofloxacin, diphenhydramine, memantine, mianserin, ofloxacin/levofloxacin, rosuvastatin, sotalol and tetracycline, clindamycin, diphenhydramine, fluconazole, sotalol, tetracycline, rosuvastatin	Umea in Northern Sweden	Seven pump stations municipal, hospital, sewage water influx	up to 300 mg/L	LC-MS system, heated electrospray (HESI)	(Lindbe Östman Olofsso Grabic, Fick, 20
Salicylic acid, clofibric acid, paracetamol, caffeine, gemfibrozil, triclosan, diclofenac, and carbamazepine	Western Greece	The wastewater treatment plant of the city receives combined wastewaters (household, stormwater, and hospital wastes)	28.1 - 1673 ng/L	GC-MS, QP-2010	(Stamat Konstar ou, 201

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentration range**	**Identification Method**	**Referer**
Acetaminophen, Caffeine, Carbamazepine, Clozapine,	Msunduzi	Five (5) sampling sites along the	0.001-	LC/MS/MS	(Matong

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Erythromycin, Metronidazole, Ibuprofen, Sulfamethoxazole, Sulfamethazine, Trimethoprim	River, KwaZulu-Natal, South Africa	river and three (3) sites from Darvill wastewater treatment plant (WWTP)	5.771 ng/g 0.001-2.886 ng/L	positive electrospray ionization ESI (+) and negative electrospray ionization ESI (-)	Birungi Moodle & Ndun 2015)
Sulfadiazine, sulfamethoxazole, sulfamethazine, sulfachlorpyridazine, sulfamonomethoxine, ofloxacin, enrofloxacin, ciprofloxacin, erythromycin, roxithromycin, and tylosin	Northern China	processing stages at two typical pharmaceutical wastewater treatment plants	Up to 334.3±43.2 mg L^{-1} Upto 5,481.0 mg kg^{-1}	(UPLC)–tandem mass spectrometry (MS/MS)	(Hou et 2016)
Demeclocycline, chlortetracycline, oxytetracycline, doxycycline, meclocycline, sulfadiazine, sulfamerazine, sulfamethazine, SMX, tylosin, acetaminophen, and Caffeine	Michigan, USA	The wastewater samples were collected from the raw influent, pretreatment effluent, primary effluent after the primary clarification, effluent after the aeration tank, secondary effluent after the secondary clarification, and tertiary effluent after the post-filtration aeration	2.2-288.3 ng/L 0.8-486.7 µg/kg	liquid chromatograph y system coupled to an Applied Biosystems API 3200 triple quadrupole mass spectrometer	(Gao et 2012)

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentratio n range**	**Identification Method**	**Referer**
Sulfadiazine, Lincomycin, Trimethoprim, Enoxacin,	Pakistan	surface water grab subsamples	Up to 49000	LC-MS	(Khan,

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Oxytetracycline, Ofloxacin, Levofloxacin, Norfloxacin, Pefloxacin, Ciprofloxacin, Cefotaxime, Lomefloxacin, Tetracycline, Enrofloxacin, Azithromycin, Clindamycin Sulfamethoxazole, Doxycycline, Erythromycin, Nalidixic acid Clarithromycin and Roxithromycin		were collected at 3–5 points rivers, dam, canal, and the vicinity of hospitals	ng/L	positive [M+H+] and negative [M+H2] at MRM (multiple reaction monitoring) modes	Berglun Khan, Lindgre & Fick, 2013)
Atenolol, Ibuprofen, Naproxen, Ketoprofen, Diclofenac Gemfibrozil, Benzophenone, Caffeine, Carbamazepine Sulfamethoxazole, Ampicillin, Erythromycin, Amphetamine, Methamphetamine, Ketamine, Ephedrine Heroin,Codeine ,methylenedioxymethamphetamine	Central Taiwan	Four landfills (Sites A1, A2, B, and C) in central Taiwan	Up to 8102.5 ng/L	API 4000 LC/MS/MS system	(Lu, Ch Chiou, Chen, & Fan, 20
Oxytetracycline and Chloramphenicol.	Ogun State, Nigeria	Freshwater and wastewater (2 sample each)	Up to 0.60ng/ml	SPE-HPLC	(O. J. Olatund 2014)
Acetaminophen, Acetylsalicylic acid, Diclofenac, Ibuprofen Ketoprofen, Mefenamic acid, Naproxen Carbamazepine, Clofibric acid, Gemfibrozil, Caffeine Sulfachloropyridazine, Sulfadimethoxine, Sulfamerazine Sulfamethazine, Sulfamethoxazole, Sulfamonomethoxine Sulfathiazole, Trimethoprim, Erythromycin-H2O, Roxythromycin, Tylosin, Ciprofloxacin, Lincomycin, Carbadox	Busan, Korea	wastewater treatment plants and rivers in Korea (Samples were collected from ten municipal WWTPs, one hospital WWTP and five rivers in Busan)		LC/MS/ electrospray ionization (ESI) selective ion monitoring (SIM) mode	(Sim, L & Oh, 2010)

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentration range**	**Identification Method**	**Referen**

