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# Screening of pharmaceuticals in coastal waters of the southern coast of Viti Levu in Fiji, South Pacific

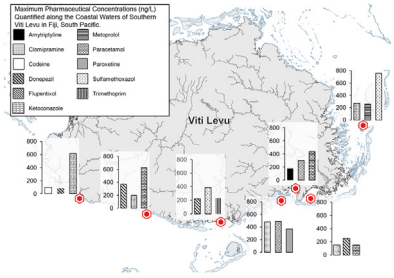
Jasha Dehm [a, *], Shubha Singh [a], Marta Ferreira [a], Susanna Piovano [a], Jerker Fick [b]

[a] School of Agriculture, Geography, Environment, Ocean and Natural Sciences, The University of the South Pacific, Laucala Bay Road, Suva, Fiji
[b] Department of Chemistry, Umeå University, 90187, Umeå, Sweden

## HIGHLIGHTS

- Seventy-two pharmaceuticals quantified in coastal water of southern Viti Levu, Fiji.
- Pharmaceutical concentrations ranged from 0.04 ng/L to 760 ng/L.
- Pharmaceutical concentrations likely result from turbulent mixing on the coastline.
- Anthropogenic marker carbamazepine present at all sites can be used for monitoring.

## GRAPHICAL ABSTRACT

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## ABSTRACT

The global reliance on pharmaceuticals coupled with the lack of effective treatment methods has resulted in pseudo-persistence of pharmaceuticals within the environment. Globally, efforts to quantify and monitor pharmaceuticals within the environment have been well underway, however few studies have been made within small Pacific Islands. This study aims at screening for the occurrence and concentration of pharmaceutical residues within the southern coastal waters of Fiji's main island, Viti Levu. Water samples were collected from a depth of ca. 0.6 m from seven sites and were analyzed for 80 pharmaceuticals via a combination of chromatography and heated electrospray ionization. Seventy-two pharmaceuticals were quantified at least once with average concentrations ranging between 0.04 ng/L (diltiazem) and 19 ng/L (ketoconazole), and with all but two pharmaceuticals (trimethoprim and biperiden) being present in less than 50% of the samples. Findings suggest that even though the release of pharmaceuticals into the marine environment is sporadic and pharmaceuticals are diluted via turbulent mixing, there are measurable concentrations of pharmaceuticals in Fiji and these pollutants are not necessarily restricted to highly populated areas.



## 1. Introduction

Increasing human activity and pressure along coastal zones have been identified as key sources of contamination of anthropogenic-based substances into the coastal marine environment (Crain et al., 2009; Fent et al., 2006; Martínez et al., 2007). One such group of substances are pharmaceuticals, i.e., medicinal compounds that are either extracted from natural sources or are chemically synthesized

* Corresponding author. Discipline of Marine Studies, School of Agriculture, Geography, Environment, Ocean and Natural Sciences, The University of the South Pacific, Laucala Bay Road, Suva, Fiji.
*E-mail addresses:* s11064756@student.usp.ac.fj, jbdehm@gmail.com (J. Dehm).

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(Fabbri and Franzellitti, 2016; Sauvé and Desrosiers, 2014). Pharmaceuticals, of which there are over 5000 types being manufactured for human and animal consumption, are developed to accomplish a specific biochemical or physiological effect (Ojemaye and Petrik, 2019; Van Doorslaer et al., 2014). However, they are rarely completely metabolized and absorption rates of orally consumed pharmaceuticals generally range between 20% and 95%, depending on the physiochemical properties of the pharmaceutical (Gaw et al., 2014; Ojemaye and Petrik, 2019; Wong et al., 2006). As a result, a significant amount of the administered pharmaceutical is excreted, either as the parent compound or as a metabolite thereof (Wong et al., 2006). Consequently, these residues end up in the aquatic environment, either due to lack of treatment or incomplete removal in sewage treatment plants, or due to more direct pathways such as agriculture runoff or improper disposal (Björlenius et al., 2018; Gaw et al., 2014; Li, 2014).

In the environment, pharmaceuticals rarely exist for long periods due to their natural elimination rates (half-life), and due to degradation brought about by varying environmental processes, such as oxidation, hydrolysis, and photolysis (Andreozzi et al., 2003; Benotti and Brownawell, 2007; Buser et al., 1998). However, the continuous and widespread usage coupled with the demand on pharmaceuticals has led to a pseudo-persistence of many pharmaceuticals within the environment (Gaw et al., 2014), which subsequently has resulted in measurable levels in various marine environments, particularly within the Northern Hemisphere where majority of the studies have taken place, e.g. Asia (Rizzi et al., 2020; Zhang et al, 2012, 2013), North America (Long et al., 2013; Nödler et al., 2014; Vidal-Dorsch et al., 2012) and Europe (Björlenius et al., 2018; Loos et al., 2013; Nödler et al., 2014; Siedlewicz et al., 2014). In the Southern Hemisphere, pharmaceutical research has mainly focused on soils, wastewater systems and in rivers and has only occasionally considered surface waters of the marine environment (Branchet et al., 2020; Madikizela et al., 2020; Ojemaye and Petrik, 2019). This data paucity is especially noticeable in the case of the broader South Pacific Ocean, where previous efforts to screen for pharmaceuticals have been limited to marine biota and wastewater effluent in New Zealand (Gielen, 2007; Stewart, 2013), within sediment and in surface water of rivers and estuaries in Australia (Anim et al., 2020; Birch et al., 2015; Hashim and Khan, 2011; Scott et al., 2014; Watkinson et al., 2007).

While concentrations of pharmaceuticals in the marine environment are generally in the low ng/L range and more frequently found in areas close to land, especially in highly populated areas, there are instances whereby pharmaceuticals have been quantified in higher levels (μg/L) in areas further from populated coastlines, such as in the Aegean Sea (Nödler et al., 2014), at proper marine sampling points in the Baltic Sea (Björlenius et al., 2018), and 400 km off the coast of China (Zhang et al., 2013). While reported concentrations are below the toxicity threshold that results in acute or long term effects on human health, the concern is that these levels may be high enough to potentially trigger a range of biological effects in aquatic organisms (Kümmerer, 2009). For example, the hormone inhibitor oestrogen ethinylestradiol (EE2) which has been detected at low (ng/L) levels in surface waters has been shown to be extremely potent in fish where it induces feminization (Jobling et al., 1998; Kidd et al., 2007; Larsson et al., 1999). Additionally, exposure to pharmaceuticals has also been associated with behavioral changes in aquatic organisms, such as in damselfly larvae, where exposure to low concentrations of diphenhydramine hindered mobility and escape responses (Jonsson et al., 2019), and perch, which have been found to become increasingly more active when exposed to oxazepam (Brodin et al., 2014).

