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Review

Pharmaceutical Contaminants in Wastewater and Receiving Water Bodies of South Africa: A Review of Sources, Pathways, Occurrence, Effects, and Geographical Distribution

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Abstract: The focus of this review article was to outline the sources, pathways, effects, occurrence, and spatial distribution of the most prescribed pharmaceuticals in wastewater and receiving waters of South Africa. Google Scholar, Web of Science, and Scopus were used to gather data from different regions. A zone-wise classification method was used to determine the spatial distribution and data deficiencies in different regions of South Africa. This review revealed that over 100 pharmaceutical compounds have been reported in South Africa's various water sources and wastewater, with most studies and highest concentrations being documented in Gauteng and Kwa-Zulu Natal. The pharmaceutical concentration in water samples ranged from ng/L to µg/L. Aspirin, ketoprofen, diclofenac, ibuprofen, naproxen, erythromycin, tetracycline, sulfamethoxazole, acetaminophen, streptomycin, ciprofloxacin, ampicillin, carbamazepine, atenolol, pindolol, efavirenz, and zidovudine residues were among the frequently detected pharmaceutical residues in water bodies and wastewaters of South Africa. Based on the spatial distribution data, Gauteng has the highest number of pharmaceuticals (108) detected in waste and surface water, with the Northern Cape having no monitoring evidence. Therefore, to precisely ascertain the geographical distribution of pharmaceutical contaminants in South Africa, this review recommends that further research be carried out to track their occurrence in aquatic environments and WWTP, especially in isolated regions like Limpopo.

Keywords: pharmaceuticals; wastewater; potential effects; geographical distribution

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1. Introduction

The presence of pharmaceutical residues, such as antibiotics, β-blocker, non-steroidal anti-inflammatory drugs (NSAIDs), antiretroviral drugs, hormones, and lipid regulators in water bodies has garnered significant attention due to their adverse effects on human health and aquatic ecosystems [1]. These persistent substances can exert detrimental effects even at trace concentrations, leading to concerns such as drug-resistant populations, infertility, cancer, endocrine disruption, and diminished plant and animal growth at trace concentrations (ng/L) [2,3]. Pharmaceutical contaminants such as ampicillin, penicillin, amoxicillin, diclofenac, paracetamol, vancomycin, sulphathiazole, carbamazepine, efavirenz, aspirin, paracetamol, and ibuprofen are commonly detected in surface water and reclaimed wastewater as well as groundwater purposes [4,5]. Generally, pharmaceutical compounds find their way into aquatic ecosystems through discharges from domestic and

industrial sewage, leaching from landfills, indiscriminate disposal of domestic and hospital waste, and stormwater runoff [6].

In South Africa, large populations greatly depend on groundwater supply, particularly in rural areas, while urban and suburban residences largely rely on surface water for domestic and drinking purposes. As a result, the presence of pharmaceutical contaminants in water resources might result in significant health risks to aquatic organisms and human health. However, pharmaceutical contaminants are yet to be regulated since they have been identified as emerging contaminants, especially in developing regions like Africa. At the same time, other regions have reported approximately and set recommendations for more than 143,000 industrial chemicals, which include pharmaceutical pollutants [7]. The frequent production and use of these chemical compounds for health purposes without regulatory evaluation, mostly in poor countries like South Africa, have increased their environmental abundance. They require immediate regulations, frameworks, and policies to recommend permissible limits for their disposal in aquatic systems.

To date, South Africa has reported more than 100 pharmaceutical residues in different water bodies, with the highest concentrations reported in wastewater. According to a report conducted by Madikizela and Ncube [7], about 60% of the information that is currently available on the occurrence of pharmaceutical residues in African aquatic systems comes from South Africa. This trend has been attributed to South Africa's higher level of development than most African nations [8]. To gain a comprehensive understanding of the occurrence, origins, potential ecotoxicological impacts, and ecotoxicological dangers in South Africa from 2012 to 2022, multiple reviews have been carried out [7,9–13]. However, the available literature did not give a comprehensive review of the spatial distribution of pharmaceutical contaminants in South Africa.

This review aims to fill this gap by providing a comprehensive overview of the sources, pathways, effects, occurrence, and spatial distribution of the most prescribed pharmaceuticals in wastewater and receiving waters of South Africa. The scope extends to discussing different classes of pharmaceuticals detected in the region and their concentrations in various water bodies. Additionally, the review outlines gaps in existing knowledge and provides recommendations for future research. The methodology involved utilizing an online library, namely Google Scholar, Web of Science, and Scopus, to gather data, and a zone-wise classification method was employed to determine spatial distribution and identify data deficiencies in different regions of South Africa.

2. Sources and Pathways of Pharmaceutical Contaminants in South African Water Sources

Aquatic systems are the primary sinks of pharmaceutical contaminants. Pharmaceutical manufacturing companies, domestic sewage, health facilities such as clinics (human health and veterinary) and hospitals, agricultural runoff, and stormwater from farms are the common sources that contribute to the environmental accumulation of pharmaceutical contaminants [14,15]. The prime pharmaceutical sources are indicated in Figure 1. Generally, it is known that pharmaceuticals are used to improve and increase human health and life span as well as food production. As a result, they are classified as veterinary and human drugs. When consumed, an animal or human body utilizes 20% of the drug and excretes 80% via feces and urine [16–18]. The excreted metabolites are then discharged as sewage from domestic, central business districts (CBDs), and health facilities into wastewater treatment plants [19,20]. Thus, domestic and health facilities sewage are the primary source of pharmaceutical residues in wastewater. It is important to note that wastewater treatment plants are crucial for removing pharmaceutical contaminants from wastewater. However, the efficacy of these treatment processes can vary, leading to the persistence of certain pharmaceuticals in the treated effluent and subsequent discharge into receiving water bodies [21,22].