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Ketoprofen, salicylic acid, and caffeine	Haute-Savoie, France	The Evian natural mineral water (NMW) outflows near the Evian city	N.A	SPME-GC–MS LC-MS/MS	(Dévier al., 201
Diclofenac, Ibuprofen, Ketoprofen, Naproxen, Salicylic acid Sulfamethoxazole, Trimethoprim, Carbamazepine Propranolol, Caffeine, 17α-Ethinylestradiol, 17β-Estradiol Estriol, Estrone, Clofibric acid, Gemfibrozil	Doñana Park (Spain)	The sediment samples were collected in the area of Doñana National Park	Up to 52.1 µg/kg dm)	ultraviolet diode array detector and a rapid scan fluorescence detector connected online. Agilent 1200 series	(Camac Muñoz, Martín, Santos, Aparici Alonso, 2013)
carbamazepine, caffeine, diltiazem, diphenhydramine, naproxen, ibuprofen, diclofenac, gemfibrozil	Singapore	Seawater samples were collected below the surface (3 m depth) from eight points	Up to 95 ng/L	liquid-chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS)	(Bayen, Zhang, Desai, C & Kelly 2013)
Diclofenac, Chloroquine, Paracetamol and Ciprofloxacin HCl	Ogun State, Nigeria	4 different locations (an irrigation-canal and 3 wells respectively) in a pharmaceutical industrial area of Sango Ota, Ogun State-Nigeria.	0/86-17.25 µg/L	HPLC analysis	(J. O. Olatund Chimez Tolulop & Amir 2014)

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentration range**	**Identification Method**	**Referen**
Carbamazepine, atenolol, metoprolol, sotalol	River Fyris and in Lake Mälaren in	Samples were collected from the effluent of a wastewater treatment plant (WWTP), at one	Up to 437.3 ± 117.3 ng/L	HPLC-system	(Danesh , Svanfe Kronber

	central Sweden	upstream site, and five downstream sites			Prévost, Weyher yer, 201
Sulfadiazine, sulfamethoxazole, ofloxacin, azithromycin, and erythromycin	Chongqing, China	Four full-scale municipal WWTPs	NA	high-performance liquid chromatography/tandem mass spectrometry	(Yan et 2014)
Alprazolam, atenolol, bromazepam, carbamazepine, chlordiazepoxide, chlorpromazine, diazepam, diltiazem, fluoxetine, furosemide, hydrochlorothiazide, loratadine, lorazepam, metoprolol, oxazepam, paroxetine, phenytoin, propranolol, sertraline, venlafaxine, zolpidem, Demethylsertraline, desmethylvenlafaxine, irbesartan, L-dopa, losartan, terbutaline, valsartan, and warfarin	Llobregat River (NE-Spain	drinking water production consists of surface water	up to 1200 ng/L	ESI-MS/MS	(Huerta Fontela, Galcera & Ventu 2011)
1,7-Dimethylxanthine, Acetaminophen, Caffeine, Carbamazepine, Cotinine, d-Amphetamine, Diphenhydramine, Gemfibrozil, Ibuprofen, Methamphetamine, Morphine, Naproxen Sulfadiazine, Sulfamethoxazole, Triclosan 4-Androstenedione, 17 α-Estradiol, 17 α-Trenbolone 17 β-Trenbolone, Androstanedienedione, Androsterone Epitestosterone, Estriol, Estrone, Progesterone, Testolactone Testosterone	Hawaiian Islands	Disturbed soil samples were collected across the state of Hawai'I and four wastewater treatment plants	Up to 96.5 $\mu g L^{-1}$	liquid chromatography-tandem mass spectrometry (LC-MS/ MS)	(D'Ales et al., 20

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentration range**	**Identification Method**	**Referen**
Aspirin, Ibuprofen, Paracetamol, Caffeine, Ranitidine Diclofenac, Carbamazepine, Codeine, Diazepam	Delhi (India)	Samples were taken from Vasantkunj sewage treatment plant STP (installed treatment capacity 14 MLD) located in	0.05-97.86 $\mu g L^{-1}$	GC-MS	(Mutiya Mittal, 2013)

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		south Delhi.			
Salicylic acid, Ibuprofen, Paracetamol, Caffeine, Phenazone Gemfibrozil, Naproxen, Triclosan, Fenofibrate, Diclofenac Carbamazepine	Greece	municipal and hospital wastewaters treatment plant in Greece	Up to 429.1 ng/l	GC–MS analysis	(Kosma Lambro lou, & Albanis 2010)
Acetaminophen, Ibuprofen, Naproxen, Salicylic acid Meloxicam, Ketoprofen, Tenoxicam, Piroxicam, Diclofenac Codeine, Indomethacin, Phenazone, Ciprofloxacin Azithromycin, Ofloxacin, Clarithromycin, Sulfamethoxazole Trimethoprim, Erythromycin, Venlafaxine, Paroxetine Citalopram, Trazodone, Carbamazepine, Atenolol Metoprolol, Nadolol, Gemfibrozil, Bezafibrate, Atorvastatin Valsartan, Irbesartan, Losartan, Furosemide Levamisole, Thiabendazole, Ranitidine, Iopromide, Xylazine	Spain	Wastewater samples were collected from the municipal WWTP at Celrà (Catalonia, Spain	NA	chased from Waters Corporation. The UPLC instrument was coupled to a 5500 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer	(Collado al., 2014
Iopromide, atenolol, musk ketone, naproxen, carbamazepine, caffeine, and benzophenone	Seoul, South Korea	Six total river samples were taken from the Han River, from both upstream and downstream sites. Four effluent-dominated creek sites	(56 ng/L–1013 ng/L)	(LC-MS/MS) with electrospray ionization (ESI) and	(Yoon, Ryu, Oh Choi, & Snyder, 2010)

