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Occurrence and distribution of selected pharmaceuticals in fresh fish along the Kenyan coast and assessment of potential human health risks†

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Fish consumption is known to have several health benefits. However, consuming fish contaminated with pharmaceuticals can potentially lead to long-term detrimental effects and other health risks for consumers. This study aimed to assess the potential human risks associated with fish consumption from Tudor creek. The creek is one of the peri-urban creeks near the East African coastal city of Mombasa, Kenya. A novel comprehensive analysis of 14 selected pharmaceuticals was conducted for the first time in different fish species from Tudor creek. The concentrations of pharmaceuticals in fish muscles and gills from Tudor creek ranged between detection limit (DL)–1623.98 ng g^{-1} and between DL–1785.60 ng g^{-1}, respectively. High pharmaceutical concentrations were observed in fish species *Platax pinnatus*, *Lethrinus mahsena*, and *Acanthurus blochii* with total concentrations of ∑3870.80 ng g^{-1}, ∑3435.57 ng g^{-1} and ∑3329.37 ng g^{-1}, respectively. The estimated daily intake (EDI) of pharmaceuticals through consumption of fish ranged between 1.01–1441.70 ng kg^{-1} bw per day. The Target Hazard Quotients (THQs) for trimethoprim, the parent tetracycline compound, and caffeine exceeded 5%, suggesting that all three substances posed health risks. There is a need to create public awareness of the impact caused by pharmaceuticals discharged into aquatic/marine environments. Furthermore, there is a need for policies and legislation on the disposal of pharmaceuticals. Effective monitoring and enforcement will also be necessary to help prevent negative impacts on livelihood, sustainability of our marine environment, and human health.

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Environmental significance

Data on the occurrence and distribution of contaminants of emerging concern are limited, particularly on the African continent and especially along the coastlines of East Africa. This study combined household surveys on fish consumption with the determination of levels and distribution of 14 selected pharmaceuticals in fresh fish typically consumed by people living in the area. Various common pharmaceutical compounds were detected in fish, and consumption of the fish poses a potential human health risk. There is a need for new policies and regulations on the responsible disposal of pharmaceuticals, as well as the development of collaborative networks between relevant government structures, local industries, communities, and other stakeholders to address the issue and ensure the sustainable use of our oceans and coastal areas.

Introduction

Seafood consumption rates have increased worldwide in recent years, mainly due to rising urbanization and awareness of its nutritional benefits.[1,2] Seafood, such as fish, crustaceans, and mollusks, plays an important role in providing 17% of animal protein and 7% of all essential protein to over 3 billion people in developing countries.[2] It is the most accessible and affordable source of animal protein, including micronutrients like vitamins (*e.g.* A, D, and B_{12}) and essential minerals, and typically has low calorific values and fat content, which can be beneficial for human health.[3–5] Furthermore, seafood is known for its positive influence on the health of young children and has been widely recognized as "nature's superfood".[3,6,7] Despite the multiple health benefits of seafood in addressing food and nutritional security among poor and vulnerable populations, even in small quantities, seafood from polluted water bodies can be hazardous to human health due to exposure to

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potentially harmful substances, such as emerging organic contaminants. This risk is especially significant for populations with high fish consumption rates.[8,9]

In recent decades, there has been growing concern about the occurrence and level of pharmaceutical compounds and their residues in various environmental compartments (*e.g.* water, sediment and biota). Due to their extensive use and the potential harm they can cause to human and ecological health, pharmaceutical compounds and their residues are considered emerging organic contaminants.[8,10] These compounds are consumed worldwide for the treatment and prevention of human diseases and in several veterinary applications.[11,12] Pharmaceuticals are introduced into the aquatic environment *via* both treated and untreated wastewater, discharged from households, pharma manufacturing and packaging facilities, animal husbandry farms, aquaculture facilities, and hospitals. This leads to the 'pseudo-persistence' of pharmaceuticals in the aquatic environment, as the rate of input exceeds the rate of degradation.[8,13,14] The main concern with the release of pharmaceutical residues into marine waters is their potential to bioconcentrate and bioaccumulate at significantly higher levels than in the surrounding water. This occurs through diffusion across the gills, digestive tract, and skin of aquatic organisms due to the polar nature of pharmaceuticals and their high bioavailability to filter-feeding organisms.[13,15,16] Currently, the occurrence and bioaccumulation of pharmaceuticals in marine organisms have attracted a lot of attention, with several studies reporting their presence in marine fish.[17–21] Some aquatic organisms bio-accumulate pharmaceuticals by direct partitioning from the abiotic environment through inhalational exposure (bio-concentration) or dietary sources (trophic transfer).[22,23] Aquatic life faces potential risks from exposure to even low concentrations of pharmaceuticals in the environment.[8,9,24] For instance, research has shown that non-steroidal anti-inflammatory drugs (NSAIDs), including diclofenac, can have detrimental effects on the kidneys of fish and disrupt the ovulation process within fish populations.[25,26] The antidiabetic drug metformin has also been reported to cause the feminization of male fish in the aquatic environment.[27] A recent study on South Asian clams (*Corbicula fluminea*) found that sulfamethoxazole at environmentally relevant concentrations had neurotoxic effects on the clams,[28] and another study on Mediterranean mussels (*Mytilus galloprovincialis*), found moderate effects on the mussels when exposed to various non-steroidal anti-inflammatory drugs.[29] Further information on studies examining the effects of pharmaceutical compounds on various aquatic organisms can be found in a number of reviews in the literature.[30,31] The impacts of pharmaceuticals on human health range from direct effects, such as consuming seafood containing hazardous compounds, to indirect impacts, such as contributing to antimicrobial resistance.[32] Therefore, there is a need to determine their concentration in seafood.

The peri-urban creeks along the Kenyan coast, particularly Tudor Creek, are among the largest in Kenya and serve as important nursery grounds for many fish species.[33] Data on fish species and the quantities from different fish landing sites are available. However, information on the frequency and quantities of marine fishery products consumed by households along Tudor creek is limited. Tudor creek's fish community structure has changed due to pollution and climate change.[33,34] The creek receives sewage discharge from non-functional treatment plants and wastewater leaking into storm drains, untreated effluent from informal settlements, as well as from other domestic and industrial sources due to inadequate wastewater management and sanitation facilities that have persisted for more than a decade.[35,36] Previous studies have reported high concentrations of acetaminophen, trimethoprim, sulfamethoxazole, carbamazepine, and nevirapine in the surface water of Tudor creek.[37] Hence, determining the concentration of pharmaceuticals in various fish and the average daily intake is required to assess the toxicological risk associated with fish consumption. The study aimed to determine the human health risks associated with consuming fish from Tudor creek. Fourteen pharmaceutical compounds in different fish species samples were accurately measured. The compounds were selected based on their high annual consumption[38] and previous studies on pharmaceutical distribution in the surface seawater in Tudor creek[37] as well as their occurrence in Kenyan rivers and wastewater samples.[39–42]

Materials and methods

Study area

Tudor creek is located on the eastern side of Mombasa Island (Fig. 1) and is separated from Makupa creek by a landfill. The fish were purchased dead for use in the study. Fish samples (*Epinephelus coioides*, *Sillago sihama*, *Sphyraena flavicauda*, *Pomadasys multimaculatus*, *Acanthurus blochii*, *Platax pinnatus*, and *Lethrinus mahsena*) were randomly purchased from local fishermen's daily catch in Tudor creek.