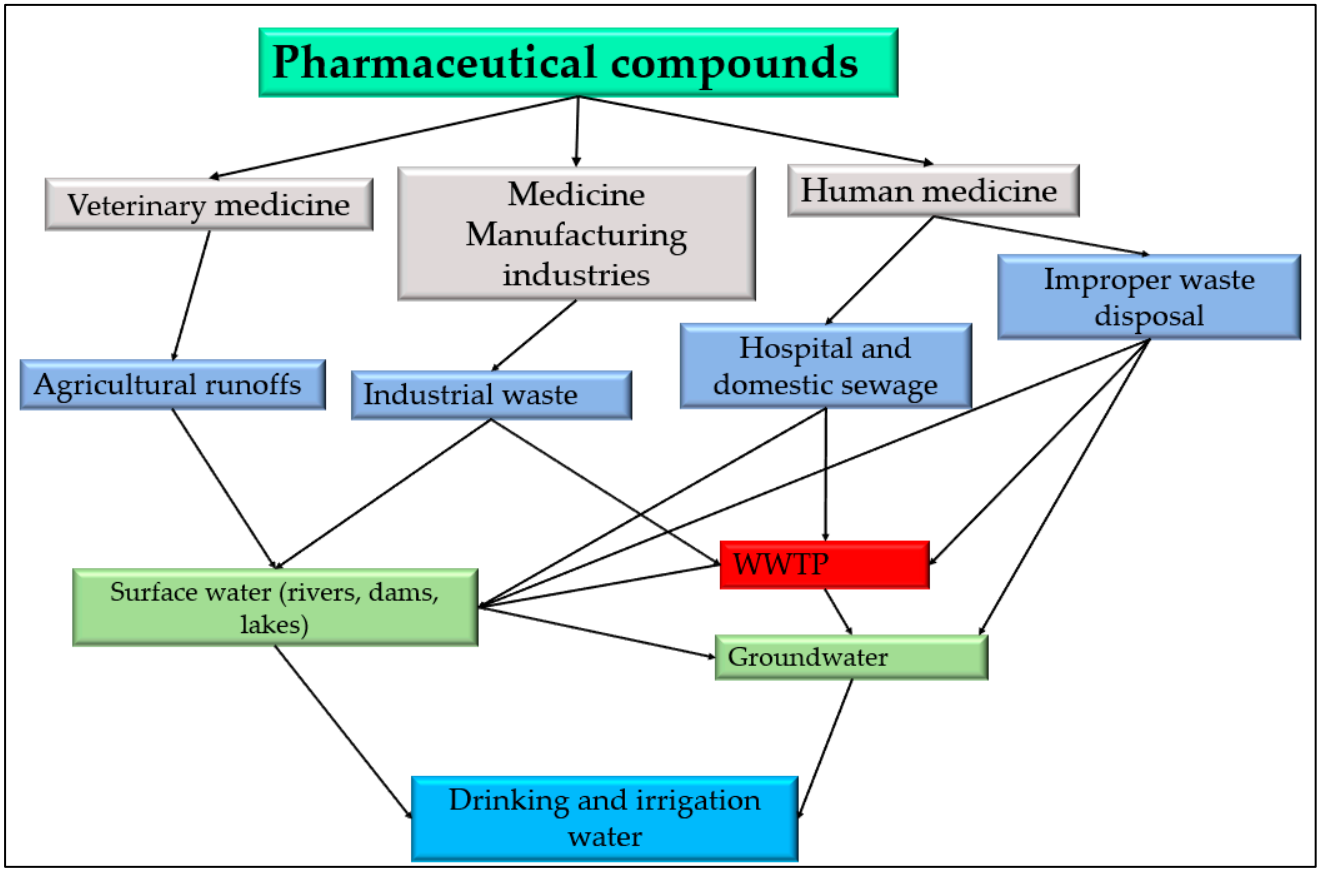

Figure 1. A diagram showing sources and pathways of pharmaceutical contaminants in water sources [10].

Additionally, wastewater treatment plants (WWTP) are the receiving end of these contaminants, making it a pharmaceutical pool that discharges pharmaceuticals into receiving water bodies [23]. Most wastewater treatment plants are composed of biological and mechanical processes as chemical purification processes to biodegrade, precipitate, and reduce the available organic and inorganic contaminants [18–20]. However, the inability of the WWTPs to reduce the presence of these contaminants has been proven by numerous studies [24,25]. For example, a study by Abafe et al. [26] examined the removal efficiency of the treatment plants towards zidovudine, didanosine, nelfinavir, ritonavir, nevirapine, stavudine, lopinavir, saquinavir, maraviroc, lamivudine, and efavirenz. The results showed the incomplete removal of the most identified pharmaceutical contaminants with >90% removal of abacavir, zidovudine, and lamivudine in all WWTP. The wastewater from DEWATS and the Phoenix WWTP accumulated atazanavir; the effluent from DEWATS and the Northern WWTP accumulated efavirenz; and the effluents from all three WWTPs accumulated lopinavir and nevirapine. As a result, effluent disposal in aquatic environments has been regarded as the main route of pharmaceutical residues into the environment [27]. Additionally, it can be recommended that more research be tailored to developing efficient removal methods for these contaminants.

The unavailability of modern toilets remains a challenge since domestic sewage or wastewater cannot be properly discharged and channeled into wastewater treatment facilities, resulting in seepage in groundwater and leakages in the environment during transportation [11,12]. During rainy seasons, pharmaceutical residues contaminate surface water, and pit latrines leach into groundwater through aquifer recharges [28]. Ebele et al. [29] reported an average of 2068 ng/L during dry seasons and 2860 ng/L in wet seasons, confirming that high levels of pharmaceuticals are introduced during wet seasons into surface and groundwater sources. However, a global data scarcity exists on seasonal

pharmaceutical distribution in water bodies, suggesting that similar studies should be conducted to provide a comprehensive picture of the seasonal variation in pharmaceutical pollutants in aquatic systems. The presence of pharmaceuticals in groundwater and drinking waters of South Africa was reported by Swanepoel et al. [30]. The authors reported a respective concentration of <low detection limit (LDL) (0.02 ng/L), <LDL (1 ng/L), and <LDL (0.3 ng/L) of lamivudine, zidovudine, and abacavir, and in groundwater of Northwest and Gauteng Provinces of South Africa.