A further concern is the potential for pharmaceuticals to bioaccumulate and subsequently biomagnify through the food web, where they can potentially lead to chronic exposure in humans (Almeida et al., 2020; Moreno-González et al., 2016; Richmond et al., 2018). This concern is especially perturbing for the small Pacific Islands where wastewater management practices are often poorly implemented and where coastal marine resources are essential in sustaining livelihoods (Barnett and Adger, 2003; Dutra et al., 2021; Todd et al., 2019). Furthermore, the lack of substantive effort in quantifying, monitoring and publishing data with regards to environmental pollutants within Pacific Islands has resulted in a knowledge gap especially with regards to pharmaceutical pollution (Dutra et al., 2021; Varea et al., 2020). As a consequence of these aspects, there is a potential for Pacific Islanders to be chronically exposed to low levels of pharmaceuticals. To address this knowledge gap, this study will make a first account of the presence of pharmaceuticals within the coastal environment of the southern coast of Viti Levu, Fiji.

Fiji, an archipelago of over 300 islands in the South Pacific, has more than half of its population living in the southern coastal area of the largest island, Viti Levu (Fiji Bureau of Statistics, 2018; Gonzalez et al., 2015). The degree to which wastewater is treated within Fiji varies considerably and remains largely understudied. Sewage treatment plants are generally restricted to urban centers, where the level of treatment varies considerably and only fractions of the population are connected. For example, in Fiji's largest urban center, Suva, only approximately one third of the sewage is treated at the Kinoya sewage treatment plant, while the remainder is primarily processed in on-site septic systems (Kumar, 2010; for more information see Table S1). Similarly, rural communities along the coast rely primarily on septic systems and pit latrines (Kumar, 2010; Taloiburi, 2009). Additionally, some hotels and resorts operate their own wastewater treatment facilities mostly in the form of biological treatment ponds and artificial wetlands (Taloiburi, 2009). Despite these efforts to treat wastewater, nutrient levels along parts of the southern coastline suggest the likelihood of sewage contamination (Mosley and Aalbersberg, 2003); similarly, effluent from the sewage treatment plants of the urban centers is actively pumped into the coastal marine environment (Campbell et al., 1982; Ferreira et al., 2020). In addition, two major landfill sites, the Naboro landfill and the Sigatoka Dump, as well as multiple agricultural activities are located along the southern coast of Viti Levu, all which have the potential to leach contaminants such as pharmaceuticals into the marine environment (Liermann, 2009; Mosley and Aalbersberg, 2003).

Considering the potential for pharmaceutical contamination within the coastal marine environment, this study aims to produce a broad screening of the occurrence and concentration of pharmaceuticals within the subsurface coastal waters along the southern coast of Viti Levu in Fiji, South Pacific. The baseline data obtained for seven sites across 200 km of coastline will allow for future comparisons by monitoring programs, which can ultimately inform management decision in the region.

## 2. Method

### 2.1. Sampling and sample shipment

Samples were collected over six sampling periods between 2017 and 2018, three in each tropical season (i.e., wet summer, dry winter). The seven sampling sites, Laucala Bay (1), Vueti Navakavu LMMA (2), Suva Harbour (3), Cuvu (4), Votua (5), Pacific Harbour (6) and Leleuvia Island (7) (Fig. 1, detailed information in Table S2) were spread along the southern coast of Viti Levu in Fiji, South Pacific. Of these sampling sites two (Laucala Bay and Suva Harbour)