Surveys were conducted in Ganahola (- 3°99′ 50.73″ S, 39°63′ 15.23″ E), Simitini (- 4°03′ 30.25″ S, 39.65′ 72.79″ E), and Bandarini (- 4°02′ 05.87″ S, 39°39′ 14.50″ E) along Tudor creek in Mombasa County to estimate the average daily fish intake rate. These three villages serve as major fish landing sites for the fish catch along Tudor creek. The Ganahola community engages in fishing activities, and relies on the creek's rich biodiversity for their livelihoods. Simitini is a coastal settlement within Mombasa County, characterized by its fishing activities whereas Bandarini contributes to the local fishing industry and offers insights into the community's interaction with the marine environment. Data on household fish consumption was collected using a semi-structured questionnaire. The household surveys were conducted systematically, with participants from every third house being interviewed. The criterion for participation was whether members of the household consumed fish as part of their diet.

Pharmaceutical analysis

Reagents and standards. HPLC-grade acetonitrile (ACN) and methanol (MeOH) LC-MS grade used in the sample analysis were purchased from Merck (Darmstadt, Germany), along withs hydrochloric acid (HCl) 37%. Ethylenediaminetetraacetic acid

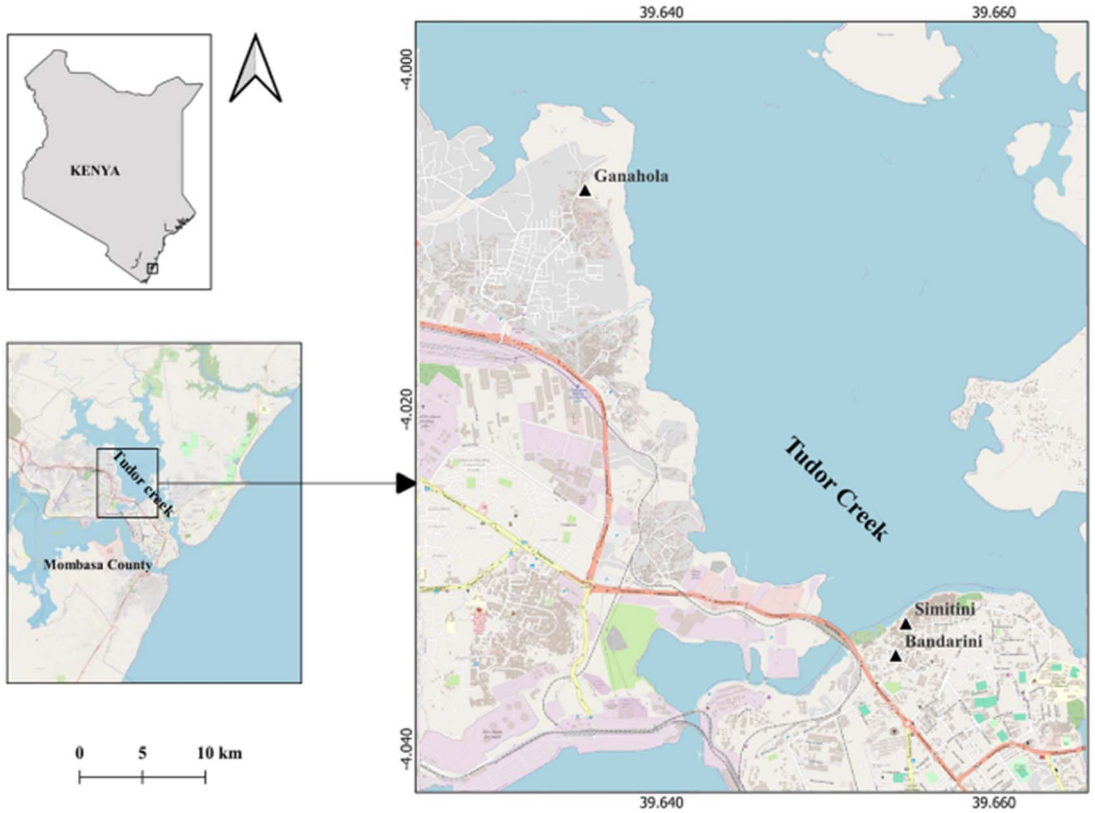

Fig. 1 A map highlighting the villages of Ganahola, Simitini, and Bandarini along Tudor Creek, where household surveys were conducted.

disodium salt dihydrate (Na_2EDTA) and formic acid (FA) 99% were bought from Sigma-Aldrich (South Africa). High-purity standards (>99%), including acetaminophen, ibuprofen, caffeine, parent tetracycline compound, acetylsalicylic acid, lidocaine, and bupivacaine were purchased from Sigma-Aldrich LTD. Erythromycin, diclofenac, carbamazepine, and trimethoprim standards, from Toronto Research Chemicals, were purchased from LGC Standards South Africa. Sulfamethoxazole and nevirapine (99%) were kindly donated by Universal Corporation Ltd, Kenya. Cetirizine dihydrochloride was purchased from Dr Ehrenstorfer GmbH and supplied by LGC Standards South Africa. The isotopically labelled compounds carbamazepine d10, diclofenac d4, and trimethoprim13C3 were used as internal standards and were obtained from Toronto Research Chemicals (Ontario, Canada) and purchased *via* LGC Standards South Africa. Individual stock standards and isotopically labeled internal standards were prepared on a weight basis in methanol (at a concentration of 1000 mg L^{-1}). These standards were stored in the dark at 4 °C. Working standard solutions containing all the pharmaceuticals were also prepared in a 50 : 50 v/v methanol/water mixture. For internal standard calibration, separate mixtures of isotopically labeled internal standards were prepared in methanol, and further dilutions were also prepared in a 50 : 50 v/v methanol/water mixture. Solid phase extraction (SPE) cartridges, specifically, Oasis hydrophilic–lipophilic balance (HLB, 6 cm3, 500 mg), were purchased from Waters (Milford, USA), and supplied by Microsep, South Africa.

Sample preparation and analysis. Four pieces of each fish species sample were individually wrapped using aluminium foil and then placed in cooler bags with ice before being transported to the laboratory. The samples were washed with Millipore water (18 MΩ) and dissected. The fish back muscles and gills were separated, packed in an aluminium container, and stored below −20 °C until further analysis. The fish sample was freeze-dried, homogenised, blended into a fine powder, and kept in a desiccator until analysis. The homogenized fish samples were extracted using the method described by Klosterhaus, Grace[40] and USEPA.[41] In brief, approximately ~0.5 g of the sample (dry weight; d.w) for each fish species was spiked with 50 μL of 100 ng L^{-1} internal standards followed by the addition of 10 mL of a mixture of methanol and acetonitrile in a ratio of 2 : 1 in a 50 mL borosilicate glass vial. The resulting mixture was vortexed for 2 min and thereafter sonicated at 25 °C for 15 min. The samples were centrifuged (Hettich EBA) at 4500 rpm for 10 min, and then the supernatant was transferred to a borosilicate glass vial. This extraction procedure was repeated with methanol and acetonitrile, followed by phosphate buffer. The extracts were combined and evaporated using a Genevac EZ-2 system (Genevac SP Scientific). Immediately after concentration, the extract was diluted with 200 mL of ultrapure water (18.2 MΩ × cm at 25 °C), pH adjusted to 2, and 0.5 g of Na_2EDTA was added to chelate the metal ions in the solution. The samples were then passed through SPE at a 1 mL min^{-1} flow rate. Once the entire

