A journey of 10 years in analytical method development and environmental monitoring of pharmaceuticals in South African waters

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ABSTRACT

Apart from the studies which reported the occurrence of steroid hormones and antibiotics in wastewater treatment plants (WWTPs) back in 2004, 2007 and 2012, the evidence for monitoring of pharmaceuticals in South African water bodies intensified from 2014. Therefore, this study reviewed the analytical methods developed and applied in South Africa for the purpose of monitoring pharmaceuticals and their metabolites in water. At the same time, pharmaceuticals and their metabolites detected in South African waters are reviewed. To date, there is over 100 pharmaceuticals detected in South African waters with most studies focussing on quantitative analysis of non-steroidal anti-inflammatory drugs (NSAID), antibiotics, antiretroviral drugs and carbamazepine. Various sources of pharmaceuticals in the environment are reported, with WWTPs found as the major contributor to their occurrence in South African rivers. Notably, a NSAID, ibuprofen, with concentrations found exceeding 100 μg L^{-1} in selected WWTPs has also been found at high levels reaching 60 μg L^{-1} in river water. Mostly, pharmaceuticals detected in wastewater are also reported in corresponding rivers. The present review details pharmaceuticals that should be included in environmental monitoring studies performed in South Africa, while also identifying areas for future research through the research gap analysis.

KEYWORDS

chromatography, environmental monitoring, pharmaceuticals, sample preparation

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INTRODUCTION

The environmental-based research focussing on the analysis of pharmaceuticals in South Africa became visible when four research articles were published in 2014 which reported the occurrence of selected drugs in South African water systems.[1–4] These four research articles provided crucial information into the existing knowledge on pharmaceutical contamination with earlier studies reported the occurrence of steroid hormones[5] and antibiotics[6] in wastewater treatment plants (WWTPs) located in South Africa. In 2013, a Water Research Commission report focussing on the verification and validation of analytical methods for monitoring pharmaceuticals and personal care products in water was published.[7] In the last decade, nearly 70 research articles focussing on analytical method development alongside the monitoring of pharmaceuticals in South African water systems have been published. These studies show the spread of different groups of pharmaceuticals in various water systems across different South African provinces (Figure 1), with most environmental surveys conducted in Gauteng and KwaZulu-Natal provinces.

Besides the occurrence of pharmaceuticals in South African water systems, these compounds have been reported in other environmental sample matrices such as sewage sludge[8] and river sediments.[9] In addition, the transfer of pharmaceuticals belonging to the therapeutic classes of non-steroidal anti-inflammatory drugs (NSAIDs) and antiretroviral drugs (ARVDs) from South African rivers and dams into aquatic plants has been documented.[9–11] Although such plants are not suitable for eating by human beings, they are regarded as food sources for other species. Recent studies conducted in South Africa have discovered the occurrence of pharmaceuticals in estuaries and seawater,[12,13] resulting in additional investigations with findings indicating the presence of the same drugs in different marine organisms which include fish and mussels.[14,15]

Due to the presence of pharmaceuticals in trace amounts in the environment and the complexity of environmental sample matrices, recent South African-based studies have investigated suitable analytical methods for the analysis of pharmaceuticals. Since chromatographic instruments are already known as suitable tools for the identification and quantitation of organics including pharmaceuticals, a great amount of time has been devoted to investigating the sampling and sample preparation tools. In this regard, passive sampling procedures and sample preparation processes which include solid-phase extraction (SPE) and hollow fibre liquid-phase microextraction (HF-LPME) have been finetuned and applied for pharmaceutical analysis.[1,3,11]

Despite the availability of numerous studies focussing on analytical method development and the occurrence of pharmaceuticals in South African water resources, the available review articles have greatly focussed on highlighting the research findings emanating from Africa as a continent.[16–20] However, upon closer navigation into an African perspective, it was discovered that 60% of research studies focussing on monitoring the occurrence of pharmaceuticals in African water bodies were conducted in South Africa.[16] Some of the existing review articles have focussed on providing the comparison of the occurrence of pharmaceuticals in African waters with those studies conducted in other continents.[21,22] There are few review articles that have entirely focussed on the occurrence of pharmaceuticals in South African water systems.[23–25] Some of these review articles focussed on selected therapeutic groups of pharmaceuticals,[25,26] while also reviewing emerging contaminants in general in a South African context.[23] Therefore, the aim of this article was to provide more comprehensive information on the analytical methods developed in South Africa to monitor pharmaceuticals in South African water systems. The present review highlights the research trends while also identifying the South African research gaps. Overall, this review is planned to play an important role in South African environmental and analytical scientists, policymakers and other relevant stakeholders by providing crucial information on the extent of water contamination with pharmaceuticals. This is necessary for raising awareness on the nature of the contamination, setting-up possible remediation strategies and investigating the ecotoxicological risks.

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Figure 1: Number of studies reporting the occurrence of pharmaceuticals in South African water bodies (last updated on 10 January 2023). Two studies did not disclose the study sites [27,28] while other three (excluded from the figure) investigated pharmaceuticals in rivers across the country [29-31]

ANALYTICAL METHOD DEVELOPMENT

South African-based research has immensely focussed on analytical method development for monitoring the occurrence of pharmaceuticals in water. Significant number of investigations have focussed on the development of sampling and sample preparation methods considering the context of South African water matrix and the influx of pharmaceuticals and other contaminants of emerging concern into water bodies. As a result, some environmental monitoring studies performed in South Africa have focussed on the analysis of single drugs in water where the sample preparation methods are finetuned to enhance selectivity,[32,33] while other studies explored the multi-drug analysis route.[34,35] The present article outlines the importance of these analytical methods while also providing important information on their applicability and drawbacks. In summary, the analytical options mostly considered in South African context are summarized in Figure 2.

Sampling methods

Grab sampling is the most used approach in South Africa for the collection of water samples required for pharmaceutical analysis.

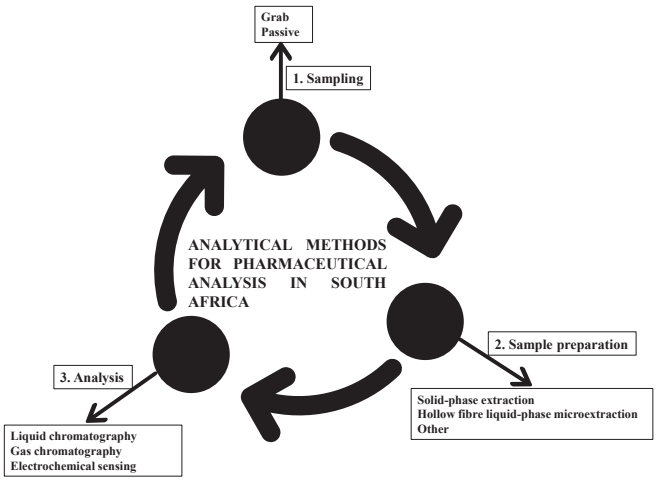

Figure 2: Analytical approach mostly considered in South Africa for the analysis of pharmaceuticals in water

Most research focussing on environmental-based analyses for pharmaceuticals in South Africa involves the development and/or optimization of sample preparation techniques. Hence, the grab sampling method is viewed as fast and becomes the most vital way of getting an environmental sample into the laboratory for validation of newly established analytical processes. Results attained for the analysis of such samples are sufficient for the validation of analytical methods and provide a snapshot of the existing environmental contamination. Variations in pharmaceutical loads reaching WWTPs during different times of the day were discovered utilizing the grab sampling approach where wastewater samples were collected in the morning, midday and afternoon, and analysed separately.[36] In this case, the attained analytical results indicated a general increase in the quantities of two NSAIDs; ibuprofen and naproxen, reaching the investigated WWTPs (Goudkoppies and Northern WWTPs, Johannesburg) from 12:30 to 15:30 during the day. In this context, passive sampling tools are designed to provide more complete synopsis of pharmaceutical load in the environment.

To the best of the author's knowledge, the first passive sampling study conducted in South Africa for monitoring the occurrence of selected pharmaceuticals in water was published in 2014.[3] In this case, a passive sampling device was based on polar organic chemical integrative sampler (POCIS) utilizing Oasis hydrophilic-lipophilic balance (HLB) sorbent which resulted in simultaneous sorption and subsequent analysis of polar pharmaceuticals, ibuprofen and naproxen, as well as triclosan which was a more hydrophobic analyte. A different study utilizing a Chemcatcher® passive sampler for emerging pollutants reported the detection of over 200 compounds which included pesticides, pharmaceuticals and personal care products, drugs of abuse and their metabolites using high-resolution tandem mass spectrometry in major rivers of Gauteng province.[34] In this case, HLB which is a non-selective material was utilized as the receiving phase, thereby, detecting approximately 180 chemicals for the first time in South African waters. With a rise in the number of medications that are being dispatched by healthcare professionals for the treatment of different ailments, this screening approach that involved the application of non-selective passive sampler which yielded interesting results should be further explored. Recent work showed that the selectivity of the passive sampler can be enhanced by employing selective sorbents such as molecularly imprinted polymers (MIPs).[37] This approach is more applicable when the environmental analysis is targeting fewer analytes. For example, Khulu et al. (2022) reported the application of MIP-based passive sampler for the selective sampling of five pharmaceuticals (carbamazepine, methocarbamol, etilefrine, venlafaxine and nevirapine) in surface water.[37] In this case, the developed passive sampler was based on the diffusion of selected pharmaceuticals from surface water through the membrane bag into the green solvent-receiving phase, followed by the selective adsorption of analytes onto the MIP cavities over a period of 14 days.

Sample preparation

Investigations on novel sample preparation procedures for isolation and pre-concentration of pharmaceuticals while eliminating the sample matrix effects have been at the centre of analytical method developments in South Africa. The sample preparation methods implemented and applied in the environmental monitoring of pharmaceuticals in South Africa include but not limited to SPE [38] and HF-LPME [10]. To a lesser extent, a vortex-assisted dispersive liquid-liquid microextraction has also been investigated.[39] These sample preparation methods have been finetuned to improve the selectivity of the analytical methods. In this case, MIPs have been widely explored as selective materials in sample preparation [40,41] and HF-LPME was applied in the extraction and pre-concentration of ionizable pharmaceuticals.[10,11]

Solid-phase extraction

Both synthetic and commercially available sorbents have been applied in SPE of pharmaceuticals in South African waters.[27,41] While SPE is appreciated as the promising sample preparation method for extraction and pre-concentration of pharmaceuticals in environmental samples, its drawbacks are associated with the single usage of commercially available cartridges which tend to generate solid waste and increase the cost of the analysis. To minimize the analysis costs, different SPE sorbents (discussed in this paper) that can be produced in a laboratory setting for the extraction of pharmaceuticals in water have been proposed.[27,32]

Commercially available solid-phase extraction sorbents

The concept of SPE for organic analytes has been reviewed and many commercially available sorbents and formats are described.[42,43] According to the literature, SPE mechanisms in existence include reversed-phase, normal phase, ion exchange, mixed-mode (ion exchange + reversed phase), adsorption and size-exclusion.[42] The commercial availability of a wide range of sorbents that extract pharmaceuticals using different mechanisms contributes to the popularity of SPE for the extraction of numerous analytes that have different polarities and physico-chemical properties.[43] In recent years, Oasis HLB sorbent gained more interest in SPE due to its ability to extract both polar and apolar compounds, high capacity, cleaning complex matrices and effectiveness in terms of removing interferences.[43] A South African-based study by Madikizela et al.[35] used Oasis HLB SPE cartridges to screen for the presence of 92 compounds which included mainly pharmaceuticals and their transformation products in surface water using ultra-high–performance liquid chromatography–quadrupole time-of-flight–mass spectrometry (UHPLC–QTOF–MS). The same SPE sorbent has been used for simultaneous extraction and pre-concentration of 156 compounds belonging to different classes such as pharmaceuticals and personal care products.[44] In a South African context, Madikizela and co-workers found Oasis HLB cartridges to be more suitable when compared to Isolute C_{18} and Oasis MAX for simultaneous extraction and pre-concentration of ketoprofen (NSAID) and triclosan (personal care product) in surface water and wastewater.[1] Furthermore, Oasis HLB was used for the simultaneous extraction of pharmaceuticals that belong to different therapeutic groups and drugs of abuse in two WWTPs located in Western Cape province.[45] Other reported applications for Oasis HLB sorbents include their use in the simultaneous extraction of pharmaceuticals, personal care products and stimulants in aqueous samples.[46] Despite its success in sample preparation, Oasis HLB seems to be more suitable for a wide range of analytes. In this regard, the selectivity concerns become prominent when it is used for fewer analytes with similar physico-chemical properties. Hence, other sorbents, more especially the synthetic ones have been investigated and applied for specific groups of pharmaceuticals from South African waters.

Supelclean™ LC-18 SPE sorbents have been used for neutral analytes.[2] Oasis MAX sorbents which are made of mixed-mode polymer sorbents with both reversed-phase and anion-exchange functionalities were used for acidic drugs.[38] Other applied commercially available cartridges for various pharmaceuticals in South African waters include Strata cartridges,[47,48] Bond Elut Plexa (Stryrene divinyl benzyl)[49] and Cleanert PEP.[50] As it stands, it looks like the choice of the sorbents to be utilized for SPE of pharmaceuticals is influenced by their availability, affordability and to a limited extent the physicochemical properties of the analytes as well as the chemical properties of the sorbent. As a result, the analytical method development in several studies investigated the effect of sample pH on the extraction of pharmaceuticals in water.[1,51] This is important as the pH of the aqueous solution controls the interactions between the sorbent and the analytes due to the chemical characteristics.

Synthetic sorbents

South African-based researchers have explored different synthetic sorbents for SPE of pharmaceuticals in water samples. These adsorbents are considered home-made materials which are designed for applications towards certain groups of chemicals.

Madikizela and co-workers investigated MIPs as promising selective sorbents for the SPE of pharmaceuticals in South African waters.[32,33,52] MIPs are described as smart materials that are designed for pre-concentration and enhancing selectivity in the extraction and quantification of organic and inorganic analytes from many complex matrices such as blood, urine and wastewater.[53] Other interesting features of MIPs include reusability, high surface area and mechanical strength. Traditional MIPs were found to be selective towards the compound used as the template molecule during their synthetic procedure.[32,33,54,55] Selectivity of MIPs is attained due to molecular recognition which is influenced by the functional groups present in the target molecule, size and shape of the analyte. Therefore, MIPs have been synthesized and applied for selective extraction of various pharmaceuticals which include ketoprofen[33], fenoprofen[52], efavirenz[32] and acetaminophen.[56] A synthesized multi-template MIP which allowed for the simultaneous extraction of naproxen, ibuprofen and diclofenac in water was investigated where the resulting polymer was found to be selective in the presence of structurally related compounds.[41,57] Furthermore, SPE approach where a multi-template MIP was used as the sorbent during the analysis of both river water and wastewater samples was proved to result in a more selective analytical method than when Oasis MAX SPE cartridges were investigated.[41] In a different experimental set-up which was based on the combination of a membrane-assisted solvent extraction and MIP, the imprinted polymer was synthesized with a single template, however the experimental approach was finetuned for cross-selectivity which allowed for the simultaneous extraction of five pharmaceuticals of different therapeutic groups in river water.[40] This highlights the various options for MIP synthesis that should be considered when a selective analysis needs to be performed. This information means a country such as South Africa with financial constraints, its researchers should consider the synthesis of single template MIPs which shows cross-selectivity for simultaneous analysis of various drugs. This will reduce the number of chemicals required in MIP synthesis.