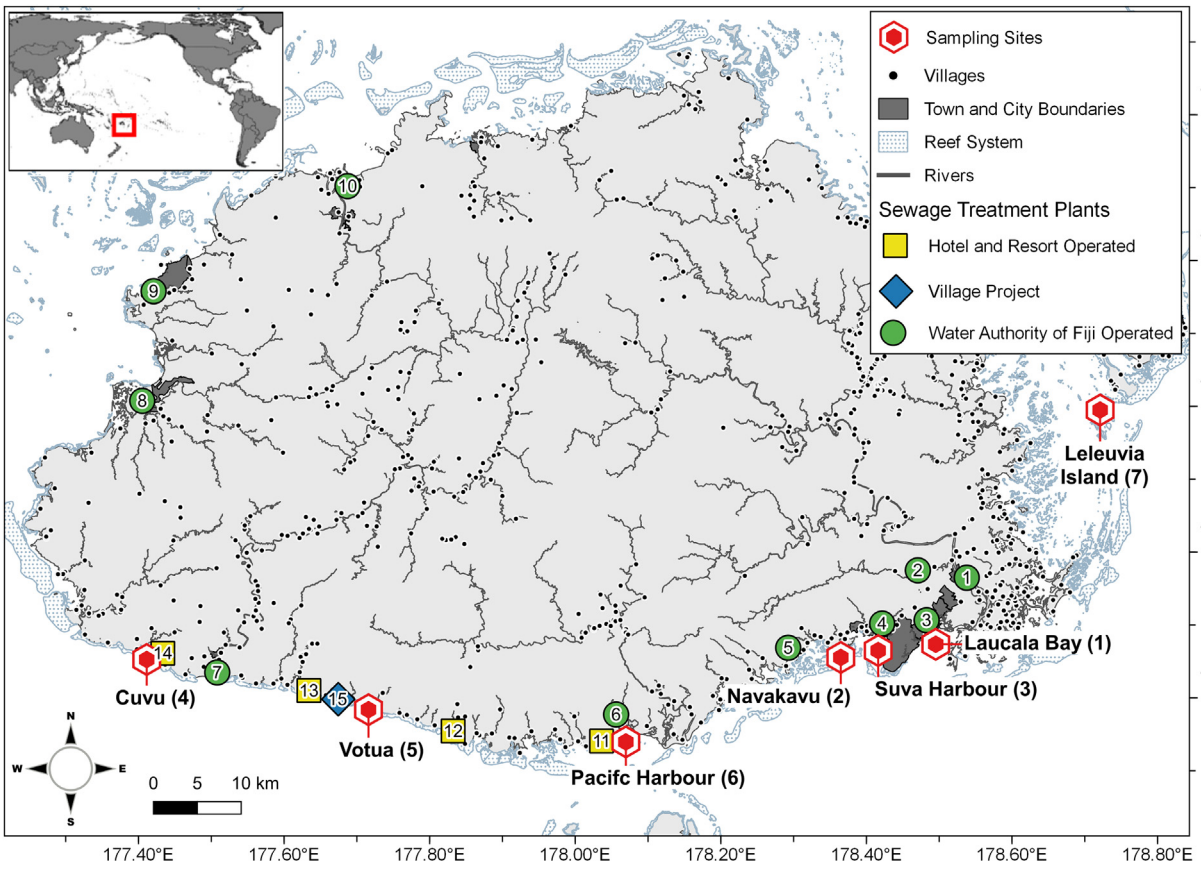


**Fig. 1.** Sampling sites along the southern coast of Viti Levu, Fiji, South Pacific. Relative location of sewage treatment plants are denoted by squares, diamonds and circles, numbers are linked to sewage treatment plant information in Table S2. Inset: location of Fiji within the Pacific Ocean.

are directly adjacent to the urban center of Suva, while one (Vueti Navakavu LMMA) is within a 5 km radius of Suva. The remaining four sites are not within the vicinity of any urban center and are considered rural sites (further distinction between rural and urban sites is described in Dehm et al., 2020). Sampling was performed according to Dehm et al. (2020); briefly, on each sampling occasion, four replicates (between 50 m and 100 m apart) of coastal water were collected from a depth of ca. 0.6 m using a Niskin bottle. Samples were transferred into new, sterile, 1 L polyethylene terephthalate bottles and were transported on ice to the Marine Campus at the University of the South Pacific, Fiji, where they were kept frozen at - 40 °C until shipment. Samples were shipped to the Department of Chemistry of Umeå University in Sweden, arrived frozen and were analyzed within 3 months from sampling. Storage stability was investigated by a 5-day freeze-thaw experiment in artificial seawater (salinity 3 ppt, −18 °C, 100 ng/L added of each analyte).

### 2.2. Selection of target compounds and standards used

A total of 80 pharmaceuticals were included in the analytical method and the selection was based on their potencies and predicted ability to bioconcentrate in fish (Fick et al., 2010; see Table S3 for a full list of the screened pharmaceuticals). Reference pharmaceutical standards and internal standards were classified as analytical grade (>98%); chemical abstract numbers and supplier are given in the supplementary information (Table S3). LC-MS grade methanol and acetonitrile (Lichrosolv — hypergrade) were purchased from Merck (Darmstadt, Germany). Purified water was prepared using a Milli-Q Advantage system, including an ultraviolet radiation source (Millipore, Billerica, USA). Formic acid (Sigma-Aldrich, Steinheim, Germany) was used (at 0.1%) to prepare the mobile chromatographic phases.

### 2.3. Analytical methods

Water samples (0.5 L) were filtered through a 0.45 μm membrane filter (MF, Millipore, Sundbyberg, Sweden) and acidified to pH 3 using sulphuric acid. Internal standards (50 ng of ach internal and surrogate standards, Table S3) were added to each sample and Oasis HLB cartridges (200 mg, Waters Corp, Milford, USA) were used for the solid phase extraction (SPE) and were dried before elution. Methanol (5 mL), followed by ethyl acetate (3 mL), were used for elution; the eluate was evaporated under a nitrogen stream to a volume of approximately 20 μL and, finally, reconstituted in 200 μL of acetonitrile.

Heated electrospray (HESI) in positive or negative ion mode was used for ionization. Key parameters were; ionization voltage 3.5 kV, sheath gas 50, auxiliary gas 35 arbitrary units, vaporizer temperature 200 °C, capillary temperature 325 °C, collision gas (argon) flow 1.5 mL/min. Both the first and third quadrupoles were operated at a resolution of 0.7 FMWH. Chromatography was done using a C18 phase Hypersil GOLD column (50 mm, 2.1 mm, ID. 5 mm particles, Thermo Fisher Scientific, San Jose, CA, USA) and a guard column (2 mm, 2.1 mm, ID. 5 mm particles). A gradient of methanol and acetonitrile in water (all solvents were acidified by 0.1% formic acid) was used for the elution of analytes starting with 200 mL/min, then 5% methanol in water for 1 min, followed by a gradient change to

20/20/60 water/acetonitrile/methanol at a flow of 250 mL/min in 8 min and a final gradient change to acetonitrile/methanol 40/60 at a flow of 300 mL/min in 11 min. These parameters were then held for 1 min and then changed back to starting conditions and held for 4 min. Specific details related to the determination of the pharmaceuticals including HESI ionizations, polarities, precursor/product ions, collision energies, tube lens values, etc. have been described in detail elsewhere (Grabic et al., 2012; Lindberg et al., 2014).

### 2.4. QA/QC

Stock solutions of each pharmaceuticals were prepared in methanol and stored at −18 °C. Calibration standards were prepared in the mobile phase. Pharmaceuticals lacking a labeled internal standard were matched with a suitable surrogate standard based on the physio-chemical properties, retention time, negative or positive ionization. Triplicate injection of Milli-Q water was injected following the calibration standards, and after every fifth sample, to assess potential memory effects. Several field blank samples and procedural blank samples were also included in the study. A seven-point calibration curve was used in this study, with a concentration range between 0.001 ng/L and 500 ng/L. The limits of quantification (LOQ) of the pharmaceuticals in seawater were based on the lowest point within the linear range on the calibration curve (Table 1) in combination with the LOQ criteria (10 x noise) in pre-treated and up-concentrated samples. For a positive identification of analytes, the ratio between two transitions, i.e., one precursor ion and two product ions, had to be within ±30% of the ratio in the calibration standard. Moreover, the retention times for all analytes had to be within ±2.5% of the calibration standard. Together, this yielded four identification points as required by the Commission Decision 2002/657/EC on the performance of analytical methods and the interpretation of the results (European Commission, 2002).