Table 1 Calibration, LOD, LOQ, and the standard deviation (% RSD) and recovery for individual analytes in fish muscles and gills

				Fish muscles		Fish gills	
Analyte	Linearity (R^2)	LOD (ng L^{-1})	LOQ (ng L^{-1})	RSD (%)	Recovery (%)	RSD (%)	Recovery (%)
Acetaminophen	0.9978	0.07	0.50	1.67	112	2.50	87
Acetyl salicylic	0.9949	0.23	1.67	7.39	91	4.19	109
Diclofenac	0.9986	0.07	0.52	16.33	82	14.56	81
Ibuprofen	0.9905	0.16	1.21	18.63	99	16.12	111
Trimethoprim	0.9958	0.10	0.73	2.76	98	4.63	108
Sulfamethoxazole	0.9975	0.08	0.61	2.43	82	3.35	76
Tetracycline	0.9958	0.11	0.80	12.98	74	12.46	104
Erythromycin	0.9930	0.20	1.46	1.46	83	2.00	95
Carbamazepine	0.9992	0.04	0.32	0.18	107	1.48	100
Nevirapine	0.9996	0.25	1.86	1.01	83	0.96	77
Caffeine	0.9997	0.02	0.18	0.42	109	0.56	114
Cetirizine	0.9991	0.06	0.42	0.45	107	0.33	95
Lidocaine	0.9983	0.05	0.39	1.33	73	1.71	70
Bupivacaine	0.9993	0.06	0.46	1.50	84	1.67	77

sample had passed through the SPE (HLB; 6 cm^3, 500 mg), 10 mL of reagent water was added to wash out the Na_2EDTA.

Using a vacuum, the cartridges were dried for 30 min. The analytes were then eluted with 3 mL of acetonitrile/methanol (50 : 50 v/v) solution. The solvent was subsequently evaporated to dryness using a Genevac EZ-2 system and reconstituted by adding 100 μL of HPLC grade water and methanol (50 : 50 v/v). Finally, the sample was injected into an Ultra Performance Liquid Chromatography (UPLC) system hyphenated to a quadrupole-time-of-flight (QTOF) mass spectrometry instrument (Waters® Synapt G2). Procedures used for analysis using the UPLC-QTOF are provided in the ESI Section (S1).†

Quality assurance and quality control. The samples were subjected to quality assurance and quality control processes (Table 1). Two procedural blanks were established per batch of 5 samples to evaluate potential contamination during the experiment. Standard calibration curves were constructed using solutions of individual pharmaceuticals at concentrations of 2.5, 5, 10, 20, 50, 100, 500, and 1000 ng L^{-1} (most calibration curves had R^2 values greater than 0.99). The recoveries ranged from 74% to 109% and 76% to 114% in fish muscles and gills, respectively. Deionized water and spiked fish samples were extracted and analyzed to check for potential laboratory contamination. Methanol blanks were run between samples to monitor for instrumental contamination and carryover. Instrumental repeatability was evaluated by spiking fish muscles and fish gills ($n = 6$) with all target analytes and the calculated relative standard deviations (RSDs) ranged between 0.04–18.63% and 0.33–16.12% in fish muscles and fish gills, respectively. The limits of detection (LODs) and limits of quantification (LOQs) were measured based on the signal-to-noise ratios of 3 : 1 and 10 : 1, respectively.

Survey on fish consumption along Tudor creek

A descriptive, cross-sectional study design was utilized to collect data for this survey. Participants in the cross-sectional study were chosen based on the inclusion and exclusion criteria.[42] Households were systematically selected, with the participants from every third house being interviewed. The inclusion criterion for participation in the survey was the consumption of fish by the household as part of their diet. Data on household fish consumption was collected by administering a semi-structured questionnaire. The questionnaire was divided into demographics and household fish consumption (see ESI Material 1†). The demographic section comprised structured questions, *i.e.*, answers were provided from which the respondent picked the most appropriate option. The section on the average quantity of fish consumption per person in a household per day for the residents of Ganahola, Simitini, and Bandarini in Tudor creek was calculated using eqn (1).

$$\text{Fish consumption per capita(g per person per day)} = \frac{\text{Amount of Fish(g)consumed in a household in a day}}{\text{number of people in the household}} \quad (1)$$

Human health risk assessment

The daily intake of pharmaceuticals was estimated based on the concentration detected in seafood (fish) and their daily consumption among a diverse group of people living along Tudor creek. The estimated daily intake (EDI; in ng kg^{-1} body weight/day bw/d) of pharmaceuticals for Tudor creek residents (Ganahola, Simitini, and Bandarini) through fish consumption in the average intake scenario was calculated using eqn (2).[9,43]

$$\text{EDI(ng kg}^{-1}\text{ bw per d)} = \frac{C_{\text{seafood}} \times M_{\text{seafood}}}{\text{BW}_{\text{people}}} \quad (2)$$

where C_{seafood} (dw) represents the pharmaceutical concentration in fish in dry weight (dw), M_{seafood} (g per (day per person)) is the average daily fish consumption in grams for residents along Tudor creek (adults per day) and $\text{BW}_{\text{people}}$ (kg bw per person) represents the average body weight which is equivalent to 60.7 kg for an average African adult.[44]

The acceptable daily intake (ADI) value refers to the amount of a substance that can be consumed daily over a lifetime without any negative impact on human health. However,

a major challenge in conducting a risk assessment for human health is the lack of ADI values for all pharmaceuticals. Hence ADI values for pharmaceuticals used to treat humans were determined using eqn (3).

$$\mathrm{ADI} = \frac{\mathrm{LTD}}{(\mathrm{BW} \times \mathrm{SF})} \times 1000 \quad (3)$$

where the units for ADI are μg per (kg per day), the units for LTD (lowest therapeutic dose) are mg per day, BW is defined as the body weight and the value used is 60.7 kg, and SF is the safety factor which is set at 1000.[45,46]

To assess the target hazard quotient (THQ), EDI values were compared with the acceptable daily intake (ADI) values eqn (4). THQ ˂ 1% indicates a negligible risk and considerable risk when the ratio is 1–5%, while THQ > 5% indicates a potential risk to human health[47,48]

$$\mathrm{THQ} = \frac{\mathrm{EDI}}{\mathrm{ADI}} \times 100 \quad (4)$$

Data analysis

Descriptive statistics, specifically, the sum, count and mean of the samples were used to summarize the results of pharmaceutical concentrations in fish muscle and gills samples. Pearson correlations tests were used to determine if there were any significant associations between the pharmaceuticals investigated. Principal Component Analysis (PCA) was performed using *R* statistical software, and statistical significance was defined at $p < 0.05$. Raw household survey data collected from three different communities along Tudor creek was entered and cleaned in Microsoft Excel. Missing values in household income were imputed from the available data to ensure a complete dataset. Descriptive statistics were generated to compute mean household sizes, incomes, and (daily) fish consumption quantities.