Carbon-based materials have been prepared and explored as adsorbents in SPE of pharmaceuticals in water samples.[27,28,58,59] In this regard, activated carbon has received numerous applications.[27,28,59] Modification of activated carbon for extraction of pharmaceuticals has been deemed necessary to enhance the interactions between the adsorbents and compounds with various functional groups. This means the choice of the adsorbent is influenced by the structural and physicochemical properties of the target pharmaceuticals. The choice of alginate and polyvinylpyrrolidone to form composite with activated carbon for extraction of nevirapine and zidovudine was influenced by the expected multifunctional properties for the adsorbent which included hydrophobicity, biocompatibility, biodegradability, the abundance of functional groups and ability to form π-π interaction, hydrogen bonding and electrostatic interactions with the target ARVDs.[59] For acidic pharmaceuticals, amine-functionalization of activated carbon resulted in efficient extraction of NSAIDs.[27] This approach is related to the extraction of the same pharmaceuticals with a MIP synthesized using nitrogen-containing compounds such as 2-vinylpyridine playing the role of functional monomer which result in the formation of hydrogen bonds with analytes.[60,61] Waste tyre-based adsorbents have been well-investigated in a drive to minimize the abundant solid waste. Such materials have been investigated for the SPE of NSAIDs[28] and antibiotics[58] in wastewater and surface water. Other investigated nanocomposite-based adsorbents for the SPE of pharmaceuticals in South African surface waters are MgO-ZnO/carbon nanofiber[62], ferric oxide-aluminium oxide carbon

nanofiber[63], magnetic mesoporous carbon/β-cyclodextrin–chitosan,[64] nanostructured *o*-hydroxyazobenzene porous organic polymer[65] and β-cyclodextrin-decorated magnetic activated carbon.[66] Thus far, these materials provided satisfactory results for the extraction of selected groups of pharmaceuticals in water samples. Efficient extraction is largely depended on the physicochemical properties of both the analytes and the adsorbent. Hence, the reported materials are less explored for screening of wide range of pharmaceuticals in waterbodies as their surfaces are finetuned for selected groups of environmental pollutants.

Hollow fibre liquid-phase microextraction

This sample preparation technique was applied for the extraction and preconcentration of selected NSAIDs and antiretroviral drugs in aqueous samples sourced from the provinces of KwaZulu-Natal and Gauteng.[10,11] This sample extraction technique is operated in two-phase and three-phase systems[67], with the latter (Figure 3) being applicable for ionizable compounds. In a simple experimental set-up displayed in Figure 2, a sample solution (donor phase) is separated from the acceptor phase with supported liquid membrane which consists of a water-immiscible organic solvent embedded in the pores of a hollow fibre.[67]

In a three-phase HF-LPME system reported for the extraction of NSAIDs and ARVDs, analytes were transferred from the sample solution by partitioning across a solution of di-(2-ethylhexyl) phosphoric acid in dihexyl ether (4.5% (w/w)) acting as the supported liquid membrane into the lumen of the hollow fibre which housed the acceptor solution.[10,11] In this case, the acceptor solutions used for NSAIDs, and ARVDs were sodium hydroxide (pH 10) and hydrochloric acid (pH 0.4), respectively. In this context, NSAIDs and ARVDs were kept neutral in the sample solution (pH 3 for NSAIDs and pH 4 for antiretroviral drugs) and charged in the lumen of the hollow fibre. Due to the nature of the operating conditions with optimum extraction parameters being unique for specific groups of analytes, HL-LPME has limitations when applied to a wide range of compounds with different physicochemical properties. For example, it becomes difficult to simultaneously extract both ARVDs and NSAIDs using this technique. This is because, NSAIDs with pKa values around

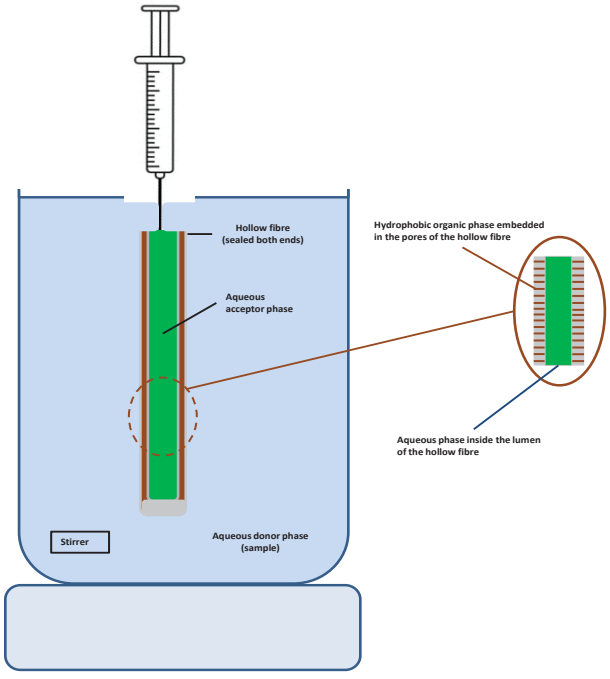

Figure 3: Schematic representation of a three-phase HF-LPME experimental set-up

4 can only become ionic at high pH values while selected antiretroviral drugs (emtricitabine, tenofovir disoproxil and efavirenz) are charged at highly acidic conditions. Hence, different acceptor solutions are required for HF-LPME of these pharmaceuticals. However, the technique is greatly appreciated for its high enrichment factors which result in sensitive analytical methods.

Other sample preparation methods

With increasing demand for the development of green analytical procedures, a vortex-assisted dispersive liquid-liquid microextraction that utilizes ionic liquid as a green solvent was developed for extraction and preconcentration of fluoroquinolones in water.[39] The analytical method which included liquid chromatographic analysis with diode array detection yielded the detection limits of 0.63–1.2 ng L^{-1} while maintaining the preconcentration factor at 10. A different study reported the development of an effective extraction method based on a combination of membrane-assisted solvent extraction and a MIP for the isolation and preconcentration of five pharmaceuticals belonging to different therapeutic classes in water.[40] In this case, a MIP acted as the selective sorbent for pharmaceuticals. Otherwise, the same extraction process with an omission of MIP can be conducted for the extraction of a wide range of pharmaceuticals. Wooding et al (2017) developed low-cost disposable samplers which consisted of polydimethylsiloxane (PDMS) tubing fashioned into a loop and placed in contaminated water samples to concentrate endocrine-disrupting chemicals and emerging pollutants.[68] Extracted compounds were thermally desorbed and analysed with gas chromatography – time-of-flight mass spectrometry. These various options in sample preparation gives researchers possibilities to be explored depending on the available resources. Some sample preparation techniques/methods were developed taking into account the green chemistry principles, while others ensure the reduced costs associated with the analytical methods.

Chromatographic analysis

Chromatographic instruments are highly successful in the analysis of pharmaceuticals in water. High-performance liquid chromatography with fluorescence and photo diode array or ultraviolet (UV) detectors has been the instrument of choice during the earlier developments of analytical methods for pharmaceutical analysis in the South African environment.[1-3] Although these detectors have been valuable tools in the pharmaceutical analysis of water samples, their applications are limited due to poor sensitivity and the inability to provide the structural identity of the detected compound. In this regard, limited research funds and infrastructure in South Africa contributed to restricted access to the most suitable equipment in the form of liquid chromatography equipped with mass spectrometry detector (LC-MS) for pharmaceutical analysis. Hence, active researchers in the field opted in channelling focus and available resources to the development of selective sample preparation methods which ensures the isolation of analyte and pre-concentration prior to chromatographic analysis. In addition, viewing the spectral identity of the analytes during their chromatographic elution in photo diode array detectors served as a qualitative tool.[1,38]

Recent studies utilized the LC-MS instruments as sensitive equipment with confirmatory tool for structural identity of the analytes in the environmental analysis of pharmaceuticals.[11,35,44,69] In several studies, LC-MS was proved to be an efficient equipment for multi-residue analysis.[34,35,44,69] It is through this analytical technique that 31 pharmaceuticals from different therapeutic groups were simultaneously detected in river water using quadrupole time-of-flight-mass spectrometry (QToF). In the same context, the occurrence of 52 antibiotics in a semi-urban stream was investigated which resulted in detection of 15 compounds using LC-QToF-MS.[69] A different study conducted in the Gauteng province using LC-QToF-MS system was a qualitative evaluation that reported the identification of 200

compounds, including pesticides, pharmaceuticals and personal care products, drugs of abuse and their metabolites.[34] Mass spectrometry detection systems are known for their high sensitivity, especially when a suitable sample preparation step is used. For example, an average method detection limit of 90.4 ng L^{-1} for ARVDs in surface water was found using a triple quadrupole mass spectrometry system.[30] Instrument quantitation limits as low as 10 ng L^{-1} were reported when the analysis was performed with LC-Orbitrap™ MS system.[44] However, LC-MS instruments still have some limitations which include the unavailability of ESI libraries making screening of unknowns difficult. This means the instruments mostly work efficiently when targeting certain compounds, resulting in missing other environmental contaminants that maybe present in the same sample.

Gas chromatography (GC) has been reported as the option for pharmaceutical analysis in cases where there is limited or no access to liquid chromatographic instruments. GC instruments have been used with SPE and disposable PDMS sorptive sampler for analysis of pharmaceuticals in surface water.[46,51,68] Limits of detections attained when analyzing a wide range of pharmaceuticals using the SPE-GC-MS system ranged from 0.041 to 1.614 µg L^{-1}. [51] While these detection limits are sufficient for the analysis of pharmaceuticals in South African surface water, GC-based methods are mostly time-consuming. This is due to a need for derivatization of pharmaceuticals to increase their volatility, reduce polarity and enhance detectability.[51]

OCCURRENCE OF PHARMACEUTICALS IN SOUTH AFRICAN WATERS

Wastewater

Non-steroidal anti-inflammatory drugs and analgesics

Pharmaceuticals belonging to the therapeutic class of NSAIDs were among the first group of pharmaceuticals monitored in South African waters with their occurrence in wastewater being first reported in 2014.[1–3] A recent review reported four NSAIDs (ibuprofen, diclofenac, naproxen and ketoprofen) as the most monitored and detected drugs in South African wastewater.[25] These NSAIDs have been reported in WWTPs located in various provinces such as those in KwaZulu-Natal, North-West and Gauteng. Other NSAIDs and analgesics detected in South African wastewater systems are given in Table 1. Their presence in wastewater is linked to their accessibility as over the counter medications, high consumption and excretion rates.[25] For example, naproxen with the excretion rate as a parent compound of 70% [25] has been found in wastewater influent with its concentrations exceeding 100 µg L^{-1}. [70] Similarly, ketoprofen with an excretion rate of 80% [25] had its concentration reaching 159 µg L^{-1} in an undisclosed South African WWTP influent.[27] Other studies have reported both ibuprofen and diclofenac as NSAIDs with high concentrations in wastewater influent.[41,71] Other NSAIDs and analgesics found in South African wastewaters include aspirin,[2] fenoprofen,[10,52] paracetamol,[56,72] codeine and tramadol.[44,72] Low and negative removal of NSAIDs in wastewater during the wastewater treatment process has been reported.[52,70,72] With Newlands Mashu decentralised wastewater treatment system recording the removal efficiency of diclofenac at 11% and tramadol at −21%,[72] this challenge is not unique to South Africa as several related reports have emerged from other African countries [73] and abroad.[74,75] In this case, the limited removal of pharmaceuticals in wastewater was reported to be influenced by several issues which include the degradation of precursors to target analytes, partitioning of pharmaceuticals sorbed into sediments and sludge to the aqueous phase, wastewater influent and effluent samples representing different portions of wastewater due to the samples collected without taking into consideration the hydraulic retention times, smaller analyte levels which have higher uncertainty and analytical error.[74]

Due to the limited removal during the wastewater treatment process, NSAIDs are constantly detected in the effluents.[2,76] In this context, a wide range of concentrations have been reported in South African WWTP effluents. In some cases, NSAIDs were not detected in selected effluents,[77] however, other researchers found high concentrations of the same pharmaceuticals in the same study sites. This could be a result of sampling plan with grab sampling known to provide a snapshot of environmental pollutants while passive sampling is more ideal for monitoring these compounds which have varying concentrations entering the WWTPs throughout the day.[36] Variations in the effluent concentrations were observed in three WWTPs (Northern, Umbilo and Umhlathuzana) located in Durban where one study found trace amounts of naproxen, fenoprofen, diclofenac and ibuprofen, with their concentrations mostly not exceeding the method quantitation limits.[77] However, other studies conducted in the same sites reported higher concentrations of the same drugs in the effluents.[38,70] For example, the maximum concentrations found for naproxen, ibuprofen and diclofenac in Northern WWTP effluent were 4, 10, 15 µg L^{-1}, respectively.[70] Such detections are translated to the introduction of these drugs from households to the nearby rivers. This is corroborated by studies that have found high loads of these drugs in WWTPs.[45,78] Hence, innovative wastewater treatment solutions for the complete removal of pharmaceuticals in WWTPs are urgently required. In addition, upgrade of the sewage treatment facilities and assurance that they efficiently work without fail are necessary.

Antibiotics

Antibiotics are common pharmaceuticals found in South African wastewaters (Table 2). In 2014, a study investigating the occurrence of antibiotics among other pharmaceuticals was published.[2] In this case, out of nine investigated antibiotics in Northern WWTP located along Umgeni water system (Durban), nalidixic acid had the highest concentration reaching 31 µg L^{-1} followed by erythromycin and tylosin.[2] The same authors reported the same antibiotic, nalidixic acid, as the most abundant with its concentrations in the range of 25-30 µg L^{-1} in Darvill WWTP (Pietermaritzburg).[79] Erythromycin was also constantly detected in rivers flowing in Eastern Cape province and WWTPs in KwaZulu-Natal. [81,82] This highlights a need to investigate the occurrence and effects of this antibiotic in a wide range of South African water bodies. Notably, the most investigated antibiotics with constant detections in wastewater are sulfamethoxazole and ciprofloxacin (Table 2). Similar observations from studies emanating from other African countries have been reported which imply a need to monitor these antibiotics in all water bodies.[16] In addition, studies that investigated the occurrence of antibiotics in South African wastewaters utilized the targeted analytical approach where a focus was directed towards a certain group of antibiotics, thereby overlooking other potential compounds that can be present in the same wastewaters. Future research should consider the suspect screening approach which is likely to result in the identification of a wide range of antibiotics in wastewater.

South African WWTPs proved to be unable to completely remove antibiotics in wastewater.[2,44] In this regard, Northern WWTP located in Durban showed removal efficiencies in the range of 70–88% for antibiotics with streptomycin having the highest removal percentage and ampicillin having the least.[2] The concentrations of several antibiotics which included sulfamethazine, sulfamerazine, oxolinic acid, ofloxacin, enrofloxacin, lincomycin, isoniazid and clarithromycin were higher in Daspoort WWTP effluent than in the influent.[44] Such increase in pollutant levels means the WWTP is unable to remove these antibiotics in wastewater which results in their negative removal efficiencies. In fact, enrofloxacin, erythromycin and sulfamerazine were only quantified in the effluent of Daspoort, implying their discharge into the receiving water body which raises concerns regarding the employed wastewater treatment system.[44] Some antibiotics reported in South African water systems are listed in Table 2. These antibiotics should be among the watchlist of chemicals to be routinely monitored in South African water systems.