### 2.5. Data process

The software QGIS v.3.12.0 (QGIS Development Team, 2020), together with spatial layers obtained from the Department of Land and Surveys of the Fiji Ministry for Lands and Mineral Resources, were used to develop spatial maps of pharmaceutical distribution. Data normalizations and visualizations were carried out in Microsoft Excel (2016). Concentration of pharmaceuticals are presented as average, minimum, and maximum ng/L. Based on common practice for calculation of average concentrations, a value of one half of the quantification limit (LOQ/2) was used when concentrations were below the LOQ (Antweiler and Taylor, 2008).

## 3. Results

The analytical method performance was stable throughout the study. All retention times were within 1.5% of the standards, no memory effects were detected, no pharmaceuticals were detected in the blank samples and stability in the freeze-thaw experiment was <95% for all included pharmaceuticals. LOQ for each pharmaceutical are presented in Table S3.

### 3.1. Chemical compounds identified

Of the 80 pharmaceuticals that were included in this study, eight were below the LOQ (Table 1) in all samples. The remaining 72 pharmaceuticals (90%) were quantified at least once and ranged in quantifiable concentration from 0.04 ng/L (diphenhydramine) to 760 ng/L (sulfamethoxazol).

### 3.2. Frequency

Overall, the frequency of detection of the 72 quantified pharmaceuticals was low, i.e., the average frequency of detection across all samples was 15% (Fig. 2). Only two pharmaceuticals were present in at least 50% of the samples, whereby trimethoprim, an antibacterial drug, was the most frequent (71%). Biperiden, an anticholinergic, was the next most frequent and was quantified in 56% of the samples, respectively. The remaining 70 pharmaceuticals were quantified in less than half (<50%) of the samples, and eleven of which were only quantified in 1% of all samples.

### 3.3. Concentrations

The average measured concentrations of the pharmaceuticals ranged between 0.04 ng/L and 19 ng/L, whereby 41 (51%) of the pharmaceuticals were quantified with average concentrations greater than 1.0 ng/L (Fig. 2). Three pharmaceuticals had average concentrations greater than 10 ng/L; namely ketoconazole (19 ng/L), paracetamol (17 ng/L), and sulfamethoxazol (13 ng/L). However, all 72 pharmaceuticals were quantified at least once at concentrations well above the respective averages, the highest of which were sulfamethoxazol, paracetamol and ketoconazole which were quantified at maximum concentrations of 760 ng/L, 630 ng/L and 620 ng/L respectively. On the other hand, analysis of the 90th percentile indicate that only 29 pharmaceuticals were quantified regularly at above 1.0 ng/L (Table 1), the highest of which were paracetamol (36 ng/L), ciprofloxacin (28 ng/L), codeine (28 ng/L), fexofenadine (20 ng/L), paroxetine (18 ng/L), trimethoprim (17 ng/L), donepezil (16 ng/L) and ketoconazole (13 ng/L), suggesting that the remaining pharmaceuticals were only sporadically present at higher levels.

### 3.4. Groups of pharmaceuticals identified

Grouped by therapeutic use, the quantified pharmaceuticals represented 25 pharmaceutical groups (Table 1). The most diverse group was found to be antidepressants, whereby 11 (14%) different pharmaceuticals were quantified at least once, namely amytriptyline, bupropion, citalopram, clomipramine, duloxetine, maprotiline, mianserin, mirtazapine paroxetine, sertraline and venlafaxine. Antihistamines and antipsychotics were the next most represented groups, with 8 (10%) and 6 (7.5%) quantified pharmaceuticals representing each (antihistamines: clemastine, cyproheptadine, desloratadine, diphenhydramine, fexofenadine, hydroxyzine, meclizine, promethazine; antipsychotics: chlorpromazine, chlorprothixene, flupentixol, haloperidol, levomepromazine and risperidone). Alpha-adrenoceptor-blockers, antiarrhythmics, antidiarrheals, antiestrogen, antilipemic, calcium-channel blockers, corticosteroids, dopamine receptor agonists, neuromuscular-blockers and opioid antagonist were the least diverse groups and were represented by only 1 (1%) quantified pharmaceutical each.

### 3.5. Distribution of pharmaceuticals

On average, 52 of the 80 (65%) pharmaceuticals were quantified across each of the seven sampling sites (Table S4). The highest frequencies of detection were at Votua, Leleuvia Island and Laucala Bay where 61 (76%), 54 (68%) and 53 (66%) pharmaceuticals were quantified, respectively. Conversely the sites with the lowest detection frequency were Cuvu and Pacific Harbour, with 47 (58%) and 46 (56%) pharmaceuticals quantified there. Thirty-six pharmaceuticals, including carbamazepine, were consistently quantified at all seven sites during each of the sampling periods (Table S5.

**Table 1**
Summary of analytical results for pharmaceuticals quantified within the subsurface coastal waters of Viti Levu, Fiji, South Pacific. Compounds are grouped according to their therapeutic use and sorted according to their frequency of occurrence (Freq in %). The lowest, median and maximum quantified concentrations (ng/L) are presented by 'Min.', 'Med.' and 'Max.' respectively; for instance, where the pharmaceutical was only quantified once the concentration is recorded as 'Max.'. The average concentration and the 90th percentile are calculated using all samples, whereby levels below LOQ were set to half the LOQ (i.e., LOQ/2).