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentration range**	**Identification Method**	**Referen**
Ibuprofen, naproxen, diclofenac, aspirin, ketoprofen, caffeine, galaxolide, tonalide, and dihydrojasmonate	La Florida located upstream from the water supply	wastewater treatment plant (WWTP) of La Florida	Up to 78.7 µg/L	gas chromatography-mass spectrometry	(Arrubla Vélez et 2016)

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	system of Pereira city Colombia				
Ampicillin, oxacillin, penicillin G, ceftazidime, cefazolin, cefotaxime, cefalexin, sulfadiazine, sulfamethazine, sulfamethoxazole, trimethoprim, norfloxacin, ciprofloxacin, ofloxacin, tetracycline, oxytetracycline, chlortetracycline, chloramphenicol, roxithromycin, erythromycin and, vancomycin	Bohai Bay, China	23 water samples were collected from 6 main rivers among the 53 ones pouring into the Bohai Bay. Except for the Dou River, the other four rivers including Suyun River, Yongding River, Duliujian River, and Ziya River are four main tributaries of the Haihe River. a total of 12 effluent samples from three aquafarms (fish pond, breeding farm and nursery plant, respectively) around the Bohai Bay	Up to 287 ng/L	UPLC-MS/MS	(Zou et 2011)
Doxycycline, Tetracycline, Oxytetracycline, Chlortetracycline Chloramphenicol, Florfenicol, Thiamphenicol, Sulfapyridine, Sulfadiazine, Sulfamethoxazole, Sulfamerazine, Sulfamethazine, Sulfachlorpyridazine, Roxithromycin, Tylosin, Norfloxacin, Ciprofloxacin, Enrofloxacin, Ofloxacin Fleroxacin, Sarafloxacin	Shanghai, China	Nineteen sampling sites (Fig. 1) were selected along the Hua-ngpu River, among which S1–S13 were located in the suburbs and S14–S19 were located in the urban area.	Upto 313.44 ng/ L	(HPLC/MS	(Jiang e al., 201

Pharmaceutical Compounds identified	**Country**	**Sampling sites & method**	**Concentration range**	**Identification Method**	**Referer**
Acetaminophen, Atenolol, Atorvastatin, Bezafibrate Carbamazepine, Chloramphenicol, Cimetidine, Clarithromycin, Clenbuterol, Clofibric acid, Diazepam Diclofenac, Enalapril, Erythromycin, Famotidine, Fenofibrate, Furosemide, Gemfibrozil, Glibenclamide,	Ebro river basin, Spain	Waste and river waters downstream of six major WWTP were Monitored. The monitoring of river water and sediment included 23 sampling	N.A	(HPLC–QqLIT–MS/MS)	(Ferreir al., 201

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Hydrochlorothiazide, Ibuprofen, Indomethacin, Josamycin Ketoprofen, Lorazepam, Mefenamic acid, Metoprolol Metronidazole, Mevastatin, Nadolol, Naproxen, Phenazone Pravastatin, Ranitidine, Salbutamol, Sotalol, Sulfadiazine Sulfamethazine, Timolol, Trimethoprim, Tylosin		sites covering the whole Ebro River Basin (11 at the Ebro River and 12 at the main tributaries). For river sediment, grab samples of surface river sediments (0–20 mm) were collected at the same sampling sites as water			
acetaminophen, acetylsalicylic acid, atenolol, caffeine, ciprofloxacin, diclofenac, ibuprofen, mefenamic acid, naproxen, roxithromycin, sulfamethazine, sulfamethoxazole, sulfathiazole, and trimethoprim	Bangkok, Thailand	Five WWTPs and the regions of their outfalls into six canals and the Chao Phraya River was chosen as the study area	Up to 4700 ng/L	HPLC/MS/MS analysis Samples	(Tewari Jindal, Kho, Ec Choi, 20
Erythromycin, sulfamethoxazole, and trimethoprim	Beibu Gulf, China	A total of thirty-five seawater samples from the Beibu Gulf and seventeen river water samples from four rivers	0.51 to 6.30 ng/L	HPLC-ESI-MS-MS	(Zheng al., 201
Dehydroerythromycin, sulfamethoxazole, fluconazole, salicylic acid, methylparaben, triclosan	China	The two municipal landfills in this study, located in the outskirt of Guangzhou	Up to 2014.4 ng L^{-1}	LC-MS/MS analysis.	(Peng e 2014)