3. Commonly Detected Pharmaceuticals in South Africa's Wastewater and Water Sources

Table 1 summarizes different categories of the most detected pharmaceuticals in South African water bodies [31–35]. The commonly detected pharmaceutical contaminants in South African waters include commonly prescribed drugs, namely analgesics, antiretroviral, non-steroidal anti-inflammatory drugs, and antibiotics. Steroids, as well as related hormones, are part of the widely detected pharmaceuticals.

Table 1. Class of pharmaceutical contaminants detected in water bodies of South Africa.

Drug Class	Types of Pharmaceuticals
Analgesics	disprin, ibuprofen, paracetamol, indomethacin codeine, phenazone
Antibiotics	vancomycin, penicillin, amoxicillin, streptomycin, ciprofloxacin sulfamethoxazole, azithromycin
NSAID	diclofenac, ketoprofen, and naproxen
Beta-blockers	betacolol, propranolol, atenolol
Steroids hormones	17-beta-oestradiol, 17-alpha-ethinyloestradiol
Antiretroviral drugs	efavirenz, zidovudine, darunavir, emtricitabine

3.1. Analgesics and NSAIDs

Analgesic drugs are generally used for pain relief, while anti-inflammatory drugs are used to reduce or treat swelling or inflammation [36]. This includes aspirin, ketoprofen, diclofenac, ibuprofen, naproxen, indomethacin, and paracetamol drugs. Analgesics are also regarded as self-prescription drugs because one can easily access them from the market. Thus, this class of pharmaceuticals is among the contaminants that are frequently detected in surface waters and wastewater of South Africa. Table 2 shows different analgesics and anti-inflammatory drugs commonly found in South African water bodies and their concentration ranges. The occurrence of ibuprofen ranging from LDL–10 µg/L in wastewater, surface water, and sediments–was reported in Kwa-Zulu Natal, the Darvill wastewater treatment plant, and the Msunduzi river [37]. Gumbi et al. [38] confirmed the presence of diclofenac (LDL–9.53 ng/g), ibuprofen (LDL–134 ng/g), and naproxen (LDL–4.31 ng/g) in the sediments of the Mgeni and Msunduzi river in Kwa-Zulu Natal, indicating surface water contamination. Archer et al. [9] confirmed the occurrence of naproxen (5–1112.8 ng/L), acetaminophen (3.1–76.1 ng/L), ketoprofen (0.5–642.2 ng/L), ibuprofen (2–312.1 ng/L), and diclofenac (3.1–1461.5 ng/L) in surface water in Gauteng province, which is connected to wastewater treatment plants. Compared to surface water, wastewater contains a higher concentration of pharmaceutical contaminants, indicating that it serves as a reservoir for these contaminants.

3.2. Antibiotics

Antibiotics are commonly used for preventing and treating infectious diseases in animals and humans. Increased use of antibiotics has continued for several decades due to their ability to treat different diseases, mainly bacterial infectious diseases. Since

2002, annual antibiotic sales have grown from 1540 to 300,000 tons [39]. An increase in sales reflects the prevalence of diseases in the human population, particularly in informal settlements, due to increased population growth. The high consumption of these drugs triggers their increased discharge into the environment. Moreover, South Africa is among the countries with high antibiotic consumption due to increased HIV infections, particularly in the Kwa-Zulu Natal and Gauteng provinces [40]. The proliferation of antibiotic-resistant bacteria and the emergence of resistant genes in both the ecological population and humans have been linked to exposure to antibiotic residues [41]. Studies by Agunbiade and Moodley [42] and Khulu et al. [43] verified the presence of sulfamethoxazole, chloramphenicol, ampicillin, and erythromycin in both wastewater as well as surface water. Faleye et al. [37] further examined the concentration of antibiotics in wastewater and surface water, where the presence of ethionamide (90–0.1 ng/L), metronidazole (24,000–18 ng/L), trimethoprim (6200–2.4 ng/L), erythromycin (290–0.01 ng/L), norfloxacin (40–2.6 ng/L), ofloxacin (730–21.7 ng/L), ciprofloxacin 15,000–478.4 ng/L), albendazole (170,000–555.4 ng/L), sulfamethoxazole (13,000–3.3 ng/L), roxithromycin (2000–1.7 ng/L), azithromycin (40–0.4 ng/L), clarithromycin (4500–3.9 ng/L), and clindamycin (60–0.1 ng/L) was reported both in influent and effluent samples. In South Africa's Buffalo and Sundays River estuaries, Ohoro et al. [43] documented the presence of antibiotics in the aquatic environment. Trimethoprim (0.52–1.62 g/L) and sulfamethoxazole (0.07–0.03 g/L) were found in water samples taken during the winter, spring, and summer seasons. Thus, the presence of antibiotics in drinking water sources can significantly cause harm to the surrounding population and aquatic life.

3.3. Beta-Blocker Drugs

Beta-blockers are medications used to reduce blood pressure and cardiovascular diseases. Beta-blockers include salbutamol, atenolol, sotalol, theophylline, propranolol, and metoprolol. The use of beta blockers has increased due to an increase in blood pressure patients over the past decade [44]. Thus, this has influenced their frequent occurrence in the aquatic environment associated with increased consumption and population growth [45]. Ramiyi et al. [46] used a passive sampling technique to screen the occurrence of emerging pollutants in the surface water of Hartbeespoort Dam catchment's Hennops and Jukskei Rivers in Gauteng Province. The study reported the presence of salbutamol, atenolol, sotalol, theophylline, propranolol, atenolol, practolol, pindolol, bisoprolol, and metoprolol in both sampling sites. However, this study did not give quantitative data regarding the concentration of the detected drugs. A study by Osunmakinde et al. [31] documented the occurrence of pindolol and atenolol in wastewater of Gauteng, with the highest values of 0.03 ng/L and 39.1 ng/L, respectively. The presence of atenolol in the surface and wastewater was also reported by Archer et al. [9], with a maximum concentration of 91.7 and 86.8 ng/L in wastewater influent and effluent, respectively, as well as 97.4 and 102.4 ng/L in the upstream and downstream. Atenolol and Pindolol were detected in the surface water of Umgani River in Pietermaritzburg, KwaZulu-Natal, at concentrations of 0.44 and 39 ng/L, respectively, [47].