Table 1: A list of NSAIDs and analgesics detected in South African water system

NSAID/ analgesic	Analytical method	Study site	Method quantitation limits (μg L^{-1})		Detected concentration (μg L^{-1})			Ref.
			Waste–water	Surface water	WWTP influent	WWTP effluent	Surface water	
Acetaminophen	SPE-LC-MS	False Bay, Western Cape	–	0.0001	–	–	0.001–0.002	14
	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.008–0.233	29
	SPE-LC-MS	Klip River, Gauteng	–	0.170	–	–	nd–0.430	35
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.882	0.882	0.155–22.9	nd–0.107	<MQL–1.680	44
	SPE-LC-MS	Msunduzi and Umgeni rivers, KwaZulu-Natal	–	0.228	–	–	54.6–171	48
	SPE-LC-DAD	WWTP in Gauteng and tap water	0.630	0.630	3.290	2.150	0.630	56
	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	0.273	0.091	5.760	nd	0.990–1.740	71
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	140	4.600	–	72
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	0.273	0.091	6.260	3.270	1.130–1.780	76
Acetylsalicyclic acid	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	0.950	0.950	nd–<MQL	nd–<MQL	nd–1.130	51
	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.097	0.097	118	44	13.7–25.3	79
Bufexamac	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	1.607	1.607	nd	nd–0.02	nd–0.003	44
Diclofenac	SPE-LC-DAD	Mbokodweni River, KwaZulu-Natal	–	0.270	–	–	1.10–1.20	9
	HF-LPME-LC-MS	Four WWTPs in KwaZulu-Natal and Hartebeespoort dam	0.590	–	0.49–1.97	0.36–3.13	–	10
	SPE-LC-MS	False Bay, Western Cape	–	0.0026	–	–	0.0026–0.0037	14
	SPE-LC-DAD	Undisclosed location	2.5	2.5	<MQL	<MQL	<MQL	27
	SPE-LC-DAD	Undisclosed location	0.80	–	20.4	9.68	–	28
	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.040–0.125	29
	SPE-LC-DAD	Kingsburgh and Umbilo WWTPs, KwaZulu-Natal	0.39	–	6.4–16	1.4–2.0	–	38
	SPE-LC-DAD	Mbokodweni River, Amanzimtoti and Northern WWTPs, KwaZulu-Natal	2.11	2.11	3.7–104	<MQL–21	nd–<MQL	41
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.184	0.184	0.012–0.246	0.005–0.244	0.005–0.082	44
	SPE-LC-MS	Two WWTPs in Western Cape	0.5	–	nd–101	<MQL–61	–	45
	SPE-LC-MS	Msunduzi and Umgeni rivers, KwaZulu-Natal	–	0.149	–	–	nd–51.9	48
	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	1.614	1.614	nd–10.2	nd	nd–1.01	51
	SPE-LC-MS	Ladysmith water resources, KwaZulu-Natal	1.00	0.80	1.2–1.3	<MQL–1.4	nd–2.6	57
	SPE-LC-DAD	Mbokodweni River and five WWTPs, KwaZulu-Natal	2.11	2.11	6.2–115	2.6–24	0.9–10	70
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	2.3	2.1	–	72
	SPE-LC-DAD	Five WWTPs in KwaZulu-Natal and receiving waterbodies	0.036	0.036	nd–21.1	nd–0.29	nd–10.0	77
	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.033	0.033	22	12	060–8.70	79
Fenoprofen	HF-LPME-LC-MS	Four WWTPs in KwaZulu-Natal and Hartebeespoort dam	0.09	–	nd–<MQL	nd–2.03	–	10
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	2.125	2.125	nd	nd–0.208	nd–0.418	44
	SPE-LC-DAD	Two WWTPs in KwaZulu-Natal	0.64*	–	33–80	6–47	–	52
	SPE-LC-DAD	Five WWTPs in KwaZulu-Natal and receiving waterbodies	0.048	0.048	0.24–47.6	nd–1.20	nd–10.5	77
Hydrocodone	SPE-LC-MS	WWTPs and their receiving water bodies, Gauteng	0.0104	0.0052	<MQL–14	0.100–0.716	<MQL–0.298	80
Ibuprofen	POCIS-LC-UV-FLD	Goudkoppies and Nothern WWTP	3.1	–	40–112	13–25	–	3
	SPE-LC-DAD	Mbokodweni River, KwaZulu-Natal	–	0.22	–	–	0.59–1.4	9
	HF-LPME-LC-MS	Four WWTPs in KwaZulu-Natal and Hartebeespoort dam	0.490	–	nd–<MQL	nd–0.92	–	10
	SPE-LC-MS	Umgeni River and selected Durban beaches	–	0.035	–	–	nd–0.278	12
	SPE-LC-MS	Klip River, Gauteng	–	0.025	–	–	nd–0.11	35
	HF-SRME-LC-UV-FLD	Goudkoppies and Nothern WWTP, Gauteng	0.7–17	–	5.2–7.2	1.1–1.6	–	36
	SPE-LC-DAD	Kingsburgh and Umbilo WWTPs, KwaZulu-Natal	0.42	–	55–69	2.1–4.2	–	38
	SPE-LC-DAD	Mbokodweni River, Amanzimtoti and Northern WWTPs, KwaZulu-Natal	3.33	3.33	6.0–221	3.9–68	nd–11	41
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	15.69	15.69	0.569–76.4	nd–7.65	nd–12.8	44
	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	0.477	0.477	<MQL–17.6	<MQL	nd–2.57	51
	SPE-LC-MS	Ladysmith water resources, KwaZulu-Natal	3.40	3.20	<MQL	<MQL	nd–6.7	57
	SPE-LC-DAD	Mbokodweni River and five WWTPs, KwaZulu-Natal	3.33	3.33	28–221	5.1–68	4.8–19	70

Table 1: (continued)

NSAID/ analgesic	Analytical method	Study site	Method quantitation limits (μg L^{-1})		Detected concentration (μg L^{-1})			Ref.
			Waste–water	Surface water	WWTP influent	WWTP effluent	Surface water	
	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	0.813	0.081	62.8	58.7	4.7–85	71
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	0.813	0.271	5.76	12.9	23–62	76
	SPE-LC-DAD	Five WWTPs in KwaZulu-Natal and receiving waterbodies	0.053	0.053	2.36–66.9	nd–9.45	nd–32.9	77
	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.0047	0.0047	1.06	1.38	0.45–0.69	79
Indomethacin	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.201	0.201	nd–0.042	<MQL–0.008	nd–0.009	44
Ketoprofen	SPE-LC-DAD	Mbokodweni River and Amanzimtoti WWTP, KwaZulu-Natal	0.26	0.26	1.7–6.4	1.2–4.3	nd–2.0	1
	SPE-LC-DAD	Undisclosed location	1.3	1.3	159	91	23.8	27
	SPE-LC-DAD	Undisclosed location	1.3	–	19.3	12.1	–	28
	SPE-LC-UV	Three WWTPs, KwaZulu-Natal	0.55–0.78	–	27.3–28.4	2.90–3.50	–	33
	SPE-LC-MS	Klip River, Gauteng	–	0.018	–	–	nd–<MQL	35
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.078	0.078	nd–0.023	nd–0.0495	nd–0.0395	44
	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	0.400	0.400	<MQL	nd–<MQL	nd–9.22	51
	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.0097	0.0097	3.15	0.38	0.39–0.44	79
Meclofenamic acid	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.052	0.052	0.011–0.091	0.005–0.055	0.0022–0.0912	44
	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	0.272	0.272	nd–<MQL	nd	nd–2.38	51
Naproxen	POCIS-LC-UV-FLD	Goudkoppies and Nothern WWTP, Gauteng	0.7	–	52–55	14–20	–	3
	SPE-LC-DAD	Mbokodweni River, KwaZulu-Natal	–	0.44	–	–	1.2–2.3	9
	HF-LPME-LC-MS	Four WWTPs in KwaZulu-Natal and Hartebeespoort dam	0.470	–	2.52–3.23	1.15–3.30	–	10
	SPE-LC-MS	Umgeni River and selected Durban beaches	–	0.025	–	–	nd–0.355	12
	HF-SRME-LC-UV-FLD	Goudkoppies and Nothern WWTP, Gauteng	0.7–17	–	1.1–2.3	0.4–0.8	–	36
	SPE-LC-DAD	Kingsburgh and Umbilo WWTPs, KwaZulu-Natal	0.12	–	15–20	0.6–1.1	–	38
	SPE-LC-DAD	Mbokodweni River, Amanzimtoti and Northern WWTPs, KwaZulu-Natal	0.49	0.49	1.2–40	nd–5.3	nd–0.7	41
	SPE-LC-DAD	Undisclosed location	2.0	2.0	<MQL	<MQL	<MQL	27
	SPE-LC-DAD	Undisclosed location	0.18	–	18.6	7.50	–	28
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.047	0.047	0.0168–0.546	0.0131–0.350	0.030–0.487	44
	SPE-LC-MS	Two WWTPs in Western Cape	2.0	–	nd–153	<MQL–42	–	45
	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	0.248	0.248	nd–59.3	nd	nd–<MQL	51
	SPE-LC-MS	Ladysmith water resources, KwaZulu-Natal	0.77	0.64	nd–<MQL	<MQL	nd–2.8	57
	SPE-LC-DAD	Mbokodweni River and five WWTPs, KwaZulu-Natal	0.49	0.49	3.0–109	2.6–14.4	1.0–6.8	70
	SPE-LC-DAD	Five WWTPs in KwaZulu-Natal and receiving waterbodies	0.053	0.053	0.24–8.9	nd–1.77	nd–9.71	77
Oxycodone	SPE-LC-MS	WWTPs and their receiving water bodies, Gauteng	0.015	0.009	0.021–7.97	0.075–1.56	<MQL–1.16	80
Phenacetin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.01	0.01	0.0003–0.066	<MQL–0.026	<MQL–0.034	44
	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	1.151	1.151	nd–1.95	nd–<MQL	nd–68.3	51
Salicylamide	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.135	0.135	0.006–0.564	0.0049–0.113	nd–0.0481	44
Tramadol	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.032	0.032	nd–0.0772	0.0007–0.290	0.0061–0.0404	44
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	0.33	0.40	–	72
	SPE-LC-MS	Four Gauteng WWTPs and receiving waterbodies	2.82	1.65	0.96–24.6	0.535–3.76	<MQL–3.27	80
Codeine	SPE-LC-MS	Two WWTPs in Western Cape	2.0	–	nd–418	<MQL–150	–	45
	SPE-LC-MS	WWTPs and their receiving water bodies, Gauteng	0.010	0.004	1.12–3.44	0.492–1.84	<MQL–1.77	80

Notes: HF-SRME – Extraction was based on a hollow fiber silicone rubber membrane; Reference 44 provided instruments quantitation limits.
*provided value is method detection limit.

Table 2: A list of antibiotics detected in South African waters

Antibiotics	Analytical method	Study site	Method quantitation limits (μg L^{-1})		Detected concentration (μg L^{-1})			Ref.
			Wastewater	Surface water	WWTP influent	WWTP effluent	Surface water	
Ampicillin	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.066	0.066	6.57	8.92	3.21–5.51	79
Amoxicillin	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.009–0.207	29
Azithromycin	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.0004	–	0.01–0.102	nd–0.0007	nd–0.0007	81
	SPE-LC-MS	Undisclosed WWTP and receiving river in Gauteng	0.8×10^{-7}	0.8×10^{-7}	0.247	0.04	0.011	83
Chloramphenicol	SPE-GC-MS	Umgeni and Msunduzi Rivers, KwaZulu-Natal	5.51	5.51	nd	nd–10.1	nd–<MQL	46
Ciprofloxacin	VA-DLLME/HPLC-DAD	Daspoort WWTP, Gauteng	0.0021	–	1.76–1.98	0.110–0.147	–	39
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	10.7	10.7	nd–0.077	nd–0.006	nd–<MQL	44
	SPE-LC-MS	Msunduzi and Umgeni rivers, KwaZulu-Natal	–	0.237	–	–	nd–38.8	48
	SPE-LC-DAD	Daspoort WWTP, Gauteng	0.53–2.17	–	<MQL	<MQL	–	58
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	1.3	1.6	–	72
	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.0039	0.0039	27.1	14.1	≤14.3	79
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.0011	–	35–88	0.17–1.14	0.061–0.708	81
	SPE-LC-MS	Undisclosed WWTP and receiving river in Gauteng	45×10^{-7}	45×10^{-7}	2.379	0.398	0.097	83
Clarithromycin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.099	0.099	nd–0.010	nd–0.075	nd–0.01	44
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00040	–	0.073–2.8	0.0002–0.038	0.003–0.038	81
	SPE-LC-MS	Five rivers in Eastern Cape	–	<0.0001	–	–	nd–3.28	82
Clindamycin	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	0.27	0.27	–	72
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00023	–	0.0085–0.031	0.0002–0.001	0.0005–0.008	81
	SPE-LC-MS	Undisclosed WWTP and receiving river in Gauteng	1.1×10^{-7}	1.1×10^{-7}	0.053	0.018	0.015	83
Danofloxacin	VA-DLLME/HPLC-DAD	Daspoort WWTP, Gauteng	0.0028	–	1.95–2.26	0.218–0.253	–	39
	SPE-LC-DAD	Daspoort WWTP, Gauteng	0.53–2.17	–	<MQL	nd	–	58
	SPE-LC-DAD	Daspoort WWTP and Apies River, Gauteng	0.0024	0.0024	0.0056	0.0017	0.0024	64
Doxycycline	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
	SPE-LC-MS	Undisclosed WWTP and receiving river in Gauteng	29.2×10^{-7}	29.2×10^{-7}	0.160	0.024	0.123	83
Enrofloxacin	VA-DLLME/HPLC-DAD	Daspoort WWTP, Gauteng	0.0040	–	1.89–2.11	0.536–0.638	–	39
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.241	0.241	nd	nd–0.001	nd–<MQL	44
	SPE-LC-DAD	Daspoort WWTP, Gauteng	0.53–2.17	–	<MQL	nd	–	58
	SPE-LC-DAD	Daspoort WWTP and Apies River, Gauteng	0.0037	0.0037	0.0073	0.0021	0.0031	64
Erythromycin	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	1.032	1.032	nd	nd–0.012	nd–0.009	44
	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	0.001	0.001	0.61	0.16	nd–0.24	71
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	0.0012	0.0004	1.13	0.24	nd–0.24	76
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00046	–	0.0055–0.059	0.001–0.022	0.0001–0.018	81
	SPE-LC-MS	Five rivers in Eastern Cape	–	0.002	–	–	nd–11.8	82
Ethionamide	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00099	–	0.011–0.038	0.0001–0.009	0.001–0.018	81
Flumequine	SPE-LC-MS	Klip River, Gauteng	–	0.06	–	–	0.23–0.26	35
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.107	0.107	nd–0.003	nd–<MQL	nd–0.0009	44
	SPE-LC-MS	Stream pouring to Klip River, Gauteng	–	16.8	–	–	0.222–00689	69
Levofloxacin	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	0.0025	0.0022	–	72
Lincomycin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.163	0.163	nd–0.002	nd–0.0207	0.011–0.201	44
Lomefloxacin	SPE-LC-MS	Klip River, Gauteng	–	0.16	–	–	nd–0.39	35
Metronidazole	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	2.89	0.962	nd	nd	nd	71
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	2.89	0.962	nd	nd	nd	76
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00056	–	0.014–21	0.003–0.021	0.001–0.018	81

Table 2: (continued)