Pharmaceutical Compounds identified	Country	Sampling sites & method	Concentration range	Identification Method	Referer
salicylic acid, clofibric acid, desmethyldiazepam, carbamazepine, 4OH propranolol, enalaprilat, cis 3OH glyburide, trans 4OH glyburide, Diclofenac Acyl-b-D-glucuronide, 2OH atorvastatin Acyl-b-D-glucuronide, Oxazepam glucuronide, N- acetyl sulfamethoxazole, Sulfamethoxazole-b-D-glucuronide, N-acetyl sulfadiazine,	Barcelona, Spain	natural bank filtration, infiltration from wastewater and water supply pipes, rainfall	Up to 1000ng/L	LC/ESI/MS/MS	(López-Serna et 2013)

N-acetyl sulfamethazine, Propranolol-b-D-glucuronide					
Ketoprofen, Naproxen, Ibuprofen, Indomethacin, Diclofenac Mefenamic acid, Acetaminophen, Salicylic acid, Propyphenazone, Phenylbutazone, Phenazone, Codeine, Clofibric acid, Bezafibrate, Fenofibrate, Gemfibrozil, Mevastatin, Pravastatin, Atorvastatin, Paroxetine, Fluoxetine, Diazepam, Lorazepam, Carbamazepine, Loratadine, Famotidine, Ranitidine, Cimetidine, Tetracycline Doxycycline, Oxytetracycline, Chlortetracycline, Erythromycin, Azithromycin, Tilmicosin, Roxithromycin, Clarithromycin, Josamycin, Tylosin A, Spiramycin, Sulfamethoxazole, Sulfadiazine, Sulfamethazine, Danofloxacin, Enoxacin, Ofloxacin, Ciprofloxacin, Enrofloxacin, Norfloxacin, Flumequine, Trimethoprim, Nifuroxazide, Chloramphenicol, Metronidazole, Atenolol, Betaxolol, Carazolol, Pindolol, Nadolol, Timolol, Sotalol, Metoprolol, Propranolol, Salbutamol, Clenbuterol	Spain	drinking water, superficial water (2 points) and effluent wastewater in the Llobregat River basin (NE Spain).	Upto 1120.33 ng/L	LC/ESI/MS/MS	(López-Serna, Pérez, Ginebre Petrovic Barceló 2010)
amlodipine, nifedipine, atenolol, metoprolol, valsartan, atorvastatin, simvastatin, bezafibrate, gemfibrozil, pravastatin	Southern China	Three WWTPs labeled as WWTPA, WWTPB, and WWTPC, located in Guangzhou and Foshan were studied	N.A	(HPLC-MS/MS) equipped with an electrospray ion source	(Huang al., 201

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Table 2 (on next page)

Methodological assessment of Articles included

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Table 2: Methodological assessment of Articles included

List of Authors	B	L	R
Aleksandra Jelic 2011	No	Yes	No
Arrubla 2016	No	Yes	No
Daneshvar 2010	No	Yes	Yes
Bartelt-Hunt 2011	No	No	No
Bianca Ferreira daSilva 2011	No	Yes	No
Camacho 2013	No	Yes	Yes
Carmona 2014	No	No	No
Clair Lacey 2012	No	No	No
Dougherty 2010	No	No	No
hou2015	No	Yes	Yes
Huang 2018	No	No	No
Jet C.Van De Steene 2010	No	Yes	No
Khan 2013	No	Yes	No
Kosmaa 2010	No	Yes	Yes
Lei Jiang 2011	No	Yes	Yes
lu 2016	No	No	Yes
Maria Gonzalez-Rey 2015	No	No	No
Maria Huerta-Fontela 2011	No	No	No
Marie-HélèneDévier 2013	No	No	No
MatteoD'Alessio 2018	No	No	No
Mira Petrović 2014	No	Yes	Yes
Miranda S.Fram 2011	No	No	No
MUTIYAR 2013	No	No	No
N.Collado 2014	Yes	Yes	Yes
Nikolaos K. Stamatis 2013	No	Yes	Yes
Olatunde 2014 (2)	No	No	No
Olatunde 2014	No	No	No
PinGao 2012	No	Yes	No
QingYan 2014	No	Yes	Yes
RebecaLópez-Serna 2010	No	Yes	Yes
RebecaLópez-Serna 2013	No	Yes	Yes
Richard H. Lindberg 2014	No	Yes	Yes
Shichun Zou 2011	No	Yes	Yes
Sim 2010	No	Yes	No
Solomon Matongo 2015	No	Yes	Yes
StéphaneBayen 2013	No	Yes	Yes

List of Authors	B	L	R
Tewari 2013	No	Yes	Yes
Tien-HsiFang 2012	No	Yes	Yes
Won-JinSim 2011	No	Yes	No
Xianzhi Peng 2014	No	Yes	Yes
XiaolinLi 2013	No	Yes	Yes
YeominYoon 2010	No	Yes	Yes
Yongshan Chen 2012	No	Yes	Yes
Zheng Q 2012	No	Yes	Yes

B= Bias assessment (i.e. Linear regression, bias plots, and analysis of variance)
L= Limit of blank (LoB), limit of detection (LOD), limit of quantitation (LOQ) and limit of decision
R=The number of replicate observations averaged when reporting results

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Table 3 (on next page)

List of Most common drugs in different kind of waste from data (2010-2018)