3.4. Steroid Drugs

Steroids are natural or man-made hormones. Steroid medications have recently become known as a class of environmental toxins that may be harmful to both human and aquatic health [43]. The steroid hormones (17-beta oestradiol (E2), estrone (E1), ethinylestradiol (EE2), estriol (E3), testosterone, and progestogen are among the endocrine-disrupting substances. Estrogen, testosterone, and progesterone have been found in the Umsunduzi River wastewater treatment facility in Kwa-Zulu Natal, with concentrations of 0–278 ng/L, 0–628 ng/L, and 0–795 ng/L in wastewater and 0–46 ng/L, 0–51 ng/L, and 0–22 ng/L in surface water by Manickum and John [47]. The study further estimated the total concentration of all the hormones detected in the wastewater obtained an average of ± 989 ng/L over the period of 2 years from 2010 up to 2012 monthly. The relative average concentrations of

all observed concentrations monthly were summarized as follows: Pro: 408 ng/L (41.4%); tes: 343 ng/L (34.7%); E2: 119 ng/L (12.0%); E1: 84 ng/L (8.5%); EE2: 30 ng/L (3.0%); and E3: 5 ng/L (0.5%). In the Limpopo Province, estradiol was recorded in wastewater by Manavhela et al. [48]. The concentration ranged from 0.32 to 348.6 ng/L in wastewater. South African researchers Van Zijl et al. assessed the occurrence of estrogens in the drinking water in 40 distinct locations throughout Pretoria and Cape Town [49]. According to the study, Cape Town had the greatest levels of estrogens in the analyzed drinking water sample, which ranged from 0.002 to 0.11 ng/L. Thus, estrogen contamination in drinking water may result through groundwater recharging with contaminated water from treated and untreated wastewater discharged into receiving water sources such as rivers and dams.

3.5. Antiviral Drugs

Antiviral medications are prescribed to treat viral infections such as hepatitis, influenza, and HIV. These drugs are among the commonly detected pharmaceutical contaminants in wastewater and different water sources. This includes zidovudine, saquinavir, ritonavir, raltegravir, nevirapine, lopinavir, efavirenz, lamivudine, and emtricitabine [50–52]. Swanepoel et al. [28] evaluated the prevalence of antiviral drugs in wastewater, surface, groundwater, and drinking across different regions of South Africa. The study reported the occurrence of abacavir, efavirenz, didanosine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, saquinavir, tenofovir, and zidovudine with concentrations ranging from below the quantification limit (LDL)–1.6 ng/L in wastewater, LDL–3.5 ng/L in drinking water, LDL–6.8 ng/L in surface water, and LDL–5.3 ng/L in groundwater. Their study recorded the highest concentrations of these pharmaceuticals in Kwa-Zulu Natal (KZN), which could be ascribed to the highest HIV statistics reported in this province.

Table 2. Concentrations of pharmaceuticals in South African waters.

Pharmaceuticals		Concentrations (ng/L)			Reference
Antibiotics	**Region**	**WWT**	**Surface**	**Tap Water**	
Erythromycin	KZN, Eastern Cape		LDL–4		[51,52]
Tetracycline	KZN, Northwest		LDL–4		[51,53]
Streptomycin	KZN		LDL–10		[51]
Sulfamethoxazole	KZN, Gauteng; Eastern Cape	LDL–1013.2	LDL–9		[51,52]
Acetaminophen	KZN, Gauteng, Gauteng		LDL–135		[51,52]
Streptomycin	KZN		LDL–11		[51,54]
Tylosin	KZN, Eastern Cape, Gauteng		LDL–11		[52,55,56]
Chloramphenicol	KZN		LDL–2.5		[51]
Ciprofloxacin	KZN, Gauteng, Eastern Cape, Northwest	LDL–35.5	LDL–4		[9,36,51–53,57]
Ampicillin	KZN		LDL–5		[36,51,58]
Nalidixic acid	KZN, Gauteng		LDL–7		
Trimethoprim	KZN, Gauteng	LDL–898.7	LDL–2.8		[36]
Metronidazole	KZN		LDL–5.77		
Oxytetracycline	Gauteng	LDL–42			[32]
Clarithromycin	Eastern Cape		LDL–3280.4		[52]
Ofloxacin	Gauteng, Northwest	LDL–100			[32,55]
Oxolinic acid	Gauteng	LDL–37	LDL–0.25		[32,59]
Sulfamethazine	Gauteng, Eastern Cape	LDL–56.3	LDL–0.4		[32,43,60]
Sulfaguanadin	Gauteng	LDL–17.9			[32]
Sulfadoxin	Gauteng	LDL–78.6			
Sulfadimethoxine	Gauteng	LDL–621.4			
Enrofloxacin	Gauteng	LDL–0.74			
Trimethoprim	Gauteng, Eastern Cape	LDL–577.6			[9,32,44]
Lincomycin	Gauteng	LDL–20.65			[32]
Isoniazid	Gauteng	LDL–93.8			
Sulfadiazine	Gauteng	LDL–53			[9,32]
Sarafloxacin	Gauteng	LDL–8.33			[32]