| Class | Pharmaceutical | *LOQ (ng/L)* | Count (#) | Freq. (%) | Min. (ng/L) | Med. (ng/L) | Max. (ng/L) | Average (ng/L) | 90Per (ng/L) |
|---|---|---|---|---|---|---|---|---|---|
| Acetylcholinesterase Inhibitor | **Donepezil** | *0.05* | 57 | 34 | 0.61 | 9.7 | 180 | 6.9 | 16 |
| | **Memantine** | *0.05* | 11 | 7 | 0.72 | 1.0 | 23 | 0.24 | 0.030 |
| Alpha-Adrenoceptor-Blocker | **Alfuzosin** | *0.01* | 41 | 25 | 0.10 | 0.21 | 110 | 0.75 | 0.26 |
| Angiotensin-Receptor- Blocker | **Irbesartan** | *0.05* | 58 | 35 | 0.52 | 1.7 | 62 | 1.7 | 4.3 |
| | **Telmisartan** | *5.0* | 35 | 21 | 1.1 | 2.9 | 120 | 4.4 | 3.1 |
| | **Cilazapril** | *0.1* | 2 | 1 | 2.0 | 3.3 | 4.6 | 0.090 | 0.050 |
| Antiandrogen | **Finasteride** | *1.0* | 5 | 3 | 11 | 16 | 65 | 1.4 | 0.50 |
| | **Flutamide** | *0.5* | 1 | 1 | 6.5 | 6.5 | 6.5 | 0.29 | 0.25 |
| Antiarrhythmic | **Flecainide** | *0.01* | 52 | 31 | 0.10 | 0.18 | 7.5 | 0.14 | 0.22 |
| Antibacterial | **Trimethoprim** | *0.01* | 119 | 71 | 0.13 | 3.5 | 230 | 7.4 | 17 |
| | **Ciprofloxacin** | *1.0* | 38 | 23 | 11 | 23 | 170 | 8.8 | 28 |
| | **Sulfamethoxazol** | *0.5* | 21 | 13 | 5.5 | 17 | 760 | 13 | 8.5 |
| | **Clarithromycine** | *0.1* | 3 | 2 | 2.4 | 5.2 | 6.3 | 0.13 | 0.050 |
| | **Clindamycine** | *0.1* | 3 | 2 | 1.3 | 40 | 51 | 0.60 | 0.050 |
| Anticholinergic | **Biperiden** | *0.01* | 94 | 56 | 0.11 | 0.48 | 29 | 0.91 | 1.5 |
| | **Orphenadrine** | *0.01* | 60 | 35 | 0.10 | 0.32 | 16 | 0.53 | 0.87 |
| Antidepressant | **Clomipramine** | *0.05* | 67 | 40 | 0.54 | 2.3 | 480 | 5.6 | 4.9 |
| | **Bupropion** | *0.01* | 54 | 32 | 0.10 | 0.19 | 1.8 | 0.090 | 0.33 |
| | **Paroxetine** | *1.0* | 27 | 16 | 11 | 20 | 370 | 6.9 | 18 |
| | **Amytriptyline** | *0.5* | 26 | 16 | 5.4 | 11 | 180 | 3.9 | 8.4 |
| | **Mianserin** | *0.1* | 20 | 12 | 1.0 | 1.6 | 120 | 1.0 | 1.1 |
| | **Sertraline** | *1.0* | 15 | 9 | 12 | 22 | 140 | 4.2 | 0.50 |
| | **Duloxetine** | *0.1* | 5 | 3 | 1.0 | 1.4 | 2.4 | 0.10 | 0.050 |
| | **Mirtazapine** | *1.0* | 5 | 3 | 12 | 16 | 43 | 1.1 | 0.50 |
| | **Maprotiline** | *0.5* | 4 | 2 | 6.6 | 8.8 | 12 | 0.46 | 0.25 |
| | **Citalopram** | *0.5* | 3 | 2 | 7.0 | 14 | 85 | 0.88 | 0.25 |
| | **Venlafaxine** | *0.05* | 2 | 1 | 5.7 | 7.0 | 8.4 | 0.11 | 0.030 |
| Antidiabetic | **Repaglinide** | *0.05* | 46 | 28 | 0.52 | 1.8 | 89 | 1.6 | 2.6 |
| | **Glibenclamide** | *1.0* | 4 | 2 | 18 | 25 | 45 | 1.2 | 0.50 |
| | **Glimepiride** | *1.0* | 4 | 2 | 13 | 35 | 55 | 1.3 | 0.50 |
| Antidiarrheal | **Loperamide** | *0.05* | 17 | 10 | 0.65 | 1.9 | 150 | 1.3 | 0.66 |
| Antiepileptic | **Carbamazepin** | *0.1* | 58 | 35 | 1.0 | 2.8 | 190 | 2.8 | 4.5 |
| | **Clonazepam** | *0.5* | 3 | 2 | 5.1 | 5.9 | 17 | 0.41 | 0.25 |
| Antiestrogen | **Tamoxifen** | *0.5* | 7 | 4 | 5.3 | 23 | 140 | 1.8 | 0.25 |
| Antifungal | **Clotrimazol** | *0.1* | 24 | 14 | 1.0 | 1.6 | 95 | 1.0 | 1.3 |
| | **Ketoconazole** | *5.0* | 22 | 13 | 10 | 31 | 620 | 19 | 13 |
| | **Fluconazole** | *0.05* | 16 | 10 | 0.51 | 0.69 | 22 | 0.23 | 0.12 |
| | **Miconazole** | *0.5* | 1 | 1 | 75 | 75 | 75 | 0.70 | 0.25 |
| Antihistamine | **Hydroxyzine** | *0.05* | 52 | 31 | 0.58 | 2.4 | 37 | 2.1 | 7.0 |
| | **Desloratidin** | *0.05* | 46 | 28 | 0.58 | 4.2 | 40 | 2.2 | 8.6 |
| | **Diphenhydramine** | *0.005* | 43 | 26 | 0.050 | 0.12 | 2.8 | 0.070 | 0.14 |
| | **Fexofenadine** | *0.5* | 40 | 24 | 5.2 | 15 | 77 | 5.6 | 20 |
| | **Clemastine** | *0.05* | 15 | 9 | 0.74 | 5.5 | 49 | 0.70 | 0.030 |
| | **Cyproheptadine** | *0.5* | 2 | 1 | 5.3 | 10 | 15 | 0.37 | 0.25 |
| | **Promethazine** | *1.0* | 2 | 1 | 11 | 11 | 11 | 0.63 | 0.50 |
| | **Meclozine** | *0.5* | 1 | 1 | 11 | 11 | 11 | 0.31 | 0.25 |
| Anti-Inflammatory/Analgesics | **Codeine** | *0.05* | 76 | 46 | 0.50 | 7.3 | 130 | 7.6 | 28 |
| | **Pizotifen** | *0.05* | 44 | 26 | 0.50 | 1.2 | 66 | 1.2 | 1.7 |
| | **Paracetamol** | *1.0* | 35 | 21 | 10 | 32 | 630 | 17 | 36 |
| | **Diclofenac** | *1.0* | 12 | 7 | 11 | 18 | 66 | 2.4 | 0.50 |
| Antilipemic | **Fenofibrate** | *1.0* | 1 | 1 | 54 | 54 | 54 | 0.82 | 0.50 |
| Antipsychotic | **Risperidone** | *0.01* | 57 | 34 | 0.10 | 0.57 | 32 | 0.62 | 1.1 |
| | **Haloperidol** | *0.01* | 51 | 31 | 0.11 | 0.24 | 34 | 0.35 | 0.34 |
| | **Chlorpromazine** | *0.5* | 18 | 11 | 5.5 | 11 | 41 | 1.7 | 6.1 |
| | **Flupentixol** | *0.5* | 17 | 10 | 5.3 | 47 | 370 | 8.8 | 5.7 |
| | **Chlorprothixene** | *1.0* | 10 | 6 | 11 | 16 | 51 | 1.7 | 0.50 |
| | **Levomepromazine** | *5.0* | 1 | 1 | 55 | 55 | 55 | 2.8 | 2.5 |
| Benzodiazepine | **Oxazepam** | *0.5* | 18 | 11 | 1.0 | 11 | 190 | 3.4 | 2.5 |
| | **Flunitrazepam** | *1.0* | 12 | 7 | 20 | 45 | 94 | 4.1 | 0.50 |
| | **Alprazolam** | *1.0* | 4 | 2 | 10 | 15 | 29 | 0.91 | 0.50 |
| | **Zolpidem** | *0.05* | 2 | 1 | 0.78 | 1.7 | 2.6 | 0.040 | 0.030 |
| Beta-Adrenoceptor-Blocker | **Sotalol** | *0.05* | 53 | 32 | 0.54 | 1.3 | 160 | 1.7 | 2.2 |
| | **Bisoprolol** | *0.01* | 46 | 28 | 0.10 | 0.16 | 30 | 0.46 | 0.33 |
| | **Atenolol** | *0.5* | 11 | 7 | 5.1 | 8.7 | 260 | 2.6 | 0.25 |
| | **Metoprolol** | *0.5* | 11 | 7 | 5.3 | 7.0 | 260 | 2.2 | 0.25 |
| Calcium-Channel-Blocker | **Diltiazem** | *0.05* | 1 | 1 | 1.7 | 1.7 | 1.7 | 0.040 | 0.030 |
| Corticosteroids | **Budesonide** | *1.0* | 4 | 2 | 10 | 24 | 190 | 2.0 | 0.50 |
| Dopamine-Receptor-Agonists | **Bromocriptine** | *0.5* | 3 | 2 | 8.8 | 10 | 130 | 1.1 | 0.25 |
| Neuromuscular-Blocker | **Atracurium** | *0.05* | 11 | 7 | 0.51 | 0.71 | 1.1 | 0.070 | 0.030 |
| Opioid Antagonist | **Naloxone** | *0.1* | 35 | 21 | 1.0 | 2.0 | 250 | 2.2 | 2.0 |
| Statin | **Atorvastatin** | *5.0* | 3 | 2 | 12 | 82 | 110 | 3.6 | 2.5 |
| | **Rosuvastatin** | *1.0* | 3 | 2 | 13 | 14 | 29 | 0.83 | 0.50 |