Antibiotics	Analytical method	Study site	Method quantitation limits (μg L^{-1})		Detected concentration (μg L^{-1})			Ref.
			Wastewater	Surface water	WWTP influent	WWTP effluent	Surface water	
Nalidixic acid	SPE-GC-MS	Umgeni water system, KwaZulu-Natal	0.620	0.620	nd	nd	nd–2.53	51
	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.028	0.028	25.2	29.9	12.5–23.5	79
Norfloxacin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	17.6	17.6	nd–0.032	nd–0.009	nd	44
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00073	–	0.062–0.143	nd–0.003	0.0005–0.001	81
Ofloxacin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	14.9	14.9	0.025–0.068	0.012–0.087	nd–0.031	44
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00073	–	1.58–5.74	0.015–0.094	0.009–0.066	81
Oxolinic acid	SPE-LC-MS	Klip River, Gauteng	–	0.112	–	–	nd–0.36	35
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.06	0.06	nd–0.0002	nd–0.0002	nd	44
Oxytetracycline	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	8.117	8.117	nd–0.021	nd–0.0002	nd	44
Roxithromycin	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00030	–	0.024–1.28	nd–0.0002	nd	81
Sulfamerazine	SPE-LC-MS	Klip River, Gauteng	–	0.35	–	–	nd–0.40	35
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.421	0.421	nd–0.0262	nd–0.0419	nd–0.0049	44
	SPE-LC-MS	Stream pouring to Klip River, Gauteng	–	39.2	–	–	nd–0.133	69
	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	0.681	0.227	nd	nd	nd–1.09	71
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	0.681	0.227	nd	1.10	nd–1.24	76
Sulfamethoxazole	SPE-LC-MS	False Bay, Western Cape	–	0.0017	–	–	0.0003–0.0048	14
	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.013–0.252	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.106	0.106	0.0529–2.41	0.0349–0.504	nd–0.297	44
	SPE-LC-MS	Two WWTPs in Western Cape	5.0	–	nd–766	<18–419	–	45
	SPE-LC-MS	Msunduzi and Umgeni rivers, KwaZulu-Natal	–	0.376	–	–	2.65–398	48
	SPE-LC-MS	Stream pouring to Klip River, Gauteng	–	25	–	–	nd–<MQL	69
	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	1.241	0.413	nd	nd	nd–1.09	71
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	12	2.5	–	72
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	1.241	0.413	59.3	nd	nd–1.24	76
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.0005	–	0.85–4.57	0.13–0.35	0.059–0.35	81
	SPE-LC-MS	Five rivers in Eastern Cape	–	0.0009	–	–	nd–5.974	82
	SPE-LC-MS	Undisclosed WWTP and receiving river in Gauteng	17.1×10^{-7}	17.1×10^{-7}	4.440	0.411	0.018	83
	SPE-UV-Vis	Daspoort WWTP and undisclosed river, Pretoria	1.7	1.7	910	720	590	84
Sarafloxacin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	2.723	2.723	nd–0.0083	nd	nd	44
Sulfadiazine	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.598	0.598	nd–0.0004	nd	nd	44
Sulfamethizole	SPE-LC-MS	Stream pouring to Klip River, Gauteng	–	26.9	–	–	nd–0.111	69
Sulfadimethoxine	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.095	0.095	nd–0.0006	nd–0.0004	nd–0.0018	44
Sulfadoxin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.092	0.092	nd–0.0068	nd–0.0013	nd–0.0007	44
Sulfaguanadin	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	4.61	4.61	nd–0.0115	nd	nd	44
Sulfanilamide	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.241	0.241	nd–0.004	nd–0.010	nd–<MQL	44
Sulfapyridine	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.192	0.192	nd–0.110	nd–0.023	nd–0.0012	44
Tetracycline	SPE-LC-DAD	Daspoort WWTP and Pienaars River, Gauteng	0.63	0.63	2.92	<MQL	<MQL	85
Trimethoprim	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.019	0.019	0.0017–0.578	nd–0.137	0.0069–0.171	44
	SPE-LC-MS	Stream pouring to Klip River, Gauteng	–	12.4	–	–	nd–<MQL	69
	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	0.411	0.137	nd	nd	nd–0.29	71
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	1.4	0.29	–	72
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	0.411	0.137	0.13	0.16	nd–0.87	76
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00036	–	0.40–1.93	0.007–0.23	0.01–0.16	81
Vancomycin	SPE-LC-MS	Msunduzi and Umgeni rivers, KwaZulu-Natal	–	0.407	–	–	nd–22.4	48

Notes: References 45 and 69 gave instrument quantitation/detection limits; VA-DLLME – vortex assisted-dispersive liquid-liquid microextraction

Antiretroviral drugs

In recent years, this group of pharmaceuticals has been extensively monitored in the African aquatic environment where most of the environmental monitoring data has been gathered in South Africa and Kenya. The availability of analytical data in Africa has been correlated to the extensive consumption of these pharmaceuticals due to the spread of HIV in Africa.[86] A recent review article on the occurrence of ARVDs in African waters identified both South Africa and Kenya as the hotspots owing to the recurrent presence of these pharmaceuticals in various water bodies.[26] As this review article[26] is very recent with its focus being exclusively on ARVDs in water from both South Africa and Kenya, the author of the present article (who also co-authored the review by Zitha et al (2022)) opted to limit the discussion on these drugs. The previous works co-authored by the author of the present review can be consulted for additional information in this regard.[16,26,86,87] Based on historical detections in South African waters, the ARVDs that can be considered for inclusion in environmental studies conducted in South Africa are given in Table 3. As cited in Table 3, these ARVDs have been previously detected in South African wastewaters and surface waters. Most interestingly, is the detection of the metabolites of these drugs in wastewater[47] which means their presence should be investigated alongside their transformation products. In this case, the detected metabolites originate from the two commonly detected drugs, efavirenz and nevirapine.

Carbamazepine

Carbamazepine is the only anti-convulsant drug that is constantly monitored in South African waters. This could be related to its consumption and excretion rates when compared to other drugs with similar therapeutic properties. This drug has been detected alongside its metabolite, 10,11-dihydro-11-hydroxycarbamazepine, in South African-based WWTPs.[45] One study indicated that in WWTPs located in KwaZulu-Natal, carbamazepine concentrations did not exceed the method quantitation limit of 2.9 μg L^{-1},[46] while there was no detection in Daspoort WWTP (Pretoria, Gauteng).[64,90] However, a different scenario was presented in the same province indicating high levels of this drug in both influents and effluents of five WWTPs (Northern, Umbilo, Umhlathuzana, Amanzimtoti and Darvill) located in KwaZulu-Natal.[77] All the influent samples contained carbamazepine with the highest concentration of 24 μg L^{-1} found in Darvill WWTP.[77] It was the same WWTP that had the highest concentration of 3.3 μg L^{-1} in the effluent. This concentration is comparable with 1.46 μg L^{-1} found for the same drug in Northern WWTP effluent (Durban, KwaZulu-Natal province).[76] However, lower levels (2.21 μg L^{-1} in influent and 0.91 μg L^{-1} in effluent) of this drug in Darvill WWTP have also been reported.[71] Similarly to the Daspoort WWTP in Pretoria, carbamazepine was detected in both the influent and effluent samples.[44,62] A negative reduction of its concentration in a WWTP in Western Cape was reported.[78]

Table 3: ARVDs previously detected in South African waters

ARVD	Analytical method	Study site	Method quantitation limits (ng L^{-1})		Detected concentration range (μg L^{-1})			Ref.
			Waste–water	Surface water	WWTP influent	WWTP effluent	Surface water	
Abacavir	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
	SPE-LC-MS	Nationwide survey of surface water	–	0.01	–	–	nd–<MQL	30
	SPE-LC-DAD	Northern WWTP and Umgeni estuary, KwaZulu-Natal	–	–	41	24	22	55
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	0.10	0.54	–	72
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	15	–	nd–14	nd	–	88
Atazanavir	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.289	0.289	nd	nd–0.31	nd	44
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	3.1	3.0	–	72
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	12	–	0.064–1.4	0.078–0.74	–	88
Darunavir	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	14	10	–	72
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	38	–	0.069–43	0.13–17	–	88
Didanosine	SPE-LC-MS	Nationwide survey of surface water	–	0.2	–	–	nd–0.054	30
	SPE-LC-MS	22 river water sites, Gauteng	–	0.05	–	–	0.85–24.6	89
Efavirenz	HF-LPME-LC-MS	Four WWTPs in KwaZulu-Natal and Hartebeespoort dam	530	380	1.02–26.3	3.27–37.3	<MQL	11
	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.003–0.696	29
	SPE-LC-MS	Nationwide survey of surface water	–	4.7	–	–	nd–<MQL	30
	SPE-LC-DAD	Four WWTPs in Durban and Msunduzi River	1390	1390	11.1–140.4	2.79–93.1	<MQL–2.45	32
	SPE-LC-MS	Klip River, Gauteng	–	50	–	–	nd–<MQL	35
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.179	0.179	0.051–2.17	0.21–2.04	0.117–0.514	44
	SPE-LC-MS	Two WWTPs in Western Cape	0.02	–	1.42–15.4	0.982–18.1	–	47
	SPE-LC-MS	Hartbeespoort dam and Umgeni River	–	0.0003	–	–	0.002–0.354	49
	SPE-GC-MS	WWTP in Gauteng	25.9	–	5.5–14	<4	–	50
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	31	–	24–34	20–34	–	88
	SPE-LC-MS	22 river water sites, Gauteng	–	1.69	–	–	0.8–38.5	89
8,14-dihy-droxy-efavirenz	SPE-LC-MS	Two WWTPs in Western Cape	0.02	–	1.48–12.4	<MQL–8.04	–	47
Emtricitabine	HF-LPME-LC-MS	Four WWTPs in KwaZulu-Natal and Hartebeespoort dam	33	33	nd–3.10	0.11–0.35	<MQL	11
	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	nd–0.361	29
	SPE-LC-MS	Two WWTPs in Western Cape	0.04	–	31.3–172	<MQL–41.7	–	47
	SPE-LC-MS	Hartbeespoort dam and Umgeni River	–	0.0001	–	–	nd–0.013	49

Table 3: (continued)

ARVD	Analytical method	Study site	Method quantitation limits (ng L^{-1})		Detected concentration range (µg L^{-1})			Ref.
			Waste–water	Surface water	WWTP influent	WWTP effluent	Surface water	
Indinavir	SPE-LC-MS	Nationwide survey of surface water	–	4.5	–	–	nd–<MQL	30
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	12	–	0.26–0.59	0.025–0.042	–	88
Lamivudine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	nd–0.021	29
	SPE-LC-MS	Nationwide survey of surface water	–	1.7	–	–	nd–0.242	30
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	14.9	14.9	nd–1.00	nd–0.32	nd–0.010	44
	SPE-LC-MS	Two WWTPs in Western Cape	0.03	–	3.67–20.9	<MQL	–	47
	SPE-LC-MS	Msunduzi and Umgeni rivers, KwaZulu-Natal	–	0.146	–	–	nd–33.99	48
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	74	130	–	72
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	65	–	0.84–2.2	nd–0.13	–	88
Lopinavir	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.001–0.859	29
	SPE-LC-MS	Nationwide survey of surface water	–	0.5	–	–	nd–<MQL	30
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	16	–	1.2–2.5	1.9–3.8	–	88
	SPE-LC-MS	22 river water sites, Gauteng	–	1.94	–	–	0.036–1.30	89
Maraviroc	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	34	–	0.082–0.32	nd–0.039	–	88
Nevirapine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL–0.379	29
	SPE-LC-MS	Nationwide survey of surface water	–	0.02	–	–	nd–1.480	30
	MASE-MIP-LC-MS	Hennops (Gauteng) and Umdloti (KwaZulu-Natal) Rivers	–	0.39	–	–	0.499–1.64	40
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.033	0.033	<MQL–0.026.4	<MQL–0.0805	<MQL–0.011	44
	SPE-LC-MS	Two WWTPs in Western Cape	0.01	–	<MQL–0.681	<MQL–0.764	–	47
	SPE-LC-MS	Hartbeespoort dam and Umgeni River	–	0.0007	–	–	nd–0.071	49
	SPE-GC-MS	WWTP in Gauteng	6	–	<0.200	0.092–0.47	–	50
	SPE-LC-DAD	Wastewater and river water, Pretoria	0.67	0.67	1.72	0.87	0.70	59
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	0.35	0.35	–	72
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	20	–	0.67–2.8	0.54–1.9	–	88
	SPE-LC-MS	22 river water sites, Gauteng	–	0.05	–	–	0.64–1.95	89
12-hydroxy-ne-virapine	SPE-LC-MS	Two WWTPs in Western Cape	0.02	–	<MQL–0.519	<MQL	–	47
Raltegravir	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	4.1	3.5	–	72
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	38	–	0.061–17	nd–3.5	–	88
Ritonavir	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.055–1.130	29
	SPE-LC-MS	Nationwide survey of surface water	–	0.15	–	–	nd–<MQL	30
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.297	0.297	0.0041–0.394	0.0144–0.676	nd–0.0588	44
	SPE-LC-MS	Two WWTPs in Western Cape	0.06	–	<MQL	<MQL	–	47
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	16	–	1.6–3.2	0.46–1.5	–	88
	SPE-LC-MS	22 river water sites, Gauteng	–	0.80	–	–	3.68	89
Saquinavir	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	22	–	nd–0.18	nd	–	88
Stavudine	SPE-LC-MS	Nationwide survey of surface water	–	18.1	–	–	nd–0.778	30
Tenofovir disoproxil	HF-LPME-LC-MS	Four WWTPs in KwaZulu-Natal and Hartebeespoort dam	100	60	<MQL–0.250	nd–<MQL	0.110	11
	SPE-LC-MS	Nationwide survey of surface water	–	48	–	–	nd–0.243	30
Zalcitabine	SPE-LC-MS	Nationwide survey of surface water	–	23.3	–	–	nd–0.071	30
Zidovudine	SPE-LC-MS	Nationwide survey of surface water	–	1.2	–	–	nd–0.973	30
	SPE-LC-DAD	Wastewater and river water, Pretoria	0.75	0.75	1.23	0.83	<MQL	59
	SPE-LC-MS	DEWATS, Northern and Phoenix WWTPs, KwaZulu-Natal	15	–	6.9–53	0.087–0.5	–	88

Steroid hormones

Table 4 indicates that steroid hormones are among the groups of compounds that appear prominently in South African wastewaters and surface waters. This is expected as the discovery of the occurrence of this group of compounds in South African WWTPs was first reported over a decade ago, with estrone, estradiol, and estriol detected in Western Cape.[5] To date, other related compounds have been reported in WWTPs located in different parts of the country (Table 4). The concentrations of these compounds in wastewater are generally lower

Table 4: Steroid hormones that have been detected in South Africa waters

Steroid hormone	Analytical method	Study site	Method quantitation limits (μg L^{-1})		Detected concentration (μg L^{-1})			Ref.
			Waste–water	Surface water	WWTP influent	WWTP effluent	Surface water	
Estriol	ELISA	Darvill WWTP and Umsunduzi River, KwaZulu-Natal	–	–	0.003–0.009	<1	<1–0.002	4
	ELISA	WWTP effluents in the Kuils River water catchment area	–	–	–	<0.0011	–	5
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	23.9	23.9	0.053–1.31	0.057–0.779	0.081–0.546	44
Estrone	ELISA	Darvill WWTP and Umsunduzi River, KwaZulu-Natal	–	–	0.013–0.35	0.003–0.078	0.001–0.032	4
	ELISA	WWTP effluents in the Kuils River water catchment area	–	–	–	<0.0002–0.0106	–	5
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.345	0.345	nd–0.036	nd–0.061	nd–0.063	44
	SPE-LC-MS	Rietspruit and Vaal rivers, Gauteng	–	0.0001	–	–	0.0003–0.046	65
	SPE-LC-DAD	WWTP and river in Gauteng	0.033	0.033	0.0157–0.126	0.0104–0.0578	0.0104–0.0631	66
	SPE-LC-MS	Rivers and WWTPs in Eastern Cape	0.0003*	0.0003*	0.0124–1.060	nd–0.0151	nd–0.0613	91
	SPE-LC-MS	Surface water in Gauteng	–	0.0002	–	–	0.0009–0.0043	92
	LC-MS	Drinking water samples from Pretoria and Cape Town	–	–	–	–	nd–0.0034	93
Estradiol	ELISA	WWTP effluents in the Kuils River water catchment area	–	–	–	0.0008–0.0047	–	5
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	9.01	9.01	0.066–2.21	0.154–7.1	0.134–0.931	44
17-α-ethinyl-estradiol	ELISA	Darvill WWTP and Umsunduzi River, KwaZulu-Natal	–	–	0.010–0.095	0.001–0.008	nd–0.004	4
	LC-MS	Drinking water samples from Pretoria and Cape Town	–	–	–	–	nd–0.00002	93
17β-estradiol	ELISA	Darvill WWTP and Umsunduzi River, KwaZulu-Natal	–	–	0.020–0.20	0.004–0.107	0.001–0.066	4
	SPE-LC-DAD	Three WWTPs and two river systems (Gauteng and Free State)	0.083	0.083	0.102–0.161	0.037–0.049	nd	63
	SPE-LC-MS	Rietspruit and Vaal rivers, Gauteng	–	0.0001	–	–	0.0002–0.046	65
	SPE-LC-DAD	WWTP and river in Gauteng	0.067	0.067	0.143–6.234	0.0674–2.207	0.124–0.948	66
	SPE-LC-MS	Rivers and WWTPs in Eastern Cape	0.0003*	0.0003*	0.0061–0.1350	nd–0.0026	nd–0.0163	91
	LC-MS	Drinking water samples from Pretoria and Cape Town	–	–	–	–	nd–0.00005	93
Diethylstilbes-trol	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	4.04	4.04	nd–0.091	nd–0.547	nd–0.368	44
Hydrocortisone	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.001–0.025	29
	SPE-LC-MS	Rietspruit and Vaal rivers, Gauteng	–	0.0002	–	–	0.0024–0.055	65
	SPE-LC-DAD	WWTP and river in Gauteng	0.10	0.10	<MQL–0.0875	<MQL–0.0373	<MQL	66
Medroxyproges-terone	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.062	0.062	nd–0.0169	nd–0.0048	nd–0.0098	44
Mestranol	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	19.5	19.5	nd–0.123	nd–0.110	nd–0.0196	44
Progesterone	ELISA	Darvill WWTP and Umsunduzi River, KwaZulu-Natal	–	–	0.16–0.90	nd–0.025	nd–0.060	4
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.05	0.05	nd–0.0145	nd–0.0040	<MQL–0.0036	44
	SPE-LC-MS	Rietspruit and Vaal rivers, Gauteng	–	0.0005	–	–	0.0006–0.049	65
	SPE-LC-DAD	WWTP and river in Gauteng	0.033	0.033	<MQL–0.127	<MQL–0.0783	<MQL–0.0683	66
Testosterone	ELISA	Darvill WWTP and Umsunduzi River, KwaZulu-Natal	–	–	0.12–0.64	nd–0.026	0.003–0.019	4
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.052	0.052	nd–0.0441	nd–0.0058	nd–0.0024	44