Table 2. *Cont.*

Pharmaceuticals		Concentrations (ng/L)			Reference
Norfloxacin	Gauteng, Northwest	LDL–319			[32,55]
Sulfapyridine	Gauteng	LDL–39			[32]
Sulfanilamide	Gauteng	LDL–50			
Flumequine	Gauteng, Western Cape		LDL–0.25		[60]
Lomefloxacin	Gauteng		LDL–0.35		[59]
Azithromycin	Gauteng	LDL–24.6			
Anti-psychotics					
Clozapine	KZN, Gauteng		0–2.08		[36,61]
Bezafibrate	KZN, Gauteng, Northwest	85.76–4878	0–80.3		[32,36,43,50,52,62–64]
Caffeine	Gauteng, Western Cape, Eastern Cape, Northwest, Mpumalanga	1170–60,136	LDL–927		
Carbamazepine	KZN, Gauteng, Eastern Cape, Northwest, Free State, Mpumalanga	LDL–52.35	LDL–52.35	0.02–0.3	
Mevastatin	Gauteng	LDL–3.32			[65]
Simvastatin	Gauteng	LDL–11.7			[65]
Clofibric acid	Gauteng	LDL–12.96			[65]
Triclocarban	Gauteng, Northwest	8.973–276.1			[32,53]
Pravastatin	Gauteng	LDL–4.82			[34,65]
Fluvastatin	Gauteng	LDL–1.97			
Lovastatin	Gauteng	LDL–8.03			
Fenofibrate	Gauteng	LDL–0.78			
Fenofibric acid	Gauteng	LDL-19.9			
Ifosfamide	Gauteng	LDL–5.43			[32]
Lidocaine	Gauteng	LDL–424.6			
Methylparaben	Gauteng	1.649–600.4			
Paraxanthine	Gauteng	4963–35,286			
Prednisolone	Gauteng	LDL–36.17			
Procaine	Gauteng	LDL–14.52			
Ractopamine	Gauteng	LDL–2.29			
Salbutamol	Gauteng	LDL–8.60			
Terbutaline	Gauteng	LDL–1.44			
Tonalide	Gauteng	0.21–80.16			[9]
Tramadol	Gauteng	0.718–289.8			[9,51,65]
Venlafaxine	Gauteng	LDL–52.35	LDL–94.6		[32,66]
Atorvostatin	Gauteng	LDL–3.73	LDL–150.6		
Gabapentin	Gauteng	LDL–146.4			
Gemfibrozil	KZN Gauteng	LDL–598.6			
Analgesics/anti-inflammatory					
Aspirin	KZN, Gauteng		LDL–427		[51]
Ketoprofen	KZN, Gauteng, Northwest	LDL–57			[51,53,59,60,64,66,67]
Diclofenac	KZN, Gauteng, Northwest	LDL–21,100	LDL–309		
Ibuprofen	KZN, Gauteng, Northwest	LDL–66,900	LDL–0.113		
Naproxen	Gauteng, KZN	LDL–8990			[32,38,64,66,67]
Indomethacin	Gauteng	LDL–31.55			
Mefenamic acid	Gauteng, KZN	11.30–91.15			[32,38]
Paracetamol	Gauteng, KZN	155.3–22,889			
Phenacetin	Gauteng, KZN	0.32–68.58			
Salicylamide	Gauteng	5.47–563.50			[32]
Tramadol	Gauteng	0.718–289.8			
Fenoprofen	KZN	LDL–47,600			[64]
Meclofenamic	Gauteng, KZN		LDL–0.849		[38]
Beta Blockers					
Atenolol	KZN, Gauteng	LDL–39.1	LDL–39.1		[9,50,68]
Pindolol	Gauteng	LDL–0,03	LDL–0,03		[9,30]
Antiretroviral drugs					

Table 2. *Cont.*

Pharmaceuticals		Concentrations (ng/L)			Reference
Darunavir	KZN	LDL–43			[26,61]
Efavirenz	KZN, Gauteng, Limpopo	LDL–140	LDL–135		[14,48,69,70]
Emtricitabine	KZN, Gauteng	LDL–172	0–0.13		[48,50]
Lamivudine	Gauteng	LDL–1001	LDL–242		[32,49,50]
Nevirapine	Gauteng, KZN	LDL–1480	LDL–148		[32,49]
Penciclovir	Gauteng, KZN	LDL–104.8			[32,49]
Zidovudine	KZN, Gauteng, Free State	LDL–243	LDL–973	LDL–0.07	[26,49]
Ritonavir	Gauteng	LDL–393.90			[32]
Atazanavir	Gauteng	LDL–10.69			
Famciclovir	Gauteng	LDL–17.67			[31,32]
Didanosine	Free State, Gauteng		LDL–54.1		[49,66]
Tenofovir disoproxil	Gauteng, KZN, Free State	0.16–0.19	LDL–243		[49,50,66]
Zalcitabine	Gauteng, Free State		LDL–71.3	LDL–0.008	[49]
Stavudine	Gauteng		LDL–778		
Ribavirin	Gauteng	LDL–0.02			[31]
Steroid hormones					
Estriol	Western Cape, Gauteng, Eastern Cape, Northwest, Limpopo	LDL–1313			[32,46,58,71]
Estrone	Eastern Cape, Limpopo, Gauteng, Western Cape, Northwest	LDL–60.83			[32,47]
Estradiol	Northwest, Western Cape, Limpopo, Gauteng	154.1–7133			[32,72]
Medroxyprogesterone	Mpumalanga, Gauteng	LDL–16.85			[32,72]
Mestranol	Gauteng	LDL–123.4			[32]
Diethylstilbesterol	Mpumalanga, Gauteng	LDL–547.7	0.001–0.01		[32,72]
Progesterone	Limpopo, Western Cape, KZN, Gauteng	LDL–14.52			[32,47,71,73]
Testosterone	KZN, Western Cape, Gauteng, Eastern Cape, Limpopo	LDL–44.09			[32,47,71,73]
Other drugs					
Amphetamine	Gauteng		LDL–37		
Nicotine	Gauteng		LDL–245.5		
Cotinine	Gauteng		LDL–31.7		
Gliclazide	Gauteng		LDL–53.9		
Metformin	Gauteng		LDL–81.7		[9]
Irbesartan	Gauteng		LDL–554.4		
Valsartan	Gauteng		LDL–924.7		
Iopromide	Gauteng		LDL–598.3		
Codeine	Gauteng	LDL–1.61			
Morphine	Gauteng	LDL–4.82			
Meperidine	Gauteng	LDL–3.68			
Hydrocodone	Gauteng	LDL–10.9			
Oxycodone	Gauteng	LDL–4.9			
Heroin	Gauteng	LDL–42.2			
Hydromorphone	Gauteng	LDL–12.5			
Oxymorphone	Gauteng	LDL–74.9			
Thebaine	Gauteng	LDL–21.1			
Buprenorphine	Gauteng	LDL–22.3			[74]
Fentanyl	Gauteng	LDL–25.9			
Ketamine	Gauteng	LDL–11.6			
Methadone	Gauteng	LDL–147			
Dihydrocodeine	Gauteng	LDL–4.29			
Alfentanyl	Gauteng	LDL–4.29			
Levorphanol	Gauteng	LDL–17.6			
Tramadol	Gauteng	LDL–24.6			
Ethylmorphine	Gauteng	LDL–19.9			
Remifentanyl	Gauteng	LDL–28.9			