Results and discussion

Demographics of the respondents

A total of 93 respondents were interviewed during the survey (Table 2), including fishermen, fish dealers, food vendors, small-scale business owners, and casual laborers. The survey respondents comprised 71% ($n = 66$) men and 29% women ($n = 27$). The male respondents predominated over the female respondents, which could be because fishing has traditionally been considered as a male occupation. The mean household size in the survey was seven, with the maximum size recorded as twenty and the minimum as one.

Table 2 Summary of the sampled population along Tudor creek

$N = 93$	Site	Percentage of respondents
$N = 28$	Ganahola	30
$N = 32$	Simitini	34
$N = 33$	Bandarini	35

The ages of the respondents ranged from 18 to over 80 years, with a mean of 40 years. Regarding education levels, 51% of the respondents had little or no formal education (*e.g.*, only madrassa or incomplete primary school), whereas 36% had completed only primary school, 8% had completed secondary school, and 5% had tertiary education. In terms of employment, 69% of the people surveyed were self-employed, 18% were formally employed, and 13% were unemployed (Fig. S1a†).

Small-scale businesses (42%) and fishing activities (27%) were the main sources of livelihood among the self-employed category for the households of Ganahola, Simitini, and Bandarini (Fig. S1b†). Among the respondents in Ganahola (47%) and Simitini (36%), it was observed that small-scale business was the main source of livelihood. In contrast, most respondents in Bandarini were involved in fishing activities (55%).

Fish consumption was common among the households, with 94% of the respondents having consumed fish within the week before this survey. Most respondents (78%) consumed fish frequently throughout the year, while 22% consumed fish mainly during the Northeast Monsoon, from November to March/April, when fish were more abundant. Among the respondents, 25% consumed fish ranging from 0.5 to 1 kg per day per household. The majority, which accounted for 68%, consumed less than 0.5 kg of fish daily per household. Only a small percentage, specifically 7%, reported consuming more than 1 kg of fish per day per household (Fig. S2a†). Compared to Simitini and Bandarini, a higher percentage of fish consumption was observed in Ganahola (Fig. S2b†). Low fish consumption was observed in Bandarini with 11% consuming <0.5 kg and 13% consuming 0.501–1 kg, despite fishing being the main source of livelihood. This is because household financial resources heavily influence fish consumption.

From the survey, the four most preferred fish species were the Gempylidae, Siganidae, Lethrinidae, and Gerreidae (Fig. 2) due to their taste, nutritional value, fewer bones, and more steak. However, these species of fish are rarely found in Tudor creek, and the most commonly fished and consumed fish species found in high numbers in Tudor creek were Serranidae, Sillaginidae, Sphyraenidae, Pomacentridae, Acanthuridae, and Pinguipedidae. The average quantity of fish consumption per person in a household per day for the residents of Ganahola, Simitini, and Bandarini was 170 g per person per day as per a questionnaire based on fish consumption survey conducted in Tudor creek.

It was noted that 65% of the respondents acquired fish by either fishing or purchasing directly from the landing sites. In contrast, 28% obtained fish from the local market, and 8% sourced it from local fish shops. Regarding the preferences for fish, 66% of the respondents bought fresh fish, 29% opted for smoked fish, and 6% preferred frozen fish.

Pharmaceutical concentration in fish muscles and gills

The concentrations of pharmaceuticals in fish muscle from Tudor creek ranged between DL–1624.0 ng g^{-1}. These values were consistent with those reported in Kalk Bay harbor (not detected (nd)–1812.0 ng g^{-1}) in South Africa[20] but higher than

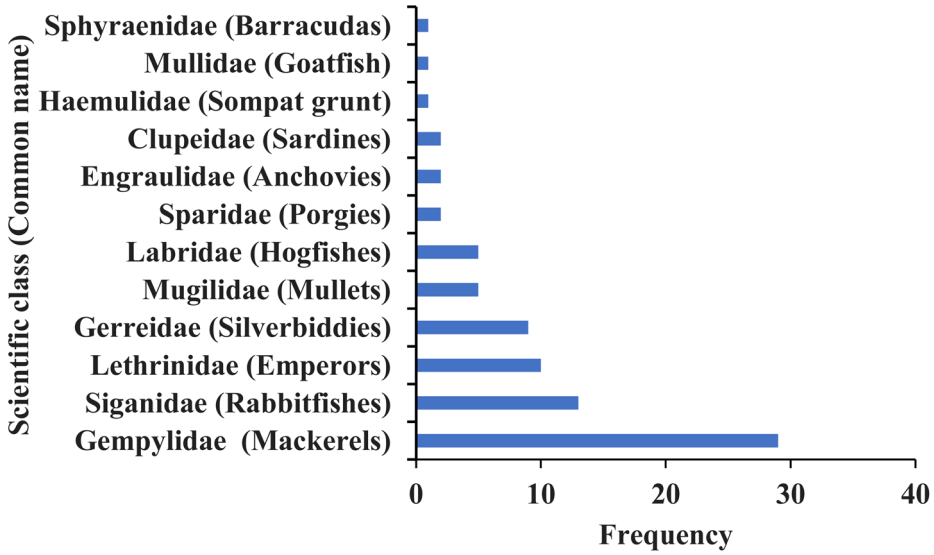

Fig. 2 Most preferred fish by the households along Tudor creek.

those reported in fish samples (nd–231.1 ng g^{-1}) from Coastal waters of the Saudi Red Sea,[49] the Mar Menor lagoon (nd–3.5 ng g^{-1}) in the Mediterranean Sea, SE Spain,[19] and Laizhou Bay, (40–110 ng g^{-1}) in North China.[21] In fish muscle, the concentrations of lidocaine, caffeine, carbamazepine, and trimethoprim were high, with total concentrations of $\sum$295 ng g^{-1}, $\sum$299 ng g^{-1}, $\sum$302 ng g^{-1}, and $\sum$3608 ng g^{-1}, respectively (Fig. 3). On the other hand, fish gill samples showed high concentrations of tetracycline, ibuprofen, acetylsalicylic acid, and nevirapine, with total concentrations of $\sum$3297.76 ng g^{-1}, $\sum$537.15 ng g^{-1}, $\sum$808.73 ng g^{-1}, and $\sum$10.19 ng g^{-1}, respectively.