Notes: *The provided values are method detection limits; ELISA-Enzyme-linked immunosorbent assay

than other groups of drugs discussed in this review. In the Eastern Cape province, steroid hormones were detected in environmental samples to a lesser extent when compared to other investigated endocrine disruptive compounds.[91] However, their detection frequency in a WWTP influent and effluent in Pretoria ranged from 69–100%.[44] For example, the concentrations of 17β-estradiol in wastewater samples collected in Gauteng and Free State did not exceed 161 ng L^{-1}.[63] Mpupa et al investigated the occurrence of estrone, β-estradiol, hydrocortisone and progesterone in a WWTP, and detected all the analytes in the effluent.[66] In this case, it was β-estradiol that displayed the highest detected concentration of 2.2 μg L^{-1} in wastewater effluent. Like other compounds of different classes, their presence in WWTP effluents demonstrates their discharge into the surface water which could equate to unintended consumption by humans. But, thus far, the South African WWTPs seem to be able to reduce the amounts of these compounds in wastewater with the concentrations in the effluent mostly observed to be lower than in the influent.[63,66]

Surface water

Non-steroidal anti-inflammatory drugs and analgesics

As easily accessible and commonly used drugs, NSAIDs are among the most investigated pharmaceuticals in South African surface waters (Table 1). As a result, Madikizela and Ncube (2021) recently reviewed the presence of these drugs in the South African aquatic environment with great emphasis on interrogating the available data while also highlighting the gaps for future research.[25] These pharmaceuticals are constantly detected in South African surface waters with recent studies reporting their presence in seawater and marine organisms.[12,14] Furthermore, recent studies on screening the occurrence of a wide

range of pharmaceuticals in Gauteng surface waters found NSAIDs to be among the most detected pharmaceuticals.[34,35,44] Madikizela et al (2022) identified 47 pharmaceuticals (with transformation products) out of 92 investigated drugs in Klip River (Gauteng province), with 14 of the detected compounds belonging to NSAIDs and analgesics.[35] In this case, acetaminophen, ibuprofen and ketoprofen were among those pharmaceuticals that were quantified with their levels not exceeding 0.432 μg L^{-1}. However, much higher quantities of these pharmaceuticals in South African waters have been reported in recent years. For example, ibuprofen has been detected in surface water with concentrations reaching 62 μg L^{-1} in Umgeni River and Msunduzi River confluence.[76] In a different river, the highest concentration of 24 μg L^{-1} was reported for ketoprofen.[27]

Although pharmaceuticals belonging to this therapeutic group are constantly detected in South African water systems, some drugs have been recently identified in selected water sources. In this context, Madikizela et al (2022) identified NSAIDs and analgesics (phenacetin, hydromorphone, indomethacin, propyphenazone, phenazone and ketorolac) in Klip River which are not commonly monitored in South African water systems.[35] Notably, indomethacin and phenacetin have also been detected in wastewater and surface water in Pretoria.[44] Meclofenamic was detected in surface water with a maximum concentration of 2.38 μg L^{-1}.[51] This means these drugs should be among those that are investigated for their presence in other South African waters. Concerningly, environmental monitoring of these drugs and others in South African waters is mostly performed in major cities resulting in lack of scientific information emerging from rural locations and small towns. This continues to happen despite the detection of three NSAIDs (naproxen, ibuprofen and diclofenac) in a river flowing in the small town of Ladysmith.[57] This should serve as an indication that a national survey of these pharmaceuticals is required taking into account the representation of rivers flowing in small towns and rural communities.

Antibiotics

As shown in Table 2, the detection of antibiotics in South African surface waters is common. Like other pharmaceuticals, antibiotics found in WWTPs are also detected in surface waters, more especially, the WWTP effluent receiving water bodies. This causes great concern due to the rise of antimicrobial resistance genes and bacteria, which reduce the therapeutic potential against human and non-human animal bacterial pathogens.[24] To date, several antimicrobial resistance genes and bacteria have been detected in South African surface rivers which include the drinking water sources,[94-96] that are accessible to humans and animals, thereby increasing the exposure risks. In fact, antibiotic resistance profiles of environmental isolates in a South African river were first discovered two decades ago.[96] However, the great challenge with environmental monitoring studies more especially in South Africa is the lack of long-term monitoring of environmental pollutants. For example, it would be interesting to establish the environmental trends over a long period.

Sulfamethoxazole and erythromycin appear prominently in South African surface waters (Table 2). In particular, a study that investigated several compounds in surface water from KwaZulu-Natal which included acetaminophen, lamivudine, ciprofloxacin, vancomycin, diclofenac and ivermectin; sulfamethoxazole was the most frequently detected pharmaceutical with highest concentrations.[48] Both sulfamethoxazole and erythromycin are among those that have been found to occur conspicuously in sediments of rivers in KwaZulu-Natal.[76] In fact, sulfamethoxazole had the highest concentrations of ~500 ng g^{-1} in sediments collected from the confluence of Msunduzi and Umgeni Rivers.[76] Therefore, the consistence occurrence of such antibiotics in South African rivers could also be a result of their release from the sediments into the surface waters. This is corroborated by the detection of erythromycin in WWTP effluent while it was not found in the corresponding influent,[44] suggesting a possible release from sewage sludge. This means the presence of such pharmaceuticals in South African environment must not only be monitored in the aqueous phase. In addition, long-term studies are required which take into account the climatic changes which have the potential to influence the release of antibiotics from the sediments into the corresponding water body.

Antiretroviral drugs

Since 2015, significant number of studies have monitored the occurrence of ARVDs in South African surface waters where several drugs have been detected (Table 3). In this case, over 10 ARVDs have been detected in South African surface waters with efavirenz and nevirapine being the most investigated and constantly detected drugs. The maximum concentration of efavirenz recorded in Msunduzi River which is now known as the pollution hotspot in KwaZulu-Natal was 2.45 μg L^{-1}.[32] In the same province, near a WWTP outfall, efavirenz concentration reached 37.3 μg L^{-1}.[11] In this case, efavirenz concentration was nearly 170 times higher than the levels found for the other investigated ARVDs (emtricitabine and tenofovir disoproxil), where differences in consumption rates were believed to greatly influence the research findings. In comparison with zidovudine, nevirapine concentrations were generally higher in wastewater and river water samples collected in Pretoria.[59] In comparison with pharmaceuticals of different therapeutic classes, nevirapine had higher concentrations in surface water than carbamazepine, etilefrine and methocarbamol.[40] However, the same study reported that nevirapine concentrations were mostly lower when compared to those found for venlafaxine.[40] A detection frequency of 100% was reported for both efavirenz and nevirapine in Apies River (Pretoria).[44] A negative removal of nevirapine in WWTP as reported elsewhere[44] and consumption pattens followed by excretion could be a result of its frequent detection in surface water. Thus far, South Africa is one of the leading countries in investigating the occurrence of ARVDs in environmental waters.[26] This is expected as a significant number of HIV-positive people reside in South Africa.[26] Going forward, all ARVDs dispatched for consumption should be investigated in water samples with the principal aim of establishing a correlation between the levels found in the environment for each compound and the consumption pattens. This is necessary in order to understand the fate of the compounds in the environment which is currently a cumbersome exercise. With South Africa being the largest purchaser of ARVDs in the world, there is a need to establish a routine monitoring program for these drugs in South African water bodies. This is important in order to monitor any variation of concentrations of these pharmaceuticals over time. Thus far, there has been minimum variations in the concentrations of selected drugs observed in surface water since 2015. However, a logical trend can be drawn if there is continuous monitoring conducted over a long period. In this context, a study published in 2015 reported a no detection of tenofovir in Hartbeespoort dam while the concentration of efavirenz did not excced the method quantitation limit of 0.519 μg L^{-1}.[30] However, a study published in 2020 for the same dam, reported the average concentration of 0.110 μg L^{-1} for tenofovir, with efavirenz detected with its concentration not exceeding the method quantitation limit of 0.380 μg L^{-1}.[11] In 2018, Rimayi et al reported a similar trend where tenofovir was not detected, but efavirenz was reported with a maximum concentration of 0.303 μg L^{-1}.[49]

Carbamazepine

Carbamazepine is one of the pharmaceuticals that are constantly detected in South African surface waters.[35,40,49] In Apies River (Gauteng province) and several rivers in Eastern Cape, this drug had 100% detection frequency.[44,82] In recent years, Khulu et al (2022) detected this pharmaceutical in all the selected sampling sites of the two important South African rivers, Hennops and Umdloti, flowing in the provinces of Gauteng and KwaZulu-Natal, respectively.[40] In this

case, it was the Hennops River that recorded the highest concentration of 0.74 μg L^{-1}. This value (0.74 μg L^{-1}) falls within the concentration range of 0.38–1.65 μg L^{-1} previously detected in Umgeni River flowing in the province of KwaZulu-Natal.[76] The concentration range found in Msunduzi River was 0.13-3.24 μg L^{-1}.[71] In several rivers flowing in KwaZulu-Natal, the highest concentration recorded for carbamazepine was 3.8 μg L^{-1} found in Umgeni River, with findings indicating that the detected amounts are influenced by seasonal changes.[77] Madikizela et al (2022) detected the same compound in Klip River, Gauteng province, however, its concentration was below the method quantitation limit of 0.09 μg L^{-1}.[35] In fact, some studies have found the concentrations of carbamazepine in surface water to be minimal with its quantities not exceeded the method quantitation limits.[35,37,46,64] This observation could be associated with the transformation of carbamazepine into other compounds as indicated elsewhere.[45] However, some of these studies did not investigate the occurrence of the transformation products in the same samples.[37,46] This is in exception with the study conducted by Madikizela et al (2022) where two transformation products of carbamazepine, 10-hydroxy-carbamazepine and dihydro-carbamazepine, were detected in Klip River (Gauteng province).[35] The detection of trace amounts of this pharmaceutical in South African surface waters could also be due to its limited accessibility as this drug is only dispatched to patients that have medical prescriptions.[35,76] In addition, the reported detection of this drug in selected South African estuaries (Eastern Cape) serves as an indication of its potential release into the seawaters.[97] In fact, this pharmaceutical has already been detected in South African seawaters.[14]

Steroid hormones

There are currently not many South African-based studies investigating the occurrence of these compounds in surface water (Table 4). This is a narrative that should change as the presented scientific information point out the occurrence of such compounds in drinking water samples[92], which imply unintentional consumption by South Africans. Immediate response to mitigate the exposure risks to these chemicals is required. Their occurrence in river water[4,44,91] means their unintentional consumption is likely not to only affect humans, but the wildlife and aquatic organisms are also at risk. Their detection frequency which was found to reach 100% for several steroid hormones in Apies River (Pretoria)[44] is an indication of prolonged exposure to these chemicals which could result in detrimental effects to aquatic organisms and human life.

Other pharmaceuticals detected in both wastewater and surface water

The latest developments in the analytical methods for pharmaceutical analysis in environmental waters have ensured the detectability of a wide range of drugs in water bodies.[34,35,44] In South Africa, the detection of many pharmaceuticals in water has been achieved through the application of LC-MS after SPE using a non-selective sorbent in the form of Oasis HLB.[34,35,44] This has resulted in the detection of pharmaceuticals that are not routinely analysed in South African waters (Table 5). These detected pharmaceuticals belong to the different therapeutic groups, shown in Figure 4. Figure 5 shows the number of pharmaceuticals belonging from these therapeutic classes detected in wastewater and surface water samples. Notably, a study conducted by Madikizela et al (2022) focussing on suspect screening of pharmaceuticals only investigated the presence of selected pharmaceuticals and their metabolites in river water.[35] Hence, there was no direct link to the occurrence of the detected compounds between the surface water and wastewater.[35] However, a different study reported that the occurrence of pharmaceuticals and personal care products in river water cannot be always linked directly to WWTP effluents.[44] Therefore, it is justifiable to streamline the monitoring studies into the surface water when the researchers are not interested in source apportionment.