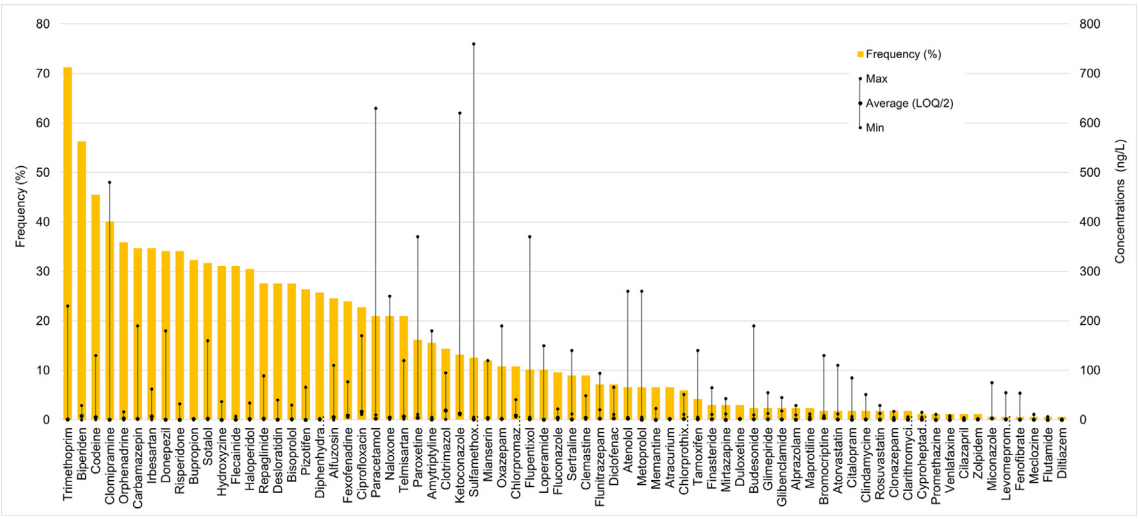


**Fig. 2.** Frequency of occurrence (yellow bar) and minimum, average, and maximum concentrations (black point-line) of quantified pharmaceuticals present within the samples. (For interpretation of the colour in this figure legend, the reader is referred to the Web version of this article.)

## 4. Discussion

By detecting and quantifying the levels of 72 pharmaceuticals within the coastal waters of Viti Levu, this study highlights for the first time the presence of pharmaceuticals within the marine environment of a small developing Pacific Island country. This baseline study contributes to the growing evidence of the global pharmaceutical pollution issue and sets the precedence to filling an emerging-pollutants knowledge gap within Pacific Islands (Varea et al., 2020) and the broader South Pacific region, where previous efforts to screen for pharmaceuticals has been limited (Branchet et al., 2020; Madikizela et al., 2020).