Abafe et al. [26] reported the presence of antiretroviral residues in influents and effluents from the Kwa-Zulu Natal wastewater treatment facilities Phoenix, DEWATS, and Northern. Zidovudine, didanosine, nelfinavir, ritonavir, nevirapine, stavudine, lopinavir, saquinavir, maraviroc, lamivudine, and efavirenz were identified in all sampling sites. The concentration ranged from 61 to 24,000 ng/L (influent), the limit of detection (LDL)–20,000 ng/L (effluent) in Phoenix WWTP; LDL–24,000 ng/L (influent), LDL–33,000 ng/L (effluent) in Northern WWTP; and LDL–53,000 ng/L (influent) and LDL–34,000 ng/L (effluent) in a DEWATS WWTP. Thus, the presence of antiretroviral drugs in aquatic environments might pose a significant risk to the surrounding population. High concentrations in wastewater samples validate that wastewater treatment plants are regarded as a pool of pharmaceutical contaminants.

3.6. Anti-Depressant and Illicit Drugs

Anti-depressant drugs are used for mental illness and are also known as opioid drugs. Examples include clozapine, bezafibrate, carbamazepine, dexamethasone, digoxigenin, gabapentin, gemfibrozil, ifosfamide methylparaben, and paraxanthine [32,33,65,66]. A study by Mhuka et al. [32] reported the presence of clarithromycin (LDL–75 mg/L), amitriptyline (LDL–56 ng/L), sarafloxacin (LDL–8.3 ng/L), paraxanthine (LDL–35,286 ng/L), and verapamil (LDL–1.21 ng/L) in wastewaters of Gauteng. Tete et al. [65] also reported the presence of mevastatin (LDL–3.15 µg/L), fenofibrate (LDL–0.78 µg/L), pravastatin (LDL–4.82 µg/L), fluvastatin (LDL–1.78 µg/L), atorvastatin (LDL–3.74 µg/L), gemfibrozil (LDL–19.76 µg/L), simvastatin (LDL–11.70 µg/L), and the corresponding metabolites (clofibric and fenofibric acids (LDL–12.96 µg/L) in Daspoort WWTP as well as Apies River in Gauteng. Both waste and surface water samples had pollutant concentrations that ranged from 0.56 to 19.90 g/L.

Illicit drugs are a group of pharmaceutical drugs used for non-medical benefits. Illicit drugs have caused a global burden of diseases related to drug-use disorders, with approximately 11 million deaths per year in 2015, and a rapid increase in these drugs has been observed [75,76]. In 2019, South Africa was ranked among the overuses of illicit drugs, with 184,030 affected people between the age of 15 and 65 years [77,78]. Studies have shown the presence of illicit drugs within South African wastewaters, with amounts ranging from LDL–42.2 ng/L [74,79]. Kamika et al. [74] documented the presence of 19 opioid compounds in wastewater from Meyerton, Leeuwkuil, Sandspruit, and Rietgat waste treatment plants in Gauteng Province and their receiving water, such as Vaal, Klip, Sun Spruit, and Soutspruit Rivers. Dihydrocodeine, codeine, hydrocodone, oxycodone, hydromorphone, fentanyl, ketamine, and thebaine are among the detected pharmaceuticals in both wastewater and receiving waters. The Leeuwkuil WWTP samples were the most contaminated, with 18 of 19 opioid concentrations > 1 µg/L. In statistical analyses of receiving waters, it was discovered that upstream surface water contained the greatest limit of quantification (LOQ) of opioids ($p = 0.05$), and dihydrocodeine, ketamine, oxycodone, fentanyl, hydromorphone, and hydrocodone were not detected. The occurrence of high concentrations of opioid metabolites in downstream surface water (298 ng/L–10.8 µg/L for Klip River, 4.49 ng/L–13.1 µg/L for Vaal River, 70.5 ng/L–10.0 µg/L for Soutspruit River, and 8.0 ng/L–2.43 µg/L for Sun Spruit River) was directly linked to their mass loads in the respective wastewater effluent samples. The presence of these drugs in water bodies in Gauteng indicates their extensive use and potential risk to the surrounding population.

4. Health Impacts of Pharmaceutical Contaminants on Aquatic Organisms

There is evidence that pharmaceutical contamination can bioaccumulate in aquatic food chains. This was validated by a compressive analysis of the presence of pharmaceuticals in limpets, sea snails, mussels, and sea urchins in the Kalk Bay harbor, Cape Town, by Ojemaye and Petric [80]. The study reported an accumulation of 3.70–4.18 ng/L in seawater, 92.08–171.89 ng/g dry weight (wt) in sediment, 67.67–780.26 ng/g dry wt of marine invertebrates, and 101.50–309.11 ng/g dry wt in seaweed, with a risk coefficient of 0.5 to 10 indicating acute and acute risk to fish. The presence of these pharmaceutical contaminants in different compartments validates their ability to bioaccumulate and transferability from different environmental compartments. However, there are no studies that have assessed the effect of these compounds on human health and aquatic organisms in South Africa.