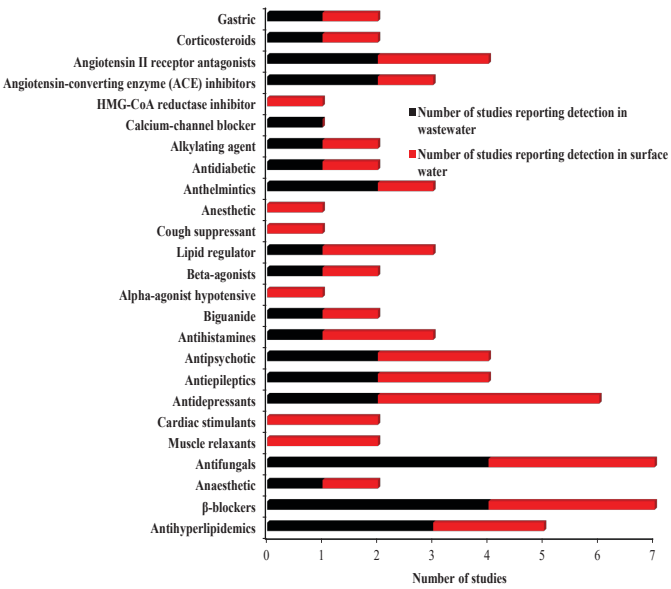

Figure 4: Other therapeutic groups detected in South African water systems

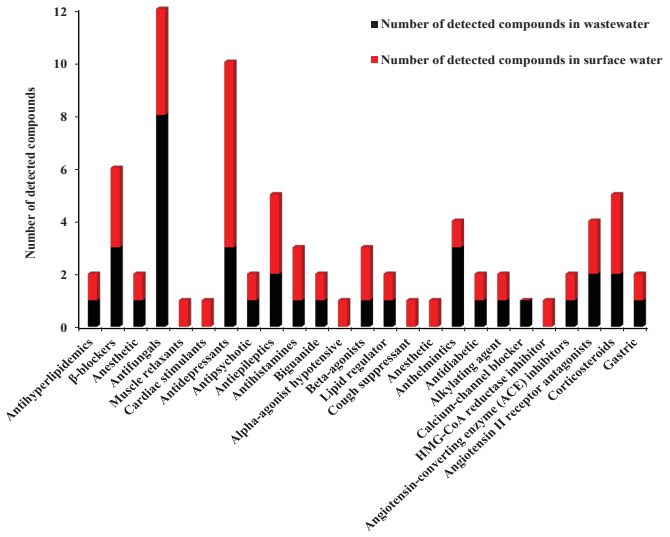

Figure 5: Number of compounds detected from each theraupeutic class

Table 5 shows that the pharmaceuticals that have been randomly detected in South African waters belong to different therapeutic groups. About 7 antidepressants have been detected in surface water which indicates a need to monitor them in wastewater and trace their sources. Among these antidepressants, venlafaxine has been monitored to the large extent. Although our research group has found this pharmaceutical in all the sampling sites along Hennops and Umdloti rivers flowing in Gauteng and KwaZulu-Natal, respectively,[40] we could not detect it in Orlando dam which is positioned in the heart of Soweto Township, Gauteng.[37] In fact, its concentrations in the range of 1.368-2.481 μg L^{-1} in Hennops and Umdloti rivers mostly exceeded those of other investigated pharmaceuticals (nevirapine, carbamazepine, etilefrine and methocarbamol).[40] Some of the detected pharmaceuticals were only investigated in single studies with no quantification performed due to the limited availability of high purity standards of compounds. But the reported positive detections warrant further investigations to understand the extent of pollution caused by these drugs in aquatic environments. In this case, pharmaceuticals in the sample extracts were identified using the online tools available in the LC-MS instruments which include the use of retention times, mass accuracy, isotopic pattern and diagnostic MS/MS fragments and confirmation with online database resources such as METLIN, KEGG, and Mass Bank.[34,35,69]

Table 5: Other pharmaceuticals that have been detected in South African water systems

Pharmaceutical	Analytical method	Study site	Method quantitation limits (μg L^{-1})		Detected concentration (μg L^{-1})			Ref.
			Waste–water	Surface water	WWTP influent	WWTP effluent	Surface water	
Albendazole	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.027	0.027	nd–0.018	nd–<MQL	nd	44
	SPE-LC-MS	Four WWTPs in Durban and receiving waterbodies, KwaZulu-Natal	0.00053	–	23–186	nd–0.683	nd–0.683	81
Amitriptyline	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.01	0.01	nd–0.006	nd–0.019	nd–0.0001	44
Atenolol	SPE-LC-DAD	Daspoort WWTP and Apies River, Gauteng	0.0023	0.0023	0.029	0.0049	0.0049	64
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	nd	0.58	–	72
Bezafibrate	SPE-LC-MS	Msunduzi River and Darvill WWTP, KwaZulu-Natal	0.088	0.088	0.194	0.012	nd–0.23	79
Chlorhexidine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.005	29
Chlorothiazide	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.090–0.468	29
Cimetidine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.030–0.052	29
Clotrimazole	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
	SPE-LC-MS	Three WWTPs (Gauteng) and Vaalkop water treatment facility (North-West)	0.02–0.24	0.02–0.24	nd–0.016	nd–0.143	nd	98
Clozapine	SPE-LC-MS	Msunduzi water system, KwaZulu-Natal	1.331	0.444	nd	9.56	2.18–8.89	71
	SPE-LC-MS	Umgeni water system, KwaZulu-Natal	1.331	0.444	8.95	14.4	17–26	76
Dexamethasone	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.189	0.189	nd	nd–0.0009	nd–<MQL	44
Diphenhydr-amine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.039–0.054	29
Econazole	SPE-LC-MS	Three WWTPs (Gauteng) and Vaalkop water treatment facility (North-West)	0.02–0.24	0.02–0.24	nd	nd–0.02	nd–0.005	98
Enalapril	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.071	0.071	nd–0.033	nd–0.0031	nd–0.0002	44
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	7.6	8.1	–	72
Etilefrine	^{PS}MASE-MIP-LC-MS	Orlando dam, Gauteng	–	0.0081	–	–	nd–0.013	37
	MASE-MIP-LC-MS	Hennops (Gauteng) and Umdloti (KwaZulu-Natal) Rivers	–	0.56	–	–	<MQL–0.647	40
Fluconazole	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.008–0.130	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.148	0.148	0.014–0.396	0.015–0.308	0.011–0.201	44
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	0.73	1.80	–	72
	SPE-LC-MS	Three WWTPs (Gauteng) and Vaalkop water treatment facility (North-West)	0.02–0.24	0.02–0.24	0.12–9.96	0.13–0.33	nd	98
Fluoxetine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	nd–0.042	29
Gabapentin	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.157–0.206	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.317	0.317	nd–0.146	<MQL–0.0418	0.002–0.019	44
Gemfibrozil	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	2.17	2.17	nd–0.599	0.004–0.479	0.009–0.545	44
Gliclazide	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	nd	0.044	–	72
Ifosfamide	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.026	0.026	nd–0.002	nd–0.005	nd–0.001	44
Isoniazid	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	–	–	nd–0.0316	nd–0.0278	nd–0.006	44
Itraconazole	SPE-LC-MS	Three WWTPs (Gauteng) and Vaalkop water treatment facility (North-West)	0.02–0.24	0.02–0.24	nd	nd–0.024	nd	98
Ivermectin	SPE-LC-MS	Msunduzi and Umgeni rivers, KwaZulu-Natal	–	0.279	–	–	nd–6.57	48
Ketoconazole	SPE-LC-MS	Three WWTPs (Gauteng) and Vaalkop water treatment facility (North-West)	0.02–0.24	0.02–0.24	nd–0.067	nd–0.007	nd	98
Lamotrigine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	nd–0.586	29
	SPE-LC-MS	Newlands Mashu decentralised WWTP	–	–	0.24	nd	–	72
Leflunomide	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.120–0.644	29
Lidocaine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.025	0.025	nd–0.093	nd–0.425	0.0013–0.112	44
Loratadine	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL	29
Mebendazole	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.031	0.031	nd–0.0618	nd–0.0294	nd	44
Metformin	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.004–0.179	29
Metoprolol	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.075	0.075	nd–0.0009	nd–0.002	nd–0.0002	44
Methocarbamol	^{PS}MASE-MIP-LC-MS	Orlando dam, Gauteng	–	0.010	–	–	0.017–0.072	37
	MASE-MIP-LC-MS	Hennops (Gauteng) and Umdloti (KwaZulu-Natal) Rivers	–	0.69	–	–	nd–<MQL	40
Metronidazole	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.043–0.060	29

Pharmaceutical	Analytical method	Study site	Method quantitation limits (μg L^{-1})		Detected concentration (μg L^{-1})			Ref.
			Waste–water	Surface water	WWTP influent	WWTP effluent	Surface water	
Miconazole	SPE-LC-MS	Three WWTPs (Gauteng) and Vaalkop water treatment facility (North-West)	0.02–0.24	0.02–0.24	nd–0.017	nd–0.016	nd–0.014	98
Posaconazole	SPE-LC-MS	Three WWTPs (Gauteng) and Vaalkop water treatment facility (North-West)	3.4	3.4	nd	nd	nd	98
Prednisolone	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.257–1.083	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.094	0.094	nd–0.0074	nd–0.036	nd–0.0361	44
Prednisone	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	<MQL–0.355	29
Pindolol	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.037	0.037	nd–0.0028	nd–0.0184	nd–<MQL	44
Praziquantel	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.021–0.167	29
Procaine	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.055	0.055	nd–0.0155	nd–0.0018	nd–0.0016	44
Propanolol	SPE-LC-DAD	Daspoort WWTP and Apies River, Gauteng	0.00033	0.0023	0.021	0.0077	0.0021	64
Salbutamol	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.13	0.13	nd–0.0052	nd–0.0086	nd–0.0013	44
Terbutaline	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.053	0.053	nd–0.0014	nd–0.0005	nd–<MQL	44
Thiabendazole	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.027	0.027	nd–0.0017	nd–0.010	nd–<MQL	44
Venlafaxine	MASE-MIP-LC-MS	Hennops (Gauteng) and Umdloti (KwaZulu-Natal) Rivers	–	0.44	–	–	1.44–2.48	40
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.016	0.016	nd–0.0076	nd–0.040	<MQL–0.0051	44
	SPE-LC-MS	Hartbeespoort dam and Umgeni River	–	0.0002	–	–	nd–0.026	49
Valsartan	SPE-LC-MS	Nationwide survey of surface water	–	–	–	–	0.008–0.425	29
	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	1.448	1.448	0.0994–1.289	0.106–0.762	0.0540–0.322	44
Verapamil	SPE-LC-MS	Daspoort WWTP and Apies River, Gauteng	0.029	0.029	nd–0.0005	nd–0.0012	nd	44

Notes: References 44 and 98 provided the instrument quantitation limits; MASE – Membrane assisted solvent extraction; [PS] passive sampling study

Occurrence of pharmaceutical metabolites and transformation products in South African waters

Madikizela and co-workers have recently identified six transformation products of pharmaceuticals which included dementhyl-dextrorphan, dextrorphan, nor-citalopram, 10-hydroxy-carbamazepine, dihydro-carbamazepine and clofibric acid, in Klip River (Gauteng province). These transformation products were reported for the first time in South African waters.[35] A metabolite of carbamazepine has also been reported in wastewaters from Western Cape.[45] Other metabolites found in South African waters include those of nevirapine (12-hydroxy-nevirapine) and efavirenz (8,14-dihydroxy-efavirenz) which were detected in Western Cape.[47] Although there is currently limited work conducted in this regard, extensive monitoring of pharmaceutical metabolites in water should be conducted in South Africa. Interestingly, some metabolites detected in South African waters originate from drugs that are constantly reported to have high concentrations in the aquatic environment. In this case, the current review has reported carbamazepine, efavirenz and nevirapine as some of the drugs that appear prominently with high concentrations in South African waters. The detection of their metabolites indicates that their quantities in South African waters could have been more enhanced if some portions of these drugs were not undergoing some transformation in the human body or the environment. Future studies should investigate the occurrence of the metabolites alongside their parent compounds. This is important to draw necessary conclusions as some drugs have not been detected in selected aqueous samples, which could be a result of the transformation of the parent compounds. Detection of the metabolite, while the parent compound is not found in the same sample, would be an indication of the release of such drugs into the environment.

TOXIC EFFECTS OF PHARMACEUTICALS FOUND IN SOUTH AFRICAN WATERS

Studies on toxic effects caused by the occurrence of pharmaceuticals in the South African environmental remain scanty. This is probably due to the fact that South African researchers are still lagging in identifying and quantifying pharmaceuticals that are present in environmental waters. The occurrence of pharmaceutical-related dugs in South African aquatic bodies was established in the early 2000s,[5] but the environmental monitoring studies for these compounds only intensified in 2014.

Despite the lack of studies evaluating the toxic effects of pharmaceuticals in water, the recent reviews collated the environmental monitoring data to provide an ecotoxicological risk assessment of selected drugs.[23,25] At the same time, the importance of attaining a comprehensive toxicological and risk assessment information of pharmaceuticals present in African waters has been emphasised.[99] Gani et al (2021) focussed on emerging contaminants in South African waters at large,[23] while Madikizela and Ncube (2021) streamlined their research to focus on NSAIDs.[25] Both these reviews established that selected pharmaceutical quantities found in both South African wastewater and surface water posed low to high environmental risks to selected aquatic organisms which included *Vibrio fischeri*, algae and *Daphnia magna*. Madikizela and his co-workers further investigated the ecotoxicological effects of pharmaceuticals detected in Klip River (Johannesburg), with oxolinic acid (with detected maximum concentration of 0.355 μg L^{-1}) showing a high risk of toxicity towards aquatic organisms.[35] Their similar study focussing on antibiotics reported moderate risk for the environment due to the presence of trimethoprim and sulfamethoxazole while the risk was high for flumequine.[69] Although there is currently limited data on the toxic effects of pharmaceuticals in aquatic environments, it has been reported that the presence of these compounds in water generally affects the behaviour and reproduction of aquatic organisms.[100] However, this was proved to affect the growth of fish to a lesser extent during the exposure of *Oreochromis mossambicus* to nevirapine.[101] Also, a commonly detected ARVD, efavirenz, has been found to cause liver damage to the fish, thereby causing a decline in its overall health.[102] Notably, these views may not be taken as fits-for-all scenarios, as the toxic effects may be influenced by the contaminant concentration, pharmaceutical concoction, and environmental

conditions, among other issues. Hence, it is necessary to investigate the toxic effects of pharmaceuticals in South African environmental conditions.

OTHER SOUTH AFRICAN-BASED RESEARCH ON PHARMACEUTICAL ANALYSIS

The context of the present paper focussed on the chromatographic-based analytical methods developed for pharmaceuticals analysis in South African aquatic environment. Although this was conceptualized as such, a significant progress has been made on the development of various sensors for the detection of pharmaceuticals and other emerging chemical pollutants in South African waters.[103–107] In this context, fluorescence sensors have been developed for various chemicals of emerging concern.[103,104] In this case, the occurrence of acetaminophen in tap and river water samples collected in Pretoria was investigated using a thiol-capped core/shell quantum dot sensor.[105] The presence of the same pharmaceutical in selected water matrices was investigated using a newly developed analytical method which utilized MIP-coated quantum dots for fluorescence sensing.[106] Both these sensing methods were found to be selective and sensitive, thus, suitable for monitoring the investigated pharmaceutical in real samples.[105,106] Due to the high demand to perform a multi-residue investigations, such sensing methods which are already deemed suitable for environmental analysis should be further developed for future applications in the simultaneous analysis of pharmaceuticals in South African waters.

Electrochemical based methods have also been investigated for the monitoring of pharmaceuticals in water.[107–109] Thus far, these methods which were developed for the analysis of single drugs in aqueous matrices have shown great potential for their application in environmental monitoring. In recent work, an electrochemical detection of nevirapine in wastewater was investigated using a sensitive analytical approach (with detection limit of 0.0064 ng L^{-1}) which was based on using a banana peel extract functionalised nickel selenide quantum dots in electrochemical sensing.[107] Literature suggested that other electrochemical sensors have been developed for few other pharmaceuticals which include 17β-estradiol and acetaminophen.[108,109] This means further research is still required in this study field for the development of sensors for monitoring pharmaceuticals in water bodies.

CONCLUSION AND WAY FORWARD

There seems to be a correlation between the pharmaceuticals found in both wastewater effluents and corresponding surface waters. This means that the compounds found in wastewater should also be monitored in nearby surface waters to ensure minimal pollution of drinking water sources. Furthermore, there is a need to monitor pharmaceuticals in rivers flowing into the rural areas where their water plays a crucial role in domestic activities, while it has flown through the urban areas which are reported as pollution hotspots. Importantly, the presented review provided a critical assessment of the available information published on the occurrence of pharmaceuticals in South African waters. With about a decade of ongoing environmental monitoring research, the present paper provided lists of pharmaceuticals that should be regarded as the watchlist in the South African environment. While extensive environmental monitoring of the presented pharmaceuticals is required, the toxic effects of the detected drugs and their removal strategies in waterbodies should be investigated. This is important as some of the pharmaceuticals have been detected in water destined for human consumption.