Table 3: List of Most common drugs in different kind of waste from data (2010-2018)

Pharmaceutical Active ingredient	**Classification**	**Formula**	**Occurrence (N)**	**Indication**	**References**
Carbamazepine	Neuropathic drug	$C_{15}H_{12}N_2O$	24	Epilepsy	(Deziel, 2014)
Ibuprofen	NSAIDs	$C_{13}H_{18}O_2$	20	pain, fever, and inflammation	(Rainsford, 2009)
Sulfamethoxazole	Antibiotics	$C_{10}H_{11}N_3O_3S$	20	A bacterial infection such as Urinary tract infection (UTI)	(Guneysel et al., 2009)
Gemfibrozil	Peroxisome Proliferator Receptor alpha Agonist	$C_{15}H_{22}O_3$	18	Lipid-lowering drug	(Friedland et al., 2012)
Naproxen	NSAID	$C_{14}H_{14}O_3$	18	Reducing pain and fever	(Todd & Clissold, 1990)
Trimethoprim	Antibiotics	$C_{14}H_{18}N_4O_3$	16	Treatment of bladder infection	(McCarty et al., 1999)
Caffeine	CNS Stimulant	$C_8H_{10}N_4O_2$	16	To restore mental alertness	(Nawrot et al., 2003)
Acetaminophen	Anti-pyretic	$C_8H_9NO_2$	15	Reducing pain and fever	(Larson, 2007)
Erythromycin	Antibiotics	$C_{37}H_{67}NO_{13}$	15	Chest infection	(Gardiner, Gavranich, & Chang, 2015)
Sulfamethazine	Antibiotics	$C_{12}H_{14}N_4O_2S$	15	Anti-infective agent	(Kidwai, Saxena, Rastogi, & Venkataramanan, 2003)
Diclofenac	NSAID	$C_{14}H_{11}Cl_2NO_2$	14	Pain killer	(Piras, Chiellini, Nikkola, Ashammakhi, & Chiellini, 2008)
Ketoprofen	NSAID	$C_{16}H_{14}O_3$	13	Analgesic and Anti-pyretic	(Marco-Urrea, Pérez-Trujillo, Cruz-Morató, Caminal, & Vicent, 2010)
Ciprofloxacin	Antibiotics	$C_{17}H_{18}FN_3O_3$	12	Bone and joint infections, intra-abdominal infections, infectious diarrhea, respiratory tract infections, skin infections, typhoid fever,	(Davies, Maesen, & Baur, 1986)
Salicylic acid	Anti-pyretic	$C_7H_6O_3$	12	Fever	(Robertson, 2011)
Metoprolol	β1 receptor blocker	$C_{15}H_{25}NO_3$	12	High Blood Pressure (HBP)	(Devi et al., 2011)
Sulfadiazine	Antibiotic	$C_{10}H_{10}N_4O_2S$	11	UTI, treatment for otitis media, rheumatic fever, chancroid, chlamydia	(Seppänen, Ylitalo, Julkunen, Räisänen, & Masar, 1980)(Catanzaro et al., 1954)(Gordon & Quan, 1972)
Atenolol	β-blockers	$C_{14}H_{22}N_2O_3$	11	High Blood Pressure	(Carlberg, Samuelsson, & Lindholm, 2004)