However, several studies have assessed the possible effects of pharmaceutical contaminants on aquatic organisms such as algae, mussels, and fish [8,81–83]. These studies revealed that exposure to pharmaceutical contaminants, even at low concentrations, can pose significant effects such as altering appetite, immunological function, reproduction, and behavioral processes and delay maturity and potentially fatal effects [84–86]. For example, a study by Capolupo et al. [87] evaluated the impact of propranolol (PROP), 17α-ethinylestradiol (EE2), and gemfibrozil (GEM) on gamete fertilization and embryonic development of mussels, and sea urchins, and on the survival of seabream larvae. The study reported inhibitory effects at environmental levels of EE2 (500 ng/L) and GEM (5000 ng/L) on sea urchins. Morphological abnormalities in either sea urchin or mussel embryos were induced by a 48-hour exposure to all pharmaceuticals. After 96 h of exposure to PROP (all treatments), EE2 (50–500 ng/L), and GEM (500 ng/L), a decrease in seabream larvae survival was reported.

Additionally, Fonseca et al. [88] assessed the bioavailability and effect of tamoxifen on polychaetes (100 ng/L) and the mussels (0.5, 10, 25, and 100 ng/L) after 14 days of exposure. At the lowest concentration (0.5 ng/ L), tamoxifen demonstrated remarkable oxidative stress and damage in polychaetes, while at the highest exposure level (100 ng/L), significant genotoxicity was reported. During the exposure days, 100 ng/L tamoxifen in mussels resulted in genotoxicity, neurotoxicity, an increase in biotransformation activity, and oxidative damage byproducts in the gills, causing endocrine disruption in the males. Overall, several findings demonstrated that current levels of pharmaceutical contaminants in aquatic systems have the potential to pose significant impacts on aquatic organisms. Thus, more research should be tailored to assess the potential risk of pharmaceutical contaminants on aquatic organisms and their implications for biodiversity in South Africa.

5. Spatial Distribution of PCs in the Aquatic System of South Africa

Several investigations have documented the presence of pharmaceutical residues in different regions of South African water sources [9,36,51–53,59]. Figure 2 represents the total number of pharmaceuticals detected and quantified, as well as the number of publications in each province. The attained data revealed that about 108 pharmaceuticals had been detected in water bodies of Gauteng, 40 in Kwa-Zulu Natal, 14 in North West, 12 in Eastern Cape, 6 in Limpopo and Western Cape, and 4 in Mpumalanga and Free State with no report in Northern Cape. The high number of pharmaceuticals reported in Gauteng province might be associated with a high population, industries, and health facilities. However, the number of studies conducted in each province determines the overall number of pharmaceuticals in each region. Thus, few pharmaceuticals in Free State, Mpumalanga, and Limpopo do not determine the absence of pharmaceuticals in the water bodies of these regions. Approximately seven classes of pharmaceuticals have been documented in the aquatic systems of South Africa.