The occurrence of pharmaceuticals at each of the seven sampling sites is suggestive of a more widespread presence within the broader coastal environment between the eastern and western boundaries of this study. However, considering that only two of the detected pharmaceuticals had a frequency of occurrence greater than 50%, it is likely that the introduction of pharmaceuticals into the coastal waters around Viti Levu was relatively sporadic. In a screening conducted within the surface brackish waters of estuaries in Sydney, similar levels of occurrence were reported, i.e., only two of the eight detected pharmaceuticals occurred in more than 50% of the samples (Birch et al., 2015). Another study from within the region, in Auckland, New Zealand, also yielded low levels of detection, whereby six of the 21 detected pharmaceuticals were present in more than 50% of the samples (Stewart, 2013). Comparison with this study is however not commendable given the difference in medium; i.e., coastal sediment as opposed to surface marine water. More comparable studies exist from various other regions around the world, particularly in the Northern Hemisphere, where a low frequency of occurrence is typical (Ojemaye and Petrik, 2019). For example, a screening of pharmaceuticals within the Baltic Sea and Skagerrak showed that 38 of the 39 quantified pharmaceuticals occurred in less than 50% of the samples, similarly only three of 15 antibiotics screened within the Yellow Sea had a frequency of occurrence greater than 50% (Björlenius et al., 2018; Du et al., 2017).

No clear trend can be identified between measured concentrations and proximity to sewage treatment plants or population density, which indicates that there is a turbulent mixing occurring along the coastline. In a previous study, microplastics were detected at all sampling sites, with no distinction between rural and urban sites, which indicates that coastal hydrodynamics play an important role in the dispersal of pollutants (Dehm et al., 2020). This is further emphasized by focusing on carbamazepine levels at all sampling sites (Fig. 3A) and time points. Carbamazepine is often selected as an anthropogenic marker since it is a pharmaceutical that is persistent, quantifiable at low ng/L levels, and has a global usage (Bjorlenius et al., 2018). Carbamazepine average concentrations ranged across sites from 1.2 ng/L at Cuvu to 8.9 ng/L at Leleuvia Island (Fig. 3A). Similarly, within each site, measured concentrations varied with regards to individual sampling locations. Our radar plot (Fig. 3B) clearly shows that measured carbamazepine levels differ both over time at the same sampling point Laucala Bay (e.g., 1A:1–6), but also in between the four replicates at each site (e.g., 1A:1-1D:1), which is a clear indication of turbulent mixing and dilution with uncontaminated seawater.

The concentrations of individual pharmaceuticals measured in our study are comparable to what is reported in a single regional study, namely Birch (2015), where a screening of pharmaceuticals in surface water from various estuaries in Sydney, Australia was conducted. Our study had four overlapping pharmaceuticals, all of which yielded similar concentrations. In Sydney estuaries, average concentrations were between; 1.9 ng/L and 2.7 ng/L for carbamazepine, 3.0 ng/L and 9.5 ng/L for codeine, 5.3 ng/L and 67 ng/L for paracetamol, and 2.4 ng/L and 45 ng/L for venlafaxine, while in our study the average concentrations are 2.8 ng/L, 7.6 ng/L 17 ng/L and 0.1 ng/L, respectively. On the other hand, from a more global perspective, pharmaceutical concentrations within our study are generally within the lower range of what is reported in literature. For example, in our study atenolol was found at an average concentration of 2.6 ng/L, as opposed to 8 ng/L to 38 ng/L in the Mediterranean Sea (Rodríguez-Navas et al., 2013), 49 ng/L in the Baltic Sea (Björlenius et al., 2018) and 57 ng/L in San Francisco Bay (Nödler et al., 2014). Clarithromycin which was found at an average concentration of 0.1 ng/L in our study has also been reported higher in other regions, such as in the Aegean Sea (16 ng/L; Nödler et al., 2014), Baltic Sea (2.0 ng/L; Björlenius et al., 2018) and Yellow Sea (89 ng/L; Du et al., 2017). Sulfamethoxazole has been reported to range between 4.1 ng/L and 2400 ng/L in the Mediterranean Sea (Tahrani et al., 2017), 63 ng/L in the Red Sea (Ali et al., 2017) and 48.1 ng/L in the Yellow Sea (Du et al., 2017) and in our study was found to be 13 ng/L on average. Trimethoprim which was reported at an average concentration of 3.0 ng/L in the Irish Sea (McEneff

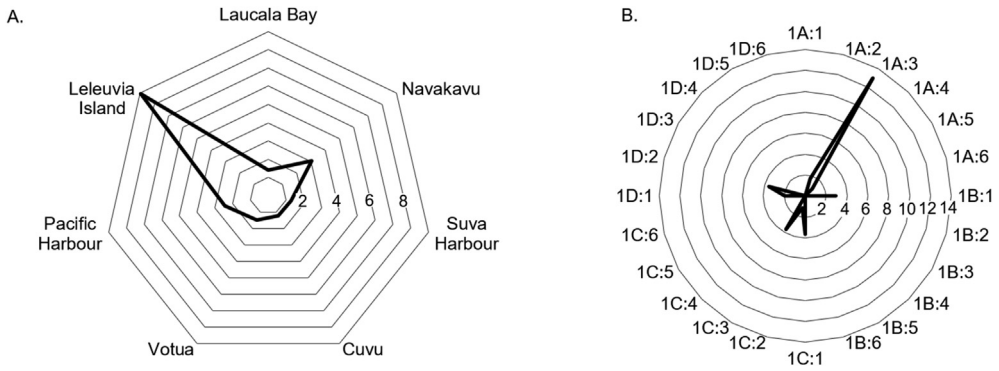


**Fig. 3.** Radar plots of average carbamazepine concentrations across the seven sampling sites; Laucala Bay, Vueti Navakavu LMMA, Suva Harbour, Cuvu, Votua, Pacific Harbour and Leleuvia Island (A.) and at all sampling periods and points, 1A:1-1D:6, at Laucala Bay (B.). Concentrations are in ng/L.

et al., 2014), between 1.5 ng/L and 3500 ng/L in the Mediterranean Sea (Tahrani et al., 2017), and between 1.4 ng/L and 96 ng/L in the Yellow Sea (Na et al., 2011) was found to be 7.5 ng/L in our study. Correspondingly, a similar trend can be noted when conducting individual comparisons of average concentrations of the remainder of the quantified pharmaceuticals, as well as when concentrations ranges are compared to global concentration ranges. Our study showed that pharmaceutical concentrations ranges from 0.04 ng/L to 760 ng/L which is comparatively low when compared to global reviews; for example, global concentrations of pharmaceuticals in seawater environments reportedly ranged between 0.01 ng/L and 6,800 ng/L (Gaw et al., 2014), while a successive review listed the range as 0.21 ng/L to 5,000 ng/L (Ojemaye and Petrik, 2019) and, most recently, the range was identified from ~0.05 ng/L to ~20,000 ng/L (Madikizela et al., 2020).