Diazepam	Anti-Depressant	$C_{16}H_{13}ClN_2O$	10	Anxiety, insomnia, panic attacks	(Power et al., 1990)
Ofloxacin	Antibiotic	$C_{18}H_{20}FN_3O_4$	9	UTI, pneumonia, cellulitis	(Kemmerich, Small, & Pennington, 1986)
Oxytetracycline	Antibiotic	$C_{22}H_{24}N_2O_9$	7	broad-spectrum antibiotic	(Pickens & Tang, 2010)
Tylosin	Antibiotic	$C_{46}H_{77}NO_{17}$	7	Veterinary bacteriostatic	(Jacob, 2015)
Tetracycline	Antibiotic	$C_{22}H_{24}N_2O_8$	7	Infection that causes cholera, brucellosis, plague, malaria, and syphilis	(Chopra & Roberts, 2001)
Propranolol	β-blockers	$C_{16}H_{21}NO_2$	7	High Blood Pressure	(Potempa, Fogg, Fish, & Kravitz, 1993)
Sotalol	β-adrenergic receptor block	$C_{12}H_{20}N_2O_3S$	7	Abnormal heart rhythms	(Singh et al., 2005)
Roxithromycin	Antibiotic	$C_{41}H_{76}N_2O_{15}$	7	Respiratory tract, urinary, and soft tissue infections.	("Roxithromycin," 1986)
Mefenamic acid	NSAID	$C_{15}H_{15}NO_2$	7	Pain killer	(Cimolai, 2013)
Atorvastatin	HMG-CoA reductase inhibitor	$C_{33}H_{35}FN_2O_5$	7	Primary prevention of heart attack, stroke	(Lennernäs, 2003)
Indomethacin	NSAID	$C_{19}H_{16}ClNO_4$	7	Reduce fever, pain, stiffness, and swelling from inflammation	(Lucas, 2016)
Clarithromycin	Antibiotic	$C_{38}H_{69}NO_{13}$	6	Strep throat, pneumonia, skin infections, H. pylori infection, and Lyme disease	(Malhotra-Kumar, Lammens, Coen Van Herck, & Goossens, 2007)
Furosemide	Diuretic	$C_{12}H_{11}ClN_2O_5S$	6	High Blood Pressure, Edema	(Oh & Han, 2015)
Chlortetracycline	Antibiotic	$C_{22}H_{23}ClN_2O_8$	6	Conjunctivitis in cats	(Biancardi & Curi, 2014)
Triclosan	Anti-microbial	$C_{12}H_7Cl_3O_2$	6	Prevent tooth decay	(Singer, Müller, Tixier, & Pillonel,
Ranitidine	Reversible inhibitor histamine H2 receptors	$C_{13}H_{22}N_4O_3S$	6	Peptic ulcer disease, gastroesophageal reflux disease, and Zollinger–Ellison syndrome	(Strum, 1983)
Metronidazole	Antibiotic and antiprotozoal	$C_6H_9N_3O_3$	6	Dracunculiasis, giardiasis, trichomoniasis, and amebiasis	(Pardanani, Trivedi, Joshi, Daulatra Nandi, 1977)(Löfmark, Edlund, & 2010)
Fluoxetine	Anti-depressant	$C_{17}H_{18}F_3NO$	6	Major depressive disorder, obsessive–compulsive disorder (OCD), bulimia nervosa, panic disorder and premenstrual dysphoric disorder	(Schmitz et al., 2001)
Nadolol	Non-selective beta blocker	$C_{17}H_{27}NO_4$	5	High Blood Pressure	(Kales et al., 1988)
Salbutamol	Selective for β2 receptor	$C_{13}H_{21}NO_3$	5	Asthma	(Patel et al., 2013)
Enrofloxacin	Antibiotic	$C_{19}H_{22}FN_3O_3$	5	Bactericidal agent for domestic pets	(Mitchell, 2006)

Chloramphenicol	Antibiotic	$C_{11}H_{12}Cl_2N_2O_5$	5	Conjunctivitis	(Rose et al., 2005)
Pravastatin	Inhibits the function of hydroxymethylglutaryl-CoA (HMG-CoA) reductase	$C_{23}H_{36}O_7$	5	Lowering cholesterol and preventing cardiovascular disease	(Sacks et al., 1996)
Estrone	Steroid	$C_{18}H_{22}O_2$	4	Menopausal hormone therapy	(Belfroid et al., 1999)
Sulfamerazine	Antibiotic	$C_{11}H_{12}N_4O_2S$	4	Long-acting antibacterial agent.	(Adams, Wang, Loftin, & Meyer, 2
Sulfathiazole	Antibiotic	$C_9H_9N_3O_2S_2$	4	Vaginal infections	(Siegler, 1946)
Lincomycin	Antibiotic	$C_{18}H_{34}N_2O_6S$	4	Antibacterial	(Augugliaro et al., 2005)
Doxycycline	Antibiotic	$C_{22}H_{24}N_2O_8$	4	Bacterial infection	(Cunha, Sibley, & Ristuccia, 1982)
Valsartan	Angiotensin II receptor antagonist	$C_{24}H_{29}N_5O_3$	4	High Blood Pressure	(Ripley, 2005)
Famotidine	H2 blocker	$C_8H_{15}N_7O_2S_3$	4	Antiulcer	(Motohashi, Uwai, Hiramoto, Okuc Inui, 2004)
Cimetidine	Histamine H_2 receptor antagonist	$C_{10}H_{16}N_6S$	4	Antiulcer	(Motohashi et al., 2004)
Loratadine	Anti-Histamine	$C_{22}H_{23}ClN_2O_2$	4	Itching, runny nose, watery eyes, and sneezing from "hay fever"	(Diav-Citrin et al., 2003)