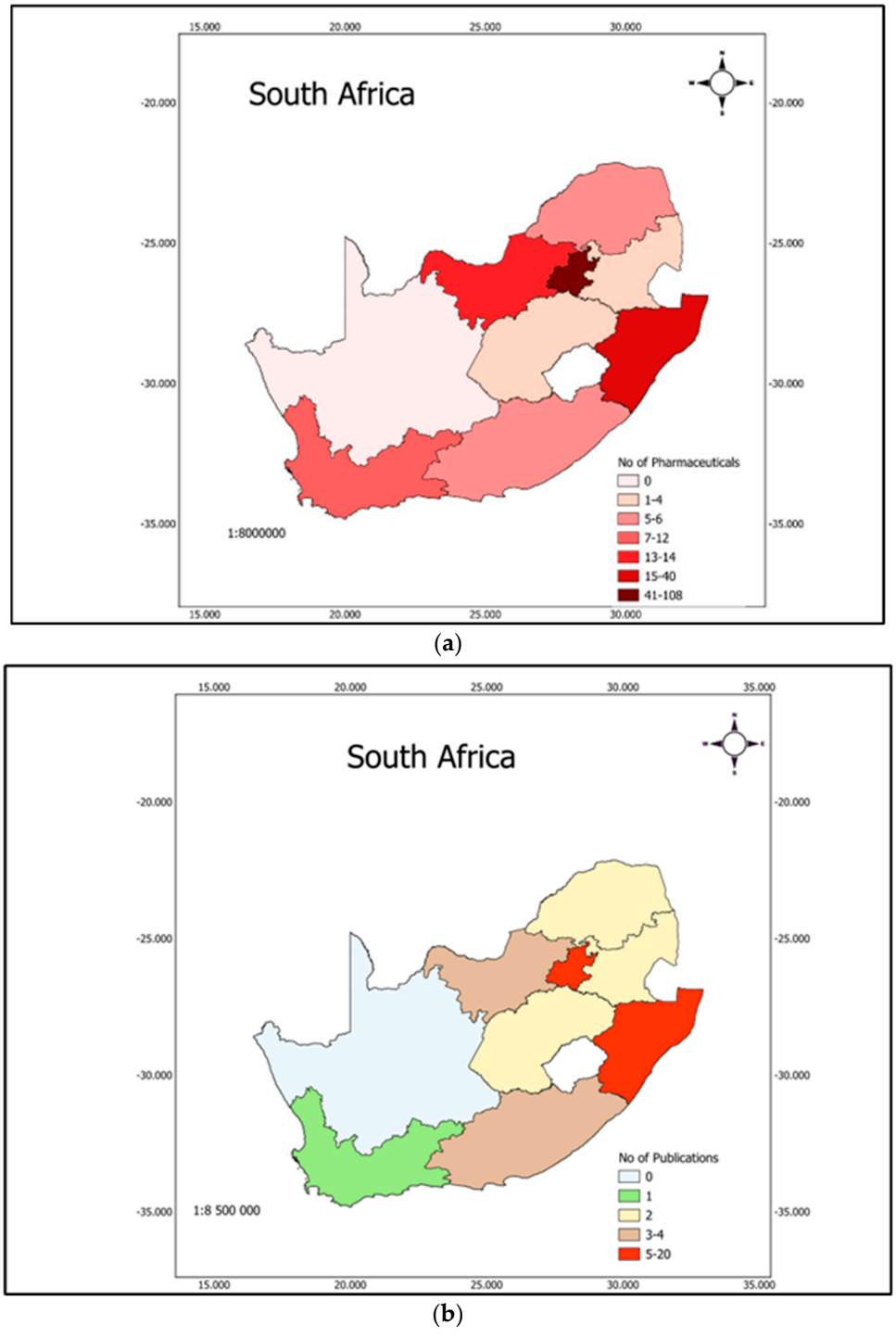

Figure 2. A number of different pharmaceutical contaminants identified in water bodies (**a**) and publications (**b**) in South Africa.

A literature search showed 23 antibiotics, 13 antiviral drugs, 12 anti-inflammatories, 23 anti-psychotics, 8 steroid hormones, 27 illicit drugs, and 2 beta blockers both in surface, wastewater, drinking, and tap water of Gauteng (Table S1). In Kwa-Zulu Natal, 13, 5, 10, 5, 5, and 2 of the respective pharmaceuticals were recorded in surface and wastewater. Approximately seven antibiotics, two anti-psychotics, and three steroid hormones have been reported in water bodies of the Eastern Cape. About five different steroid hormones and one antibiotic were detected and reported in water bodies of Western Cape province. In Mpumalanga, Limpopo, and Free State province, less than six pharmaceuticals have

been reported in surface and wastewater. Approximately two and four antiviral drugs and four steroid hormones were documented in wastewater and tape waters of Limpopo. At the same time, three antiviral drugs and one anti-psychotic drug were detected in tap water and wastewater of Free State province. Approximately two steroid hormones and two anti-psychotic drugs in water bodies of Mpumalanga province. In surface water and wastewater of the North West province, about 14 pharmaceutical residues have been identified and reported. This includes four antibiotics, three anti-inflammatory drugs, four anti-psychotics, and three steroid hormones. In the Northern Cape, no research has indicated that pharmaceutical residues are present in wastewater and aquatic environments. However, the absence of pharmaceutical occurrences report in this region does not validate their unavailability but rather a relative lack of surveys. Thus, this suggests that additional research should be carried out across all regions to acquire additional information and data accuracy on the available classes, amount, and number of pharmaceuticals in each province. Based on the obtained literature, it can be concluded that Gauteng can be treated as a hotspot area of pharmaceutical contaminants for the time being while carrying out more monitoring studies in other regions.

6. Policy and Regulatory Frameworks for Controlling Pharmaceutical Pollution in South Africa

Even though pharmaceutical contaminants have demonstrated possible human and environmental health risks, there is still debate on the legislative control approach due to inadequate risk assessment data at a global level [89]. However, to prepare for future regulation, certain industrialized nations, including the United States and the European Union, have drafted legislative standards for the monitoring of specific emerging contaminants, including pharmaceutical compounds [90,91]. Nevertheless, the lack of data on pharmaceutical contaminants, laws, and policy recommendations is still absent in Africa. Thus, the availability of more data regarding the presence of pharmaceutical contaminants in the aquatic environment of South Africa offers policymakers the opportunity to initiate the dialogue on how to handle these compounds. The draft policies will aid in regulating and providing directives on the release of these contaminants into the environment.

7. Conclusions and Future Recommendations

In conclusion, this paper reviewed the prevalence of pharmaceutical contaminants in wastewater and aquatic bodies of South Africa in different regions. The review showed that more than 100 pharmaceutical compounds have been documented in various water sources in South Africa, with more than 50 published research articles. Most of these studies were carried out in Gauteng and Kwa-Zulu Natal. The available literature further revealed that approximately 7 different categories of pharmaceutical contaminants have been documented in different regions of South Africa. This includes analgesics/anti-inflammatory drugs, anti-psychotics, antiretroviral drugs, steroidal hormones, antibiotics, illicit drugs, and beta blockers, with analgesics/anti-inflammatory drugs having the highest concentrations when compared to others. Aspirin, ketoprofen, diclofenac, ibuprofen, naproxen, erythromycin, tetracycline, streptomycin, sulfamethoxazole, acetaminophen, streptomycin, tylosin, chloramphenicol, ciprofloxacin, ampicillin, nalidixic acid, clozapine, bezafibrate, caffeine, carbamazepine, atenolol, pindolol, efavirenz, emtricitabine, zidovudine, didanosine, tenofovir disoproxil, zalcitabine, estriol, estrone, estradiol, medroxyprogesterone, mestranol, diethylstilbesterol, progesterone, and testosterone are among the commonly detected pharmaceutical contaminants in wastewater and aquatic bodies of South Africa. The presence of pharmaceuticals in the environment and wastewater suggests that additional studies are required to monitor other environmental pollutants, particularly in regions with no sufficient data, such as Northern Cape, Limpopo, Mpumalanga, and Free State. In addition, the majority of rural and urban residents in South Africa mostly rely on surface water as their main source of drinking water. Thus, most studies must be devoted to monitoring pharmaceutical occurrence in inland water sources, which are mainly used for

domestic water supply. This will further provide more details about the possible pathways of pharmaceutical contaminants. This review further encourages regulatory agencies in South Africa to establish the minimum permissible limits of pharmaceuticals in wastewater and embark on research on cost-effective pharmaceutical removal strategies in WWTPs. The established legislation will assist by restricting the release of these compounds into the environment. To lessen their introduction into various environmental systems, source reduction strategies, including raising public awareness, particularly in the manufacturing sectors and local governments, could be carried out.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/w16060796/s1, Table S1: Number of different pharmaceutical contaminants detected in wastewater and water bodies of South Africa in different regions.

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