The low levels along our sites are most likely due to the low population density coupled with efficient dilution/mixing brought about by tides and through high freshwater input. The coastal water along the southern coastline of Viti Levu is a rather narrow (~0.5 km to 2 km) and shallow (<60 m) system and although it is well sheltered, a network of channels and passages allows for short flushing period driven by the semidiurnal tidal period (Rahiman and Pettinga, 2006). In addition, the southern coastline is comprised of a three large rivers, Rewa, Sigatoka and Navua and countless smaller streams and brooks which together with the high (6 mm/day to 30 mm/day) levels of rainfall likely add to the dilution factors within local coastal waters (Moishin et al., 2020). Nonetheless, the detection and measurement of pharmaceutical compounds in the samples indicates a source of concern since the compounds can be bioactive even at low concentrations. In addition, Lal et al. (2020) showed that current driven mass particle movements have two distinct patterns depending on the phase of the El Niño-Southern Oscillation, which is a natural but irregular periodic variation of winds and currents unrelated to climate change but brought by irregular distribution of sea surface temperature (Dijkstra, 2006). During non-El Niño years currents around Viti Levu predominantly travel either west or east initially, and then southwards while during El Niño years, currents tend to oscillate, circulating in three or more directions, instead of travelling more directly away from landmasses into deeper water (Lal et al., 2020) . This suggests that pollution in the coastal zones of Fiji could reach higher levels during El Niño years, with the opposite during non-El Niño years. Our samples were taken along the coastal zones of Viti Levu in 2017 and 2018 during which there was a La Niña event (Zhang et al., 2019), suggesting that water circulation might have facilitated the dispersal of the pharmaceuticals in the water and as a result, relatively lower levels of pharmaceuticals were found.

One way to assess the risk of pharmaceuticals within the marine environment is to calculate the ratio between predicted environmental concentrations (PEC) and the predicted no effect concentration (PNEC), i.e., PEC/PNEC. However, it is difficult to perform valid risk estimations of these pollutants since there is a lack of studies on the effects of chronic or intermittent exposure on marine aquatic wildlife. Of the 20 most frequently detected (>25% detection frequency) pharmaceuticals, three had relevant, seawater based PNEC values in the ECOSAR database (Table S6). An alternative to PEC/PNEC based risk assessments is to compare predicted or measured concentrations with the critical environmental concentration (CEC), a water concentration that is predicted to cause a pharmacological effect (Fick et al., 2010). This alternative risk assessment is based on the fish plasma model, first suggested by Huggett et al. (2003), which is based on the assumption that if two species share the same drug target, the targets are expected to be activated at roughly the same plasma concentration of the pharmaceuticals in both species. Of the 20 most frequently detected pharmaceuticals, five had a maximum detected concentration that exceeded the CEC value (Table S6.) which suggest that these five, clomipramine, irbesartan, donepezil, haloperidol and pizotifen, could have a pharmacological effect on exposed marine wildlife. It should be emphasized that this only reflect the probability for a pharmacological interaction to occur, and not whether the interaction would be adverse or not.

To the best of our knowledge, there are no official regulations, environmental laws or watch lists regarding pharmaceuticals within the environment in Fiji or in other small Pacific Islands. Most regulations that exist refer to drinking water standards and are based on the World Health Organizations Drinking Water Quality Guidelines (Khatri et al., 2011). Even at a global level, regulations with regards to pharmaceuticals within the environment are limited; the European Medicines Agency and European Union Water Framework Directive are likely the most direct efforts to monitor and regulate pharmaceuticals within the environment. As a means to regulate pharmaceutical pollution, the European Medicines Agency set a threshold for predicted environmental concentrations at 0.01 μg/L (10 ng/L) (Committee for Medicinal Products for Human Use, 2006; Gaw et al., 2014) and amongst the 72 pharmaceuticals quantified within this study 85% surpassed this threshold at least once during the sampling periods. Under a similar line, the European Union Water Framework Directive has chemicals of concern listed under a watch list which includes four pharmaceuticals, three of which are antibiotics (azithromycin, clarithromycin, and erythromycin) and one is an analgesic (diclofenac), due to their potent and adverse effect on various species

(Fliedner et al., 2020; Loos et al., 2018). Within the present study, two of these pharmaceuticals, namely clarithromycin and diclofenac, were included in the screening and were quantified in 2% and 7% of the samples respectively. The presence of these pharmaceuticals in the coastal marine environment around Viti Levu is suggestive towards a need for greater national effort towards developing baseline studies and monitoring efforts for emerging contaminants such as pharmaceuticals and personal care products.

## 5. Conclusion

This study clearly shows the presence of pharmaceuticals within the southern coastal waters of Viti Levu, albeit most may be a result of sporadic introduction considering that only two pharmaceuticals were detected in more than 50% of the samples. No clear pattern is noticeable with regards to concentrations of pharmaceuticals and proximity to sewage treatments plants which suggest distribution and dilution via turbulent mixing. On the other hand, the lack of a trend between the presence of pharmaceuticals in water with regards to population suggests that pharmaceutical contaminants are distributed well beyond the domain of this study, towards other parts of Fiji and perhaps the region. The presence of clarithromycin and diclofenac as well as the fact that 85% of the 72 quantified pharmaceuticals were present at least once at levels above 10 ng/L is suggestive towards a need for increased efforts regulate and monitor the release of pharmaceuticals residues into the environment. Implementation of monitoring programs for marine coastal waters that will allow for comparison with the baseline data of this study is highly recommended. This will allow for an overall evaluation of the effectiveness of management measures (or lack thereof) implemented to reduce the diversity and amount of emerging environmental pollutants such as pharmaceuticals.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2021.130161.

## Credit roles

Jasha Dehm: Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. Shubha Singh: Investigation, Data curation, Writing – review & editing. Marta Ferreira: Conceptualization, Writing – review & editing, Funding acquisition. Susanna Piovano: Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. Jerker Fick: Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Validation.

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