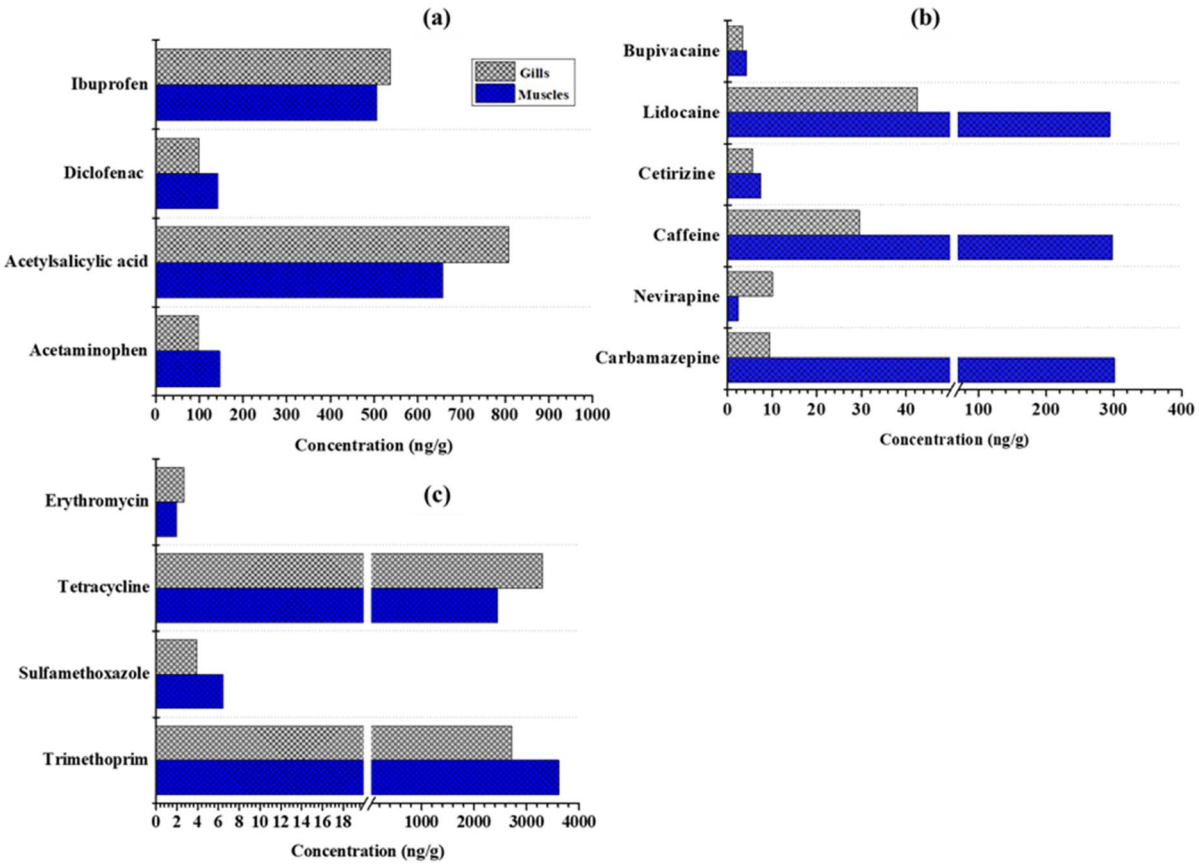

Fig. 3 Sum concentration of (a) NSAIDs, (b) selected pharmaceuticals, and (c) antibiotics in fish muscles and gills.

Table 3 Comparison of pharmaceutical concentrations (ng per g per d.w) in fish muscles and gills in this study and at other sites worldwide

Pharmaceutical	Site	Country	Concentration in muscles	Concentration in gills	References
Acetaminophen	Al Arbaeen lagoon	Saudi Red Sea	nd–62.7		50
Acetaminophen	Kalk Bay harbor	South Africa	nd–17.95	nd–33.26	21
Acetaminophen	Tudor creek	Kenya	5.41–54.39	DL–58.04	This study
Acetyl Salicylic	Tudor creek	Kenya	DL–223.06	DL–4311.84	This study
Ibuprofen	Al Arbaeen lagoon	Saudi Red Sea	nd–231.1		50
Ibuprofen	Sepetiba Bay and Parnaiba Delta	Brazilian coastal	nd–14.5		51
Ibuprofen	Tudor creek	Kenya	0.49–242.13	3.29–296.64	This study
Diclofenac	Kalk Bay harbor	South Africa	nd–1812	nd–1089	21
Diclofenac	Mar Menor lagoon	Mediterranean Sea (SE Spain)	nd–1.3		20
Diclofenac	Sepetiba Bay and Parnaiba Delta	Brazilian coastal	nd–5.6		51
Diclofenac	Tudor creek	Kenya	2.02–44.77	DL–31.69	This study
Trimethoprim	Laizhou Bay	North China	nd–18	nd–61	22
Trimethoprim	Al Arbaeen lagoon	Saudi red Sea	nd–44.9		50
Trimethoprim	Tudor creek	Kenya	5.74–1623.98	17.95–1427.43	This study
Sulfamethoxazole	Laizhou Bay	North China	11–40	nd–110	22
Sulfamethoxazole	Kalk Bay harbor	South Africa	nd–385.2	nd–75.25	21
Sulfamethoxazole	Southern Sea Korea	Southern Korea	nd		19
Sulfamethoxazole	Al Arbaeen lagoon	Saudi Red Sea	nd–11.2		50
Sulfamethoxazole	Tudor creek	Kenya	0.06–3.11	DL–1.27	This study
Erythromycin	Laizhou Bay	North China	nd–1.4	nd–20	22
Erythromycin	Southern Sea Korea	Southern Korea	nd–48.1		19
Erythromycin	Tudor creek	Kenya	DL–0.74	0.02–1.26	This study
Tetracycline	Tudor creek	Kenya	DL–1114.47	DL–1785.60	This study
Carbamazepine	Kalk Bay harbor	South Africa	nd–22.9	nd–22.83	21
Carbamazepine	Mar Menor lagoon	Mediterranean Sea (SE Spain)	bdl −6.3		20
Carbamazepine	Sepetiba Bay and Parnaiba Delta	Brazilian coastal	nd–3.8		51
Carbamazepine	Al Arbaeen lagoon	Saudi Red Sea	1.7–33.8.9		50
Carbamazepine	Tudor creek	Kenya	0.44–122.66	0.02–3.90	This study
Caffeine	Kalk Bay harbor	South Africa	nd–50.49	nd–2.030	21
Caffeine	Southern Sea of Korea	Southern Korea	nd–1.37		19
Caffeine	Tudor creek	Kenya	2.71–203.86	2.28–8.03	This study
Nevirapine	Tudor creek	Kenya	DL–1.09	DL–5.03	This study
Cetirizine	Tudor creek	Kenya	DL–4.25	DL–2.65	This study
Lidocaine	Tudor creek	Kenya	7.90–167.06	0.84–15.74	This study
Bupivacaine	Tudor creek	Kenya	DL–1.65	0.31–1.12	This study

Pharmaceutical concentrations at various coastal sites worldwide are summarized in Table 3. Analgesics (acetaminophen and acetylsalicylic acid) were detected in almost all the fish muscle samples (Fig. 4a), with the highest concentration of acetaminophen observed in *Pomadasys multimaculatus* (54.4 ng g^{-1}) and acetylsalicylic acid in *Platax pinnatus* (193.8 ng g^{-1}). Acetaminophen concentrations in fish muscles (5.4–54.4 ng g^{-1}) were consistent with concentrations detected in Al Arbaeen lagoon, Saudi Red Sea[49] but higher than those detected in Kalk Bay harbour, South Africa.[20] On the other hand, the gill samples of *Acanthurus blochii* had a higher concentration of acetaminophen (58.04 ng g^{-1}) compared to other fish species (Fig. 4b). These values were higher than the concentration found in *Pterogymnus laniarius* gill samples (33.26 ng g^{-1}) from Kalk Bay harbour, South Africa.[20] At the same time, the gills samples of *Lethrinus mahsena* showed the highest concentration of acetylsalicylic acid (431.8 ng g^{-1}) as compared to *Epinephelus coioides* and *Pomadasys multimaculatus*, whose concentrations were below the detection limit (Fig. 4b).