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DECLARATION

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REFERENCES

1. Madikizela LM, Muthwa SF, Chimuka L. Determination of triclosan and ketoprofen in river water and wastewater by solid phase extraction and high performance liquid chromatography. S Afr J Chem. 2014;67:143–150.
2. Agunbiade FO, Moodley B. Pharmaceuticals as emerging organic contaminants in Umgeni River water system, KwaZulu-Natal, South Africa. Environ Monit Assess. 2014;186(11):7273–7291. https://doi.org/10.1007/s10661-014-3926-z
3. Amdany R, Chimuka L, Cukrowska E. Determination of naproxen, ibuprofen and triclosan in wastewater using the polar organic chemical integrative sampler (POCIS): A laboratory calibration and field application. Water SA. 2014;40(3):407–414. https://doi.org/10.4314/wsa.v40i3.3
4. Manickum T, John W. Occurrence, fate and environmental risk assessment of endocrine disrupting compounds at the wastewater treatment works in Pietermaritzburg (South Africa). Sci Total Environ. 2014;468-469:584–597. https://doi.org/10.1016/j.scitotenv.2013.08.041
5. Swart N, Pool E. Rapid detection of selected steroid hormones from sewage effluents using an ELISA in the Kuils River water catchment area, South Africa. J Immunoassay Immunochem. 2007;28(4):395–408. https://doi.org/10.1080/15321810701603799
6. Hendricks R, Pool EJ. The effectiveness of sewage treatment processes to remove faecal pathogens and antibiotic residues. J Environ Sci Health Part A. 2012;47(2):289–297. https://doi.org/10.1080/10934529.2012.637432
7. Osunmakinde MNC, Tshabalala S, Dube S, Nindi MM. Verification and validation of analytical methods for testing the levels of PPHCPs (pharmaceutical & personal health care products) in treated drinking water and sewage. Water Research Commission Technical Report 2013.
8. Ademoyegun OT, Okoh OO, Okoh AI. Method validation and investigation of the levels of pharmaceuticals and personal care products in sludge ofwastewater treatment plants and soils of irrigated golf course. Molecules. 2020;25(14):3114. https://doi.org/10.3390/molecules25143114
9. Sibeko PA, Naicker D, Mdluli PS, Madikizela LM. Naproxen, ibuprofen, and diclofenac residues in river water, sediments and Eichhornia crassipes of Mbokodweni river in South Africa: an initial screening. Environ Forensics. 2019;20(2):129–138. https://doi.org/10.1080/15275922.2019.1597780
10. Mlunguza NY, Ncube S, Mahlambi PN, Chimuka L, Madikizela LM. Optimization and application of hollow fiber liquid-phase microextraction and microwave-assisted extraction for the analysis of non-steroidal anti-inflammatory drugs in aqueous and plant samples. Environ Monit Assess. 2020;192(8):557. https://doi.org/10.1007/s10661-020-08527-4
11. Mlunguza NY, Ncube S, Mahlambi PN, Chimuka L, Madikizela LM. Determination of selected antiretroviral drugs in wastewater, surface

water and aquatic plants using hollow fibre liquid phase microextraction and liquid chromatography - tandem mass spectrometry. J Hazard Mater. 2020;382:121067. https://doi.org/10.1016/j.jhazmat.2019.121067

12. Ngubane NP, Naicker D, Ncube S, Chimuka L, Madikizela LM. Determination of naproxen, diclofenac and ibuprofen in Umgeni estuary and seawater: A case of northern Durban in KwaZulu – Natal province of South Africa. Reg Stud Mar Sci. 2019;29:100675. https://doi.org/10.1016/j.rsma.2019.100675
13. Petrik L, Green L, Abegunde AP, Zackon M, Sanusi CY, Barnes J. Desalination and seawater quality at Green Point, Cape Town: A study on the effects of marine sewage outfalls. S Afr J Sci. 2017;114(1/2):1–10. https://doi.org/10.17159/sajs.2018/a0244C
14. Ojemaye CY, Petrik L. Pharmaceuticals and personal care products in the marine environment around False Bay, Cape Town, South Africa: Occurrence and risk-assessment study. Environ Toxicol Chem. 2022;41(3):614–634. https://doi.org/10.1002/etc.5053
15. Ojemaye CY, Petrik L. Occurrences, levels and risk assessment studies of emerging pollutants (pharmaceuticals, perfluoroalkyl and endocrine disrupting compounds) in fish samples from Kalk Bay harbour, South Africa. Environ Pollut. 2019;252:562–572. https://doi.org/10.1016/j.envpol.2019.05.091
16. Madikizela LM, Ncube S, Chimuka L. Analysis, occurrence and removal of pharmaceuticals in African water resources: A current status. J Environ Manage. 2020;253:109741. https://doi.org/10.1016/j.jenvman.2019.109741
17. K'oreje KO, Okoth M, Van Langenhove H, Demeestere K. Occurrence and treatment of contaminants of emerging concern in the African aquatic environment: literature review and a look ahead. J Environ Manage. 2020;254:109752. https://doi.org/10.1016/j.jenvman.2019.109752
18. Necibi MC, Dhiba D, El Hajjaji S. Contaminants of emerging concern in African wastewater effluents: Occurrence, impact and removal technologies. Sustainability (Basel). 2021;13(3):1125. https://doi.org/10.3390/su13031125
19. Ogunlaja A, Ogunlaja OO, Olukanni OD, Taylor GO, Olorunnisola CG, Dougnon VT, Mousse W, Fatta-Kassinos D, Msagati TAM, Unuabonah EI. Antibiotic resistomes and their chemical residues in aquatic environments in Africa. Environ Pollut. 2022;312:119783. https://doi.org/10.1016/j.envpol.2022.119783
20. Okoye CO, Okeke ES, Okoye KC, Echude D, Andong FA, Chukwudozie KI, Okoye HU, Ezeonyejiaku CD. Occurrence and fate of pharmaceuticals, personal care products (PPCPs) and pesticides in African water systems: A need for timely intervention. Heliyon. 2022;8(3):e09143. https://doi.org/10.1016/j.heliyon.2022.e09143
21. Mheidli N, Malli A, Mansour F, Al-hindi M. Occurrence and risk assessment of pharmaceuticals in surface waters of the Middle East and North Africa: A review. Sci Total Environ. 2022;851:158302. https://doi.org/10.1016/j.scitotenv.2022.158302
22. Waleng NJ, Nomngongo PN. Occurrence of pharmaceuticals in the environmental waters: african and Asian perspectives. Environ. Chem. Ecotoxicol. 2022;4:50–66. https://doi.org/10.1016/j.enceco.2021.11.002
23. Gani KM, Hlongwa N, Abunama T, Kumari S, Bux F. Emerging contaminants in South African water environment- a critical review of their occurrence, sources and ecotoxicological risks. Chemosphere. 2021;269:128737. https://doi.org/10.1016/j.chemosphere.2020.128737
24. Ngqwala NP, Muchesa P. Occurrence of pharmaceuticals in aquatic environments: A review and potential impacts in South Africa. S Afr J Sci. 2020;116(7/8):1–7. https://doi.org/10.17159/sajs.2020/5730
25. Madikizela LM, Ncube S. Occurrence and ecotoxicological risk assessment of non-steroidal anti-inflammatory drugs in South African aquatic environment: what is known and the missing information? Chemosphere. 2021;280:130688. https://doi.org/10.1016/j.chemosphere.2021.130688
26. Zitha AB, Ncube S, Mketo N, Nyoni H, Madikizela LM. Antiretroviral drugs in water: an African challenge with Kenya and South Africa as hotspots and plausible remediation strategies. Chem. Africa. 2022;5(5):1237–1253. https://doi.org/10.1007/s42250-022-00417-1
27. Akawa MN, Mogolodi Dimpe K, Nomngongo PN. Amine - functionalized magnetic activated carbon as an adsorbent for preconcentration and determination of acidic drugs in environmental water samples using HPLC - DAD. Open Chem. 2020;18(1):1218–1229. https://doi.org/10.1515/chem-2020-0162.
28. Akawa MN, Dimpe KM, Nomngongo PN. Ultrasonic assisted magnetic solid phase extraction based on the use of magnetic waste-tyre derived activated carbon modified with methyltrioctylammonium chloride adsorbent for the preconcentration and analysis of non-steroidal anti-inflammatory drugs in wastewater. Arab J Chem. 2021;14(9):103329. https://doi.org/10.1016/j.arabjc.2021.103329
29. Wood TP, Du Preez C, Steenkamp A, Duvenage C, Rohwer ER. Database-driven screening of South African surface water and the targeted detection of pharmaceuticals using liquid chromatography - High resolution mass spectrometry. Environ Pollut. 2017;230:453–462. https://doi.org/10.1016/j.envpol.2017.06.043
30. Wood TP, Duvenage CSJ, Rohwer E. The occurrence of anti-retroviral compounds used for HIV treatment in South African surface water. Environ Pollut. 2015;199:235–243. https://doi.org/10.1016/j.envpol.2015.01.030
31. Odendaal C, Seaman MT, Kemp G, Patterton H, Patterton HG. An LC-MS / MS based survey of contaminants of emerging concern in drinking water in South Africa. S Afr J Sci. 2015;111(9/10): 6. https://doi.org/10.17159/sajs.2015/20140401
32. Mtolo SP, Mahlambi PN, Madikizela LM. Synthesis and application of a molecularly imprinted polymer in selective solid-phase extraction of efavirenz from water. Water Sci Technol. 2019;79(2):356–365. https://doi.org/10.2166/wst.2019.054
33. Zunngu SS, Madikizela LM, Chimuka L, Mdluli PS. Synthesis and application of a molecularly imprinted polymer in the solid-phase extraction of ketoprofen from wastewater. C R Chim. 2017;20(5):585–591. https://doi.org/10.1016/j.crci.2016.09.006.
34. Rimayi C, Chimuka L, Gravell A, Fones GR, Mills GA. Use of the Chemcatcher ® passive sampler and time-of-flight mass spectrometry to screen for emerging pollutants in rivers in Gauteng province of South Africa. Environ Monit Assess. 2019;191(6):388. https://doi.org/10.1007/s10661-019-7515-z
35. Madikizela LM, Nuapia YB, Chimuka L, Ncube S, Etale A. Target and suspect screening of pharmaceuticals and their transformation products in the Klip River, South Africa, using ultra-high–performance liquid chromatography–mass spectrometry. Environ Toxicol Chem. 2022;41(2):437–447. https://doi.org/10.1002/etc.5265
36. Amdany R, Moya A, Cukrowska E, Chimuka L. Optimization of the temperature for the extraction of pharmaceuticals from wastewater by a hollow fiber silicone membrane. Anal Lett. 2015;48(15):2343–2356. https://doi.org/10.1080/00032719.2015.1033722
37. Khulu S, Ncube S, Nuapia Y, Madikizela LM, Mavhunga E, Chimuka L. Development and application of a membrane assisted solvent extraction-molecularly imprinted polymer based passive sampler for monitoring of selected pharmaceuticals in surface water. Water Res. 2022;225:119145. https://doi.org/10.1016/j.watres.2022.119145
38. Madikizela LM, Chimuka L. Simultaneous determination of naproxen, ibuprofen and diclofenac in wastewater using solid-phase extraction with high performance liquid chromatography. Water SA. 2017;43(2):264–274. https://doi.org/10.4314/wsa.v43i2.10
39. Selahle SK, Nomngongo PN. Determination of fluoroquinolones in the environmental samples using vortex assisted dispersive liquid-liquid microextraction coupled with high performance liquid chromatography. Int J Environ Anal Chem. 2020;100(3):282–294. https://doi.org/10.1080/03067319.2019.1636042
40. Khulu S, Ncube S, Nuapia Y, Madikizela LM, Tutu H, Richards H, ndungu K, Mavhunga E, Chimuka L. Multivariate optimization of a two-way technique for extraction of pharmaceuticals in surface water using a combination of membrane assisted solvent extraction and a molecularly imprinted polymer. Chemosphere. 2022;286:131973. https://doi.org/10.1016/j.chemosphere.2021.131973
41. Madikizela LM, Chimuka L. Determination of ibuprofen, naproxen and diclofenac in aqueous samples using a multi-template molecularly imprinted polymer as selective adsorbent for solid-phase extraction. J Pharm Biomed Anal. 2016;128:210–215. https://doi.org/10.1016/j.jpba.2016.05.037
42. Andrade-Eiroa A, Canle M, Leroy-Cancellieri V, Cerdà V. Solid-phase extraction of organic compounds: A critical review (Part I). Trends Analyt Chem. 2016;80:641–654. https://doi.org/10.1016/j.trac.2015.08.015
43. Gilart N, Borrull F, Fontanals N, Marcé RM. Selective materials for solid-phase extraction in environmental analysis. Trends Environ. Anal. Chem. 2014;1:e8–e18. https://doi.org/10.1016/j.teac.2013.11.002