4

Figure 1

Prisma Flow Diagram

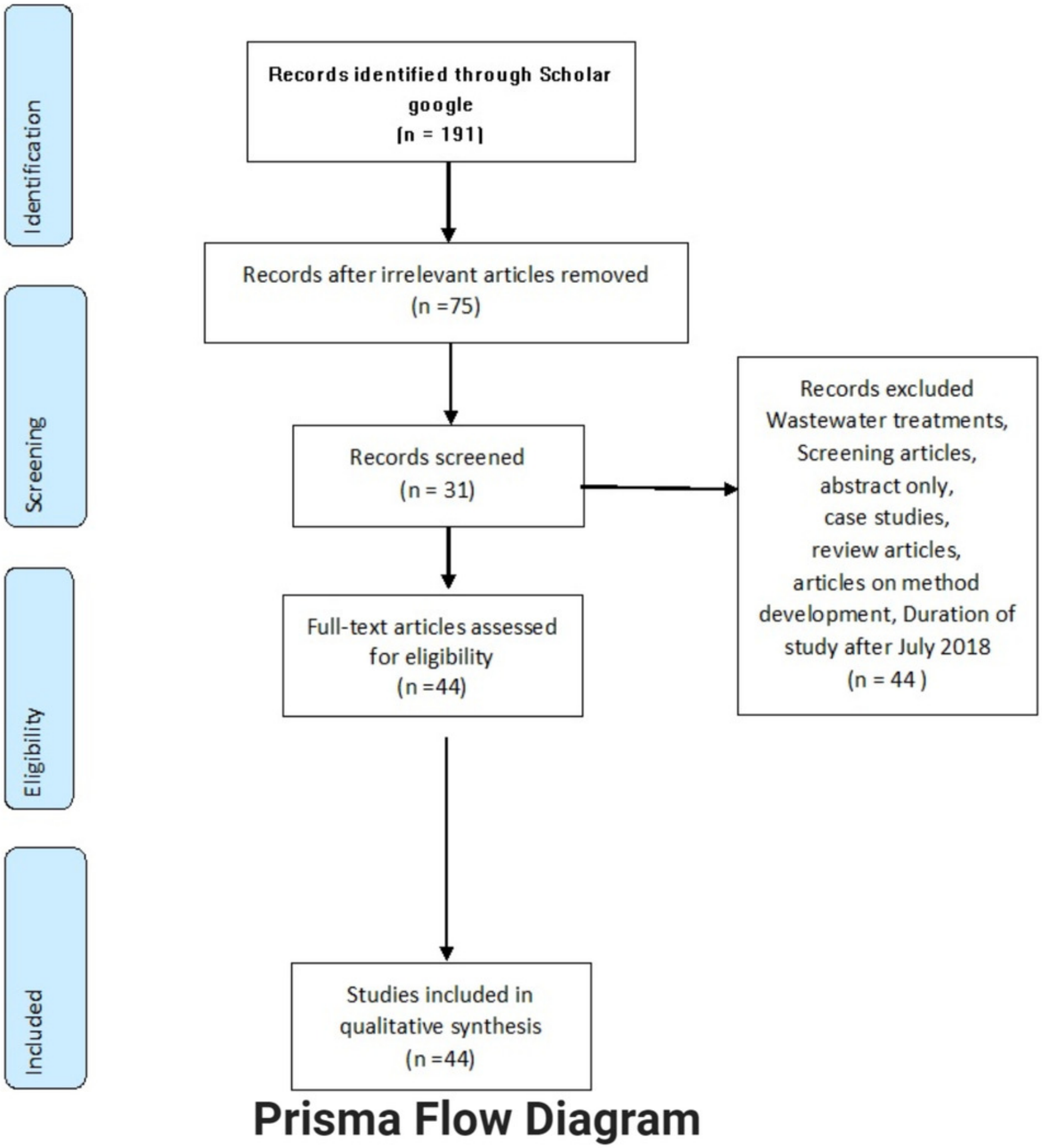

Figure 2

List of Journal along with number of articles published between January 2010 till July 2018