For the non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac and ibuprofen were detected in all the fish muscles (Fig. 4a), with the highest concentration of diclofenac (44.77 ng g^{-1}) detected in *Epinephelus coioides* which was higher than those reported in Sepetiba Bay and Parnaiba Delta, Brazilian coastal waters, nd–14.5 ng g^{-1} (ref. 52) but lower in fish muscle samples from Al Arbaeen lagoon, Saudi Red Sea, nd–231.1 ng g^{-1}.[49] However, the concentration of ibuprofen in the muscle tissue of *Acanthurus blochii* was 242.13 ng g^{-1}, which was higher than the values detected in Mar Menor lagoon, Mediterranean Sea, SE Spain, nd–1.3 ng g^{-1} (ref. 19) and Sepetiba Bay and Parnaiba Delta, Brazilian coastal waters, nd–5.6 ng g^{-1} (ref. 52) but lower than findings from Kalk Bay harbour, South Africa, nd–1812 ng g^{-1}.[20] In fish gill samples, the concentration of diclofenac and ibuprofen ranged between DL–31.7 ng g^{-1} and 3.29–296.6 ng g^{-1}, respectively (Fig. 4b). The concentration of diclofenac in fish gills in this study was nd–1089 ng g^{-1}, and this was lower than the values determined in Kalk Bay harbour, South Africa.[20]

The antibiotics in fish muscles and gills (trimethoprim, sulfamethoxazole, tetracycline, and erythromycin) were detected in most of the fish samples (Fig. 4c and d) and ranged between DL–1624.0 ng g^{-1} and DL–1785.6 ng g^{-1} respectively.

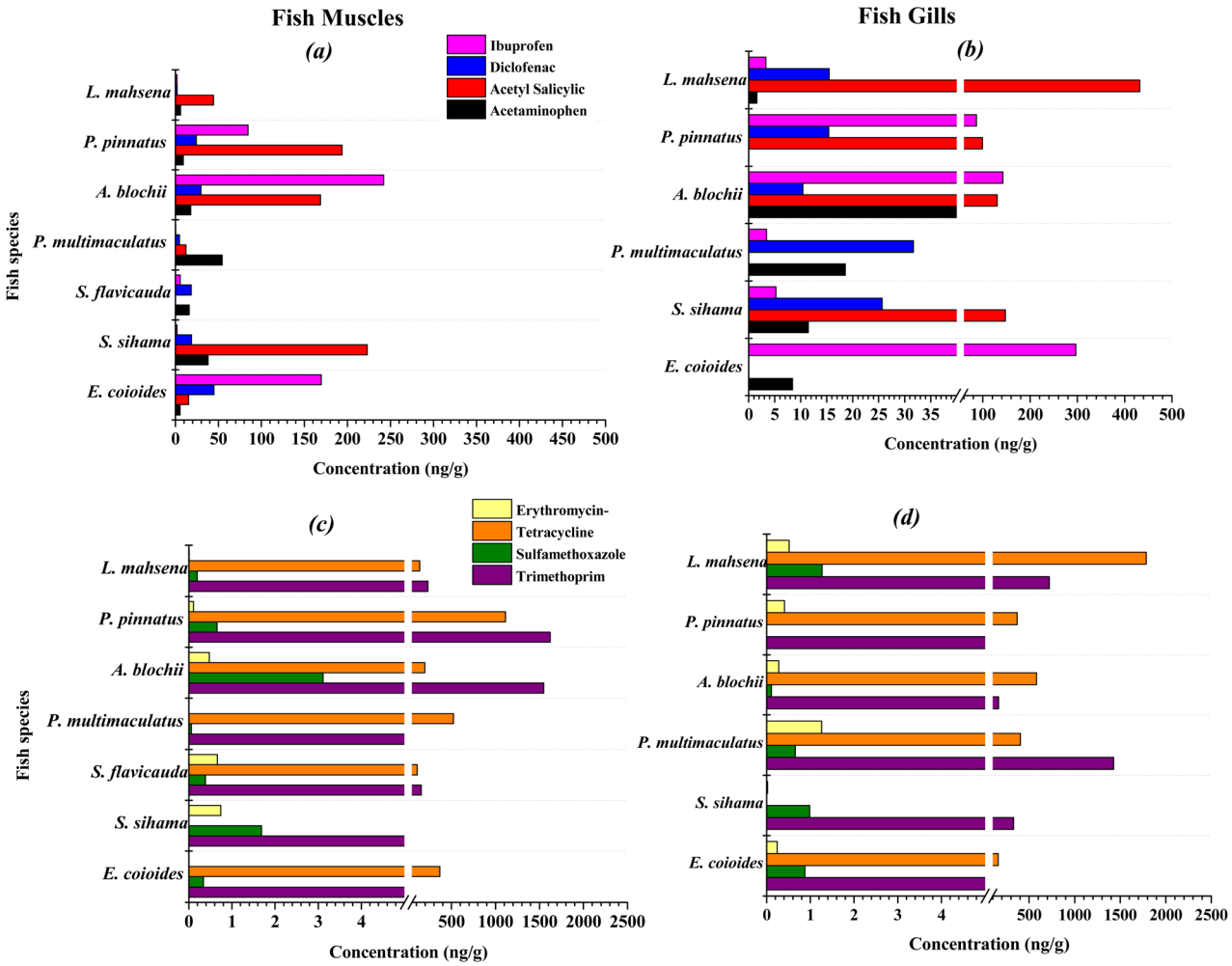

Fig. 4 Comparison of the concentration of selected NSAIDs and an analgesic in (a) fish muscles and (b) gills for different fish species. Comparison of the concentration of antibiotics in (c) fish muscles and (d) gills in different fish species.

Trimethoprim and tetracycline in fish muscles were highest in *Platax pinnatus* with concentrations of 1624.0 ng g^{-1} and 1114.5 ng g^{-1}, respectively. Trimethoprim concentrations in our study were higher than those reported in Laizhou Bay, North China, nd–18 ng g^{-1} (ref. 21) and Al Arbaeen lagoon, Saudi Red Sea, nd–44.9 ng g^{-1}.[49] At the same time, trimethoprim and tetracycline in gills ranged between 17.95–1427.43 ng g^{-1} and DL–1785.60 ng g^{-1}, respectively. Similarly, trimethoprim in gill samples (Table 3) reported in Laizhou Bay, North China[21] were lower than the findings in our study. Sulfamethoxazole concentration in fish muscles and gills ranged between 0.06–3.11 ng g^{-1} and DL–1.27 ng g^{-1}, respectively, with the highest concentration observed in *Acanthurus blochii* (in muscles) and *Lethrinus mahsena* (in gills). Liu *et al.*[21] and Ojemaye and Petrik[20] reported higher sulfamethoxazole concentrations (Table 3) compared to our study. Erythromycin concentrations in gills were higher compared to muscles, with sum concentrations of ∑2.72 ng g^{-1} and ∑1.99 ng g^{-1}, respectively. *Sillago sihama* showed a high concentration of erythromycin in fish muscle (0.74 ng g^{-1}) while *Pomadasys multimaculatus* showed in fish gills (1.26 ng g^{-1}). Liu *et al.*[21] detected higher concentrations of erythromycin (nd–20 ng g^{-1}) in fish gills in Laizhou Bay, North China, compared to the one obtained in this study.