44. Mhuka V, Dube S, Nindi MM. Occurrence of pharmaceutical and personal care products (PPCPs) in wastewater and receiving waters in South Africa using LC-Orbitrap ™ MS. Emerg Contam. 2020;6:250–258. https://doi.org/10.1016/j.emcon.2020.07.002
45. Archer E, Volschenk M, Brocker L, Wolfaardt GM. A two-year study of emerging micro-pollutants and drugs of abuse in two Western Cape wastewater treatment works (South Africa). Chemosphere. 2021;285:131460. https://doi.org/10.1016/j.chemosphere.2021.131460
46. Gumbi BP, Moodley B, Birungi G, ndungu PG. Risk assessment of personal care products, pharmaceuticals, and stimulants in Mgeni and Msunduzi Rivers, KwaZulu-Natal, South Africa. Front Water. 2022;4:867201. https://doi.org/10.3389/frwa.2022.867201
47. Mosekiemang TT, Stander MA, de Villiers A. Simultaneous quantification of commonly prescribed antiretroviral drugs and their selected metabolites in aqueous environmental samples by direct injection and solid phase extraction liquid chromatography - tandem mass spectrometry. Chemosphere. 2019;220:983–992. https://doi.org/10.1016/j.chemosphere.2018.12.205
48. Omotola EO, Olatunji OS. Quantification of selected pharmaceutical compounds in water using liquid chromatography-electrospray ionisation mass spectrometry (LC-ESI-MS). Heliyon. 2020;6(12):e05787. https://doi.org/10.1016/j.heliyon.2020.e05787
49. Rimayi C, Odusanya D, Weiss JM, De Boer J, Chimuka L. Contaminants of emerging concern in the Hartbeespoort Dam catchment and the uMngeni River estuary 2016 pollution incident, South Africa. Sci Total Environ. 2018;627:1008–1017. https://doi.org/10.1016/j.scitotenv.2018.01.263
50. Schoeman C, Dlamini M, Okonkwo OJ. The impact of a wastewater treatment works in Southern Gauteng, South Africa on efavirenz and nevirapine discharges into the aquatic environment. Emerg Contam. 2017;3(2):95–106. https://doi.org/10.1016/j.emcon.2017.09.001
51. Gumbi BP, Moodley B, Birungi G, ndungu PG. Detection and quantification of acidic drug residues in South African surface water using gas chromatography-mass spectrometry. Chemosphere. 2017;168:1042–1050. https://doi.org/10.1016/j.chemosphere.2016.10.105
52. Mbhele ZE, Ncube S, Madikizela LM. Synthesis of a molecularly imprinted polymer and its application in selective extraction of fenoprofen from wastewater. Environ Sci Pollut Res Int. 2018;25(36):36724–36735. https://doi.org/10.1007/s11356-018-3602-x
53. Madikizela LM, Tavengwa NT, Tutu H, Chimuka L. Green aspects in molecular imprinting technology: from design to environmental applications. Trends Environ. Anal. Chem. 2018;17:14–22. https://doi.org/10.1016/j.teac.2018.01.001
54. Madikizela LM, Zunngu SS, Mlunguza NY, Tavengwa NT, Mdluli PS, Chimuka L. Application of molecularly imprinted polymer designed for the selective extraction of ketoprofen from wastewater. Water SA. 2018;44:406–418. https://doi.org/10.4314/wsa.v44i3.08
55. Qwane SN, Mdluli PS, Madikizela LM. Synthesis, characterization and application of a molecularly imprinted polymer in selective adsorption of abacavir from polluted water. S Afr J Chem. 2020;73:84–91. https://doi.org/10.17159/0379-4350/2020/v73a13.
56. Mpayipheli N, Mpupa A, Nomngongo PN. Vortex-assisted dispersive molecularly imprinted polymer-based solid phase extraction of acetaminophen from water samples prior to HPLC-DAD determination. Separations. 2021;8(10):194. https://doi.org/10.3390/separations8100194
57. Madikizela LM, Mdluli PS, Chimuka L. An initial assessment of naproxen, ibuprofen and diclofenac in Ladysmith water resources in South Africa using molecularly imprinted solid-phase extraction followed by high performance liquid chromatography-photodiode array detection. S Afr J Chem. 2017;70:145–153. https://doi.org/10.17159/0379-4350/2017/v70a21
58. Mogolodi Dimpe K, Nomngongo PN. Application of activated carbon-decorated polyacrylonitrile nanofibers as an adsorbent in dispersive solid-phase extraction of fluoroquinolones from wastewater. J Pharm Anal. 2019;9(2):117–126. https://doi.org/10.1016/j.jpha.2019.01.003
59. Akawa MN, Dimpe KM, Nomngongo PN. An adsorbent composed of alginate, polyvinylpyrrolidone and activated carbon (AC@PVP@alginate) for ultrasound-assisted dispersive micro-solid phase extraction of nevirapine and zidovudine in environmental water samples. Environ. Nanotechnology. Monit. Manag. 2021;16:100559.
60. Madikizela LM, Chimuka L. Synthesis, adsorption and selectivity studies of a polymer imprinted with naproxen, ibuprofen and diclofenac. J Environ Chem Eng. 2016;4(4):4029–4037. https://doi.org/10.1016/j.jece.2016.09.012
61. Madikizela LM, Mdluli PS, Chimuka L. Experimental and theoretical study of molecular interactions between 2-vinyl pyridine and acidic pharmaceuticals used as multi-template molecules in molecularly imprinted polymer. React Funct Polym. 2016;103:33–43. https://doi.org/10.1016/j.reactfunctpolym.2016.03.017
62. Lekota MW, Dimpe KM, Nomngongo PN. MgO-ZnO/carbon nanofiber nanocomposite as an adsorbent for ultrasound-assisted dispersive solid-phase microextraction of carbamazepine from wastewater prior to high-performance liquid chromatographic detection. J Anal Sci Technol. 2019;10(1):25. https://doi.org/10.1186/s40543-019-0185-1
63. Lekota MW, Mpupa A, Dimpe KM, Nomngongo PN. Preparation of ferric oxide-aluminium oxide carbon nano fiber nanocomposites for ultrasound-assisted dispersive magnetic solid phase extraction of 17-beta estradiol in wastewater. Emerg Contam. 2020;6:162–171. https://doi.org/10.1016/j.emcon.2020.04.001
64. Mashile GP, Mpupa A, Nomngongo PN. Magnetic mesoporous carbon/β-cyclodextrin–chitosan nanocomposite for extraction and preconcentration of multi-class emerging contaminant re20sidues in environmental samples. Nanomaterials (Basel). 2021;11(2):540. https://doi.org/10.3390/nano11020540
65. Selahle SK, Mpupa A, Nqombolo A, Nomngongo PN. A nanostructured o-hydroxyazobenzene porous organic polymer as an effective sorbent for the extraction and preconcentration of selected hormones and insecticides in river water. Microchem J. 2022;181:107791. https://doi.org/10.1016/j.microc.2022.107791
66. Mpupa A, Nqombolo A, Mizaikoff B, Nomngongo PN. Beta-cyclodextrin-decorated magnetic activated carbon as a sorbent for extraction and enrichment of steroid hormones (estrone, β-estradiol, hydrocortisone and progesterone) for liquid chromatographic analysis. Molecules. 2021;27(1):248. https://doi.org/10.3390/molecules27010248.
67. Madikizela LM, Pakade VE, Ncube S, Tutu H, Chimuka L. Application of hollow fibre-liquid phase microextraction technique for isolation and pre-concentration of pharmaceuticals in water. Membranes (Basel). 2020;10(11):311. https://doi.org/10.3390/membranes10110311
68. Wooding M, Rohwer ER, Naudé Y. Determination of endocrine disrupting chemicals and antiretroviral compounds in surface water: A disposable sorptive sampler with comprehensive gas chromatography – Time-of-flight mass spectrometry and large volume injection with ultra-high performance liquid chromatography–tandem mass spectrometry. J Chromatogr A. 2017;1496:122–132. https://doi.org/10.1016/j.chroma.2017.03.057
69. Ncube S, Nuapia YB, Chimuka L, Madikizela LM, Etale A. Trace detection and quantitation of antibiotics in a South African stream receiving wastewater effluents and municipal dumpsite leachates. Front Environ Sci. 2021;9:733065. https://doi.org/10.3389/fenvs.2021.733065
70. Madikizela LM, Chimuka L. Occurrence of naproxen, ibuprofen, and diclofenac residues in wastewater and river water of KwaZulu-Natal province in South Africa. Environ Monit Assess. 2017;189(7):348. https://doi.org/10.1007/s10661-017-6069-1
71. Matongo S, Birungi G, Moodley B, ndungu P. Pharmaceutical residues in water and sediment of Msunduzi River, KwaZulu-Natal, South Africa. Chemosphere. 2015;134:133–140. https://doi.org/10.1016/j.chemosphere.2015.03.093
72. Späth J, Arumugam P, Lindberg RH, Abafe OA, Jansson S, Fick J, Buckley CA. Biochar for the removal of detected micropollutants in South African domestic wastewater: a case study from a demonstration-scale decentralised wastewater treatment system in eThekwini. Water SA. 2021;47:396–416. https://doi.org/10.17159/wsa/2021.v47.i4.3861
73. Kermia AEB, Fouial-djebbar D, Trari M. Occurrence, fate and removal efficiencies of pharmaceuticals in wastewater treatment plants (WWTPs) discharging in the coastal environment of Algiers. C R Chim. 2016;19(8):963–970. https://doi.org/10.1016/j.crci.2016.05.005
74. Golovko O, Örn S, Sörengård M, Frieberg K, Nassazzi W, Lai FY, Ahrens L. Occurrence and removal of chemicals of emerging concern in wastewater treatment plants and their impact on receiving water systems. Sci Total Environ. 2021;754:142122. https://doi.org/10.1016/j.scitotenv.2020.142122
75. Nieto-Juárez JI, Torres-Palma RA, Botero-Coy AM, Hernández F. Pharmaceuticals and environmental risk assessment in municipal

wastewater treatment plants and rivers from Peru. Environ Int. 2021;155:106674. https://doi.org/10.1016/j.envint.2021.106674

76. Matongo S, Birungi G, Moodley B, ndungu P. Occurrence of selected pharmaceuticals in water and sediment of Umgeni River, KwaZulu-Natal, South Africa. Environ Sci Pollut Res Int. 2015;22(13):10298–10308. https://doi.org/10.1007/s11356-015-4217-0
77. Hlengwa N, Mahlambi P. SPE-LC-PDA method development and application for the analysis of selected pharmaceuticals in river and wastewater samples from South Africa. Water SA. 2020;46:514–522. https://doi.org/10.17159/wsa/2020.v46.i3.8662
78. Archer E, Holton E, Fidal J, Kasprzyk-Hordern B, Carstens A, Brocker L, Kjeldsen TR, Wolfaardt GM. Occurrence of contaminants of emerging concern in the Eerste River, South Africa: towards the optimisation of an urban water profiling approach for public- and ecological health risk characterisation. Sci Total Environ. 2023;859:160254. https://doi.org/10.1016/j.scitotenv.2022.160254
79. Agunbiade FO, Moodley B. Occurrence and distribution pattern of acidic pharmaceuticals in surface water, wastewater, and sediment of the Msunduzi River, Kwazulu-Natal, South Africa. Environ Toxicol Chem. 2016;35(1):36–46. https://doi.org/10.1002/etc.3144.
80. Kamika I, Azizi S, Muleja AA, Selvarajan R, El-Liethy MA, Mamba BB, Nkambule T. The occurrence of opioid compounds in wastewater treatment plants and their receiving water bodies in Gauteng province, South Africa. Environ Pollut. 2021;290:118048. https://doi.org/10.1016/j.envpol.2021.118048
81. Faleye AC, Adegoke AA, Ramluckan K, Fick J, Bux F, Stenström TA. Concentration and reduction of antibiotic residues in selected wastewater treatment plants and receiving waterbodies in Durban, South Africa. Sci Total Environ. 2019;678:10–20. https://doi.org/10.1016/j.scitotenv.2019.04.410
82. Vumazonke S, Khamanga SM, Ngqwala NP. Detection of pharmaceutical residues in surface waters of the Eastern Cape province. Int J Environ Res Public Health. 2020;17(11):4067. https://doi.org/10.3390/ijerph17114067
83. Ekwanzala M, Lehutso R, Kasonga T, Dewar J, Momba M. Environmental dissemination of selected antibiotics from hospital wastewater to the aquatic environment. Antibiotics (Basel). 2020;9(7):431. https://doi.org/10.3390/antibiotics9070431
84. Mogolodi Dimpe K, Mpupa A, Nomngongo PN. Microwave assisted solid phase extraction for separation preconcentration sulfamethoxazole in wastewater using tyre based activated carbon as solid phase material prior to spectrophotometric determination. Spectrochim. Acta Part A Mol. Spectrochim Acta A Mol Biomol Spectrosc. 2018;188:341–348. https://doi.org/10.1016/j.saa.2017.07.039
85. Lefatle MC, Matong JM, Mpupa A, Musonde TS, Waleng NJ, Madikizela LM, Pakade VE, Nomngongo PN. Preparation, characterization, and application of chitosan – kaolin based nanocomposite in magnetic solid phase extraction of tetracycline in aqueous samples. Chem Pap. 2023;77:1601–1618. https://doi.org/10.1007/s11696-022-02577-3
86. Ncube S, Madikizela LM, Chimuka L, Nindi MM. Environmental fate and ecotoxicological effects of antiretrovirals: A current global status and future perspectives. Water Res. 2018;145:231–247. https://doi.org/10.1016/j.watres.2018.08.017
87. Madikizela LM, Tavengwa NT, Chimuka L. Status of pharmaceuticals in African water bodies: Occurrence, removal and analytical methods. J Environ Manage. 2017;193:211–220. https://doi.org/10.1016/j.jenvman.2017.02.022
88. Abafe OA, Späth J, Fick J, Jansson S, Buckley C, Stark A, Pietruschka B, Martincigh BS. LC-MS/MS determination of antiretroviral drugs in influents and effluents from wastewater treatment plants in KwaZulu-Natal, South Africa. Chemosphere. 2018;200:660–670. https://doi.org/10.1016/j.chemosphere.2018.02.105
89. Horn S, Vogt T, Gerber E, Vogt B,_Bouwman H, Pieters R. HIV-antiretrovirals in river water from Gauteng, South Africa: mixed messages of wastewater inflows as source. Sci Total Environ. 2022;806:150346. https://doi.org/10.1016/j.scitotenv.2021.150346
90. Mpayipheli N, Mpupa A, Nomngongo PN. Ultrasound assisted dispersive solid-phase extraction coupled with high-performance liquid chromatography-diode array detector for determination of caffeine and carbamazepine in environmental samples using exfoliated graphite/chitosan hydrogel. Chem Zvesti. 2022;76(11):6985–6996. https://doi.org/10.1007/s11696-022-02328-4
91. Farounbi AI, Ngqwala NP. Occurrence of selected endocrine disrupting compounds in the Eastern Cape province of South Africa. Environ Sci Pollut Res Int. 2020;27(14):17268–17279. https://doi.org/10.1007/s11356-020-08082-y
92. Mnguni S, Schoeman C, Marais S, Cukrowska E, Chimuka L. Determination of oestrogen hormones in raw and treated water samples by reverse phase ultra-fast liquid chromatography mass spectrometry – a case study in Johannesburg South, South Africa. Water SA. 2018;44:111–117. https://doi.org/10.4314/wsa.v44i1.13
93. Van Zijl MC, Aneck-Hahn NH, Swart P, Hayward S, Genthe B, De Jager C. Estrogenic activity, chemical levels and health risk assessment of municipal distribution point water from Pretoria and Cape Town, South Africa. Chemosphere. 2017;186:305–313. https://doi.org/10.1016/j.chemosphere.2017.07.130
94. Ateba CN, Tabi NM, Fri J, Bissong MEA, Bezuidenhout CC. Occurrence of antibiotic-resistant bacteria and genes in two drinking water treatment and distribution systems in the north-west province of South Africa. Antibiotics (Basel). 2020;9(11):745. https://doi.org/10.3390/antibiotics9110745
95. Mpondo L, Ebomah KE, Okoh AI. Multidrug-resistant listeria species shows abundance in environmental waters of a key district municipality in South Africa. Int J Environ Res Public Health. 2021;18(2):481. https://doi.org/10.3390/ijerph18020481
96. Lin J, Biyela PT, Puckree T. Antibiotic resistance profiles of environmental isolates from Mhlathuze River, KwaZulu-Natal (RSA). Water SA. 2004;30(1):23–28. https://doi.org/10.4314/wsa.v30i1.5022
97. Ohoro CR, Adeniji AO, Semerjian L, Okoh OO, Okoh AI. Occurrence and distribution of pharmaceuticals in surface water and sediment of Buffalo and Sundays River estuaries, South Africa and their ecological risk assessment. Emerg Contam. 2021;7:187–195. https://doi.org/10.1016/j.emcon.2021.09.002
98. Assress HA, Nyoni H, Mamba BB, Msagati TAM. Occurrence and risk assessment of azole antifungal drugs in water and wastewater. Ecotoxicol Environ Saf. 2020;187:109868. https://doi.org/10.1016/j.ecoenv.2019.109868
99. Adeola AO, Forbes PCB. Antiretroviral drugs in African surface waters: Prevalence, analysis, and potential remediation. Environ Toxicol Chem. 2022;41(2):247–262. https://doi.org/10.1002/etc.5127
100. Madikizela LM, Ncube S. Health effects and risks associated with the occurrence of pharmaceuticals and their metabolites in marine organisms and seafood. Sci Total Environ. 2022;837:155780. https://doi.org/10.1016/j.scitotenv.2022.155780
101. Nibamureke UMC, Barnhoorn IEJ, Wagenaar GM. Assessing the potential effects of nevirapine in South African surface water on fish growth: A chronic exposure of Oreochromis mossambicus. S Afr J Sci. 2019;115(3/4):2–7. https://doi.org/10.17159/sajs.2019/5516
102. Robson L, Barnhoorn IEJ, Wagenaar GM. The potential effects of efavirenz on Oreochromis mossambicus after acute exposure. Environ Toxicol Pharmacol. 2017;56:225–232. https://doi.org/10.1016/j.etap.2017.09.017
103. Adegoke O, Dabrowski JM, Montaseri H, Nsibande SA, Petersen F, Forbes PBC. Development of novel fluorescence sensors for the screening of emerging chemical pollutants in water. Water Research Commission Technical Report 2017.
104. Montaseri H, Nsibande SA, Forbes PBC. Development of novel fluorescence sensors for the screening of emerging chemical pollutants in water. Water Research Commission Technical Report 2019.
105. Montaseri H, Adegoke O, Forbes PBC. Development of a thiol-capped core/shell quantum dot sensor for acetaminophen. S Afr J Chem. 2019;72:108–117. https://doi.org/10.17159/0379-4350/2019/v72a14
106. Montaseri H, Forbes PBC. Molecularly imprinted polymer coated quantum dots for fluorescence sensing of acetaminophen. Mater Today Commun. 2018;17:480–492. https://doi.org/10.1016/j.mtcomm.2018.10.007
107. Tito GS, Kuvarega AT, Mamba BB, Feleni U. Electrochemical detection of nevirapine using banana peel extract functionalised nickel selenide quantum dots. Electrocatalysis. 2023;14:393-405. https://doi.org/10.1007/s12678-022-00805-8
108. Kantize K, Booysen IN, Mambanda A. Electrochemical sensing of acetaminophen using nanocomposites comprised of cobalt phthalocyanines and multiwalled carbon nanotubes. J Electroanal Chem (Lausanne). 2019;850:113391. https://doi.org/10.1016/j.jelechem.2019.113391

109. Olowu RA, Arotiba O, Mailu SN, Waryo TT, Baker P, Iwuoha E. Electrochemical aptasensor for endocrine disrupting 17β-estradiol based on a poly(3,4-ethylenedioxylthiopene)-gold nanocomposite platform. Sensors (Basel). 2010;10(11):9872–9890. https://doi.org/10.3390/s101109872