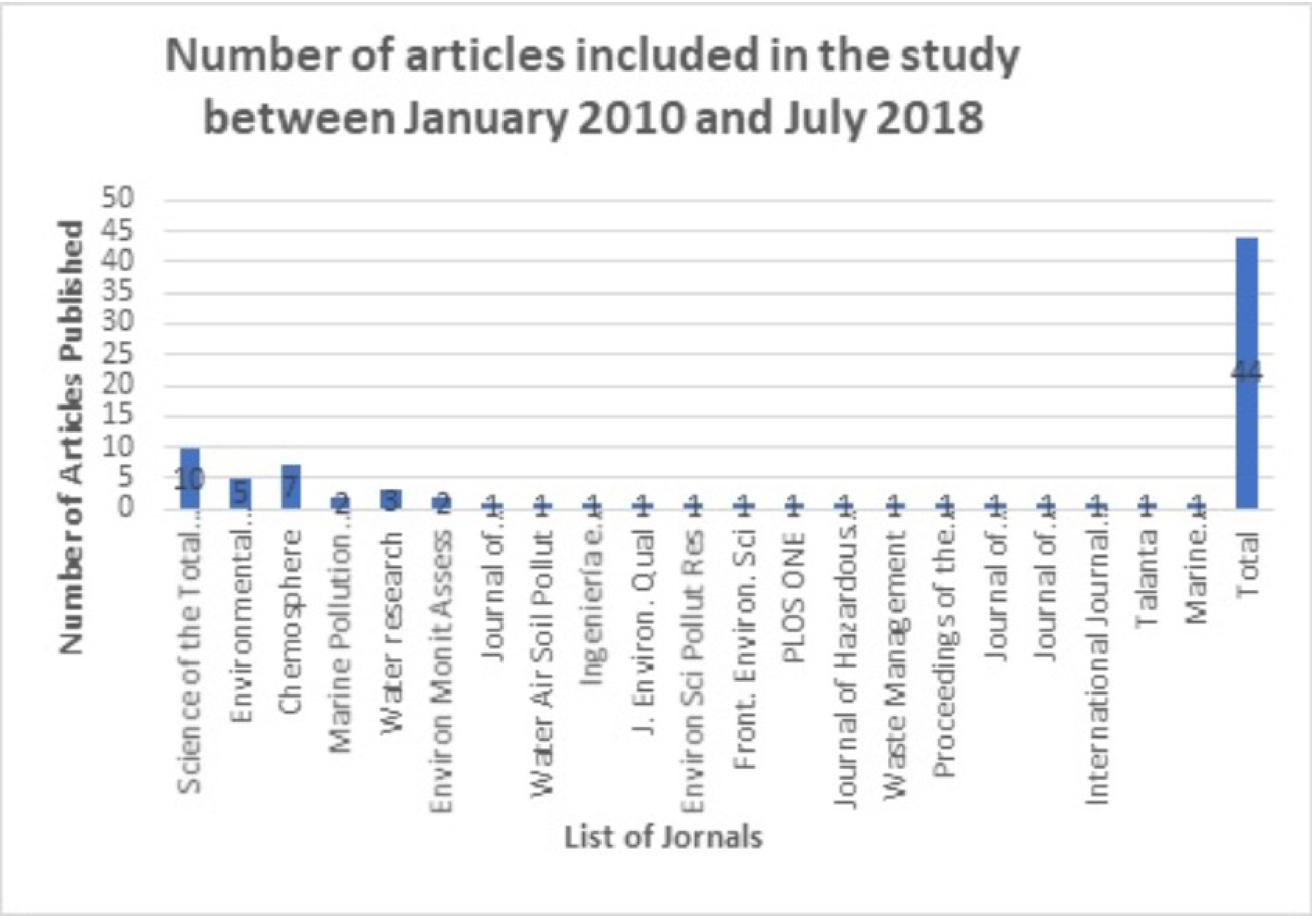

Figure 2 List of Journal along with number of articles published between January 2010 till July 2018.

Figure 3

Number of article included in the study that were published between January 2010-July 2018

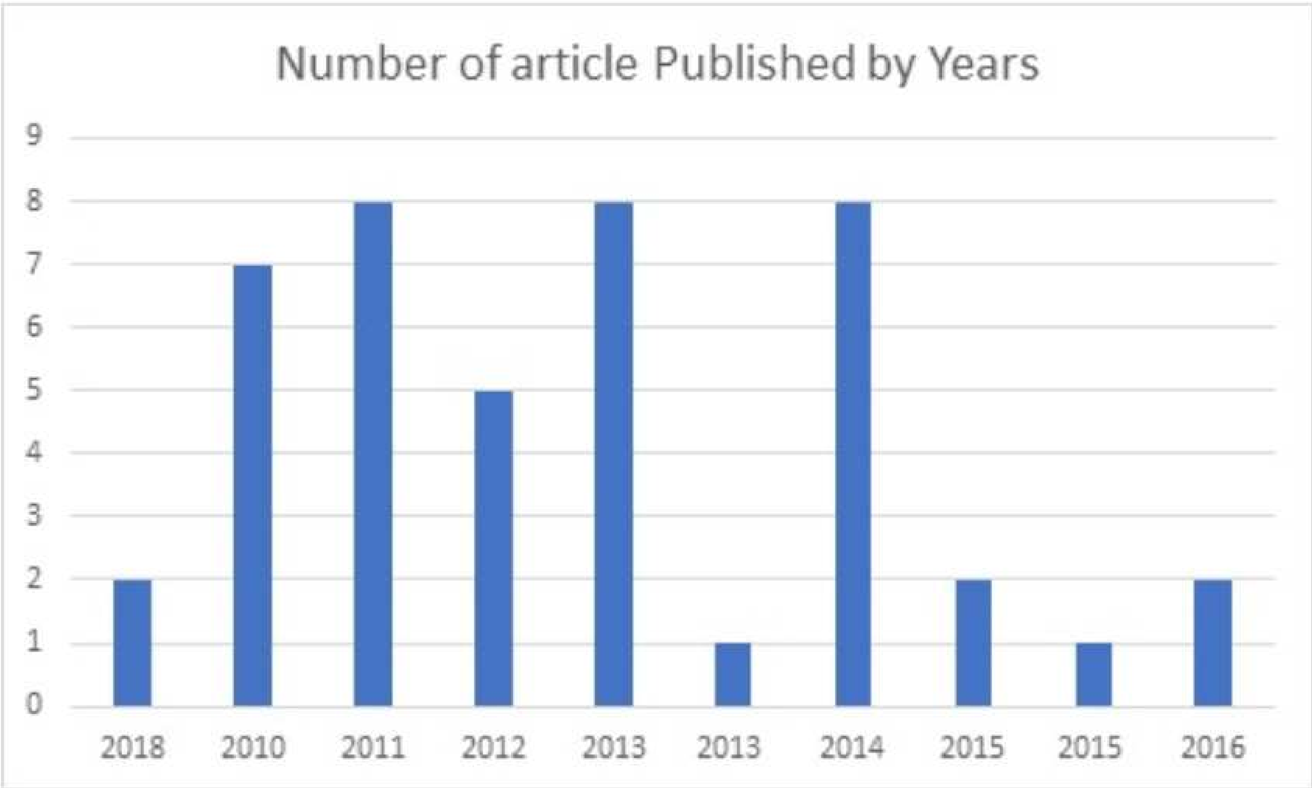

Figure 3: Number of article included in the study that were published between January 2010-July 2018