Carbamazepine and nevirapine concentrations in fish muscle ranged between 0.44–122.66 ng g^{-1} and DL–1.02 ng g^{-1}, respectively, with the highest concentration observed in *Sillago sihama species* (Fig. 5).

Carbamazepine values in our study were higher than those reported in Sepetiba Bay and Parnaiba Delta, Brazilian coastal waters[52] and in Al Arbaeen Lagoon, Saudi Red Sea[49] but lower than those reported by Ojemaye and Petrik, (2019)[20] in Kalk Bay harbor, South Africa (Table 3). In fish gills, carbamazepine and nevirapine raged between 0.02–3.90 ng g^{-1} and DL–5.03 ng g^{-1}, respectively. It's worth noting that the concentration of carbamazepine was high in fish muscle as compared to fish gills.

On the other hand, the concentration of caffeine and cetirizine in fish muscles ranged between 2.7–203.9 ng g^{-1} and DL–4.25 ng g^{-1}, respectively, with a high concentration of caffeine observed in *Sillago sihama* and cetirizine in *Pomadasys multimaculatus* (Fig. 5b). However, the concentration of caffeine in fish muscle in Kalk Bay harbor, South Africa (nd–64.78 ng g^{-1})[20] and Korea's Southern Sea (nd–64.78 ng g^{-1})[18] was lower than the one obtained in this study. In comparison, caffeine and cetirizine were found at higher concentrations in fish muscle (298.7 ng g^{-1} and 7.6 ng g^{-1}, respectively) than in fish gills (29.7 ng g^{-1} and 5.7 ng g^{-1}, respectively).

Bupivacaine and lidocaine are the commonly used local analgesic anesthetics to improve postoperative pain control and reduce the required postoperative narcotics.[53] Bupivacaine concentrations in fish muscle and gills ranged between DL–1.65 ng g^{-1} and 0.31–1.12 ng g^{-1}, respectively. *Acanthurus blochii* exhibited notably high bupivacaine in fish muscle and gills (Fig. 5a and b). In comparison, lidocaine levels in fish muscle and gills ranged between 7.90–167.06 ng g^{-1} and 0.84–15.74 ng g^{-1}, respectively, with a high concentration detected in *Platax pinnatus* (fish muscle) and *Platax pinnatus* (fish gills).

Relationships between pharmaceutical concentrations in fish

The correlation analysis of pharmaceutical concentrations in fish species is illustrated in Fig. 6a. Acetaminophen (ACN) showed a significant strong positive correlation ($p < 0.05$) with erythromycin (ERM) and bupivacaine (BCN), indicating similar pollution sources such as wastewater discharge, hospital effluents, or agricultural runoff. This correlation also suggests that these pharmaceuticals share similar bioaccumulation and uptake mechanisms that influence their absorption, metabolism, or retention in fish tissues.[54] In contrast, carbamazepine (CBZ) showed a significant ($p < 0.05$) negative correlation with trimethoprim (TMP) and tetracycline (TC), suggesting selective bioaccumulation influenced by species-specific metabolism,

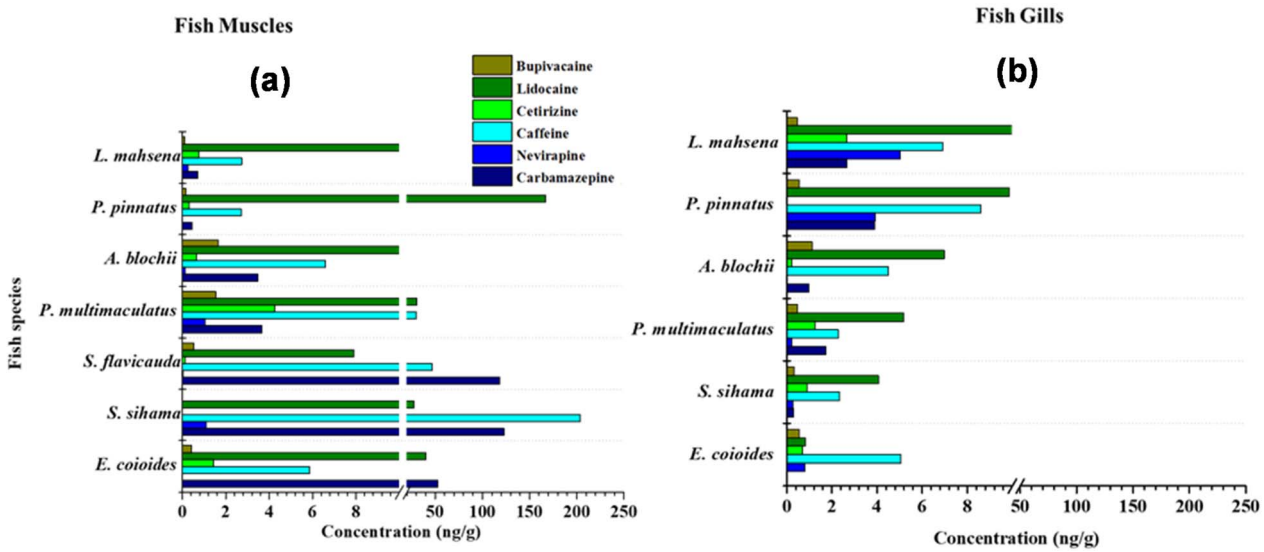

Fig. 5 Comparison of pharmaceutical concentrations in the (a) fish muscles and (b) gills of different fish species.

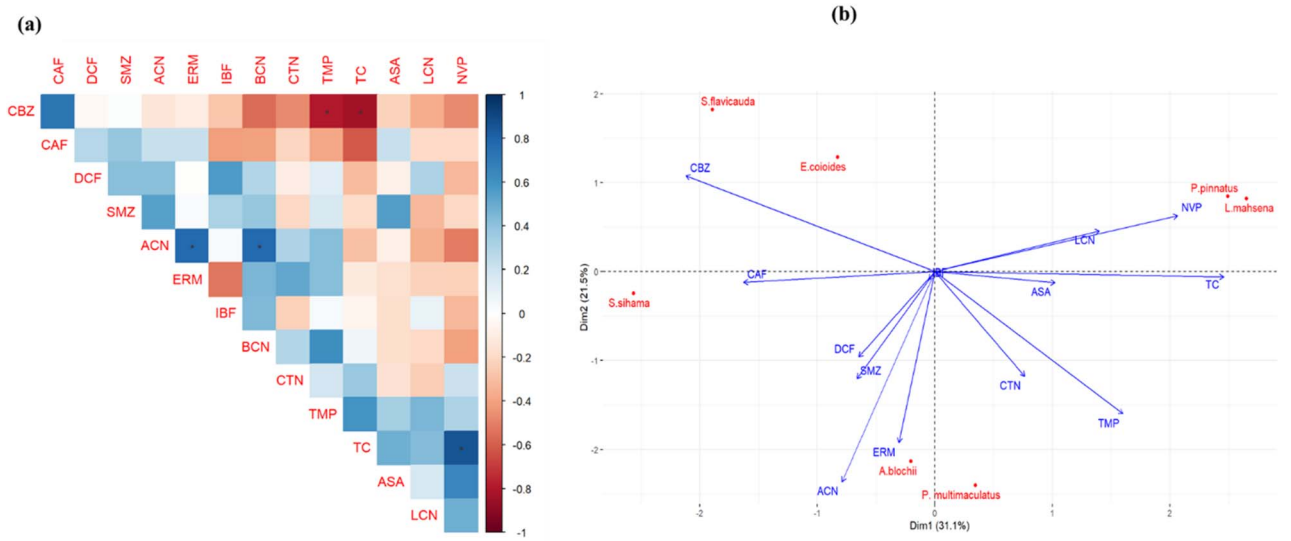

Fig. 6 (a) Pearson correlation coefficients and (b) principle component analysis (PCA) of different pharmaceuticals [acetaminophen (ACN), acetylsalicylic acid (ASA), diclofenac (DCF), ibuprofen (IBF), trimethoprim (TMP), sulfamethoxazole (SMZ), tetracycline (TC), erythromycin (ERM), carbamazepine (CBZ), nevirapine (NVP), caffeine (CAF), cetirizine (CTN), lidocaine (LCN), and bupivacaine (BCN)] in fish collected from Tudor creek [significant values 0.05 = (*)].

feeding habits, differences in metabolic pathways, or degradation interactions within the aquatic environment.

Principle component analysis (PCA) was also applied to further explore associations among pharmaceuticals in the fish species. As shown in Fig. 6b, DIM1 and DIM 2 accounted for 31.1% and 21.5% of the total variance, respectively, with DIM1 being highly associated with TC, CBZ, and NVP, while DIM 2 being highly associated with ACN and ERP suggesting that the fish species share similar pharmaceutical accumulation patterns based on their feeding habits and habitat preferences. NVP concentrations were high in *Lethrinus mahsena* and *Platax pinnatus*, whereas ERP was high in *Acanthurus blochii* and *Pomadasys multimaculatus*, indicating that these species have a higher affinity for absorbing or retaining these pharmaceuticals, possibly due to differences in metabolism, and feeding ecology.[55] It's worth noting that the pharmaceutical concentrations in *Pomadasys multimaculatus* showed a statistically significant strong positive correlation ($p < 0.05$) with *Sphyraena flavicauda*, *Acanthurus blochii* and *Lethrinus mahsena*. Similarly, *Platax pinnatus* exhibited significant correlation with *Pomadasys multimaculatus*, *Lethrinus mahsena* and *Acanthurus blochii*. These correlations may be attributed to shared pollution sources, such as wastewater discharge, hospital effluents, or agricultural runoff, which likely increase the susceptibility of these

Table 4 Comparison between estimated daily intake (EDI, ng kg^{-1} bw per day), acceptable daily intake (ADI, μg kg^{-1} per day), and target hazard quotient (THQ) of each pharmaceutical in all analyzed fish samples

Target compound	Mean concentration (ng g^{-1} dw)	EDI (adult) mean concentrations	ADI (μg per (kg per day))	THQ (adult)
Acetaminophen	20.9	58.58	10.71[a]	0.55
Acetyl salicylic	93.9	262.62	7.00[b]	3.75
Diclofenac	20.4	56.95	1.65[c]	3.46
Ibuprofen	72.2	202.03	13.18[c]	1.53
Trimethoprim	515.4	1441.73	1.65[a]	87.51
Sulfamethoxazole	0.9	2.57	6.59[c]	0.04
Tetracycline	350.1	979.26	6.59[c]	14.86
Erythromycin	0.3	0.80	5.07	0.02
Carbamazepine	43.1	120.60	3.29[c]	3.66
Nevirapine	0.4	1.01	—[d]	—[d]
Caffeine	42.7	119.35	1.20[c]	9.95
Cetirizine	1.1	3.02	0.08[c]	3.67
Lidocaine	42.1	117.83	—[d]	—[d]
Bupivacaine	0.6	1.75	—[d]	—[d]

[a] Lowest therapeutic dose (mg per day) for the pharmaceuticals were obtained from Schwab *et al.*, 2005.[57] [b] Lowest therapeutic dose (mg per day) for the pharmaceuticals were obtained from Prosser and Sibley, 2015.[58] [c] Lowest therapeutic dose (mg per day) for the pharmaceuticals were obtained from Sengar and Vijayanandan, 2022.[50] [d] Not available.

fish species to pharmaceutical bioaccumulation due to their proximity to contamination sites and feeding behaviours.

No specific trends were observed in the concentrations of pharmaceutical compounds in fish muscle and gills of all the fish species examined. However, trimethoprim and tetracycline had the highest concentrations in fish muscle and gills among all the pharmaceutical compounds. This could be due to the high concentrations of trimethoprim and tetracycline in sediment and macroalgae species in Tudor creek.[56] In addition, the acid dissociation constant (pK_a) may influence the bioaccumulation of trimethoprim and tetracycline in organisms.

Human health risk assessment

Risk assessment was conducted based on the amount of pharmaceuticals bioaccumulated by fish along Tudor creek. Table 4 shows the EDI, ADI, and THQ values for the average exposure scenarios to the studied pharmaceuticals in the communities (Ganahola, Simitini, and Bandarini) along Tudor creek, who depend on fish as a source of protein. The EDI of pharmaceuticals through fish consumption ranged between 1.01–1441.7 ng kg^{-1} bw per day. Ganahola, Simitini and Bandarini residents were exposed to trimethoprim (1441.7 ng kg^{-1} bw per day) and tetracycline (979.26 ng kg^{-1} bw per day). The THQ values of trimethoprim, tetracycline, and caffeine were greater than 5%, which potentially signifies that consumption of these fish could pose a potential human health risk. In contrast, the risk associated with fish consumption containing acetaminophen, sulfamethoxazole, and erythromycin was negligible. Shaaban and Mostafa[51] also observed that the antibiotics detected in the fish species from Saudi Arabia did not pose a potential human health risk from fish intake. In contrast, the findings of Mello, Cunha[52] in the Brazilian coastal area show that adult Brazilian fish consumers are unlikely to experience adverse health effects from pharmaceuticals through the consumption of different fish species. It should be noted that guidelines or standards that provide crucial information on the risk assessment of pharmaceuticals are only available for a few types of pharmaceuticals. Several uncontrollable factors, such as variations in metabolism, personal health habits and underlying health conditions, and dietary behaviours influence human health risks. Additionally, pharmaceuticals may also be inadvertently consumed through other food sources.

A household survey conducted in the villages of Ganahola, Simitini, and Bandarini along Tudor Creek revealed that fish consumption is prevalent among residents. Notably, pharmaceutical contaminants, particularly trimethoprim and tetracycline, were detected at elevated concentrations in the muscle and gill tissues of various fish species from Tudor creek. Regular consumption of such contaminated fish could lead to the bioaccumulation of these substances in humans, posing significant health risks over time. Exposure to tetracycline has been associated with various adverse health effects, including oxidative stress, alterations in behavior, and disruptions to the digestive, nervous, and immune systems in aquatic organisms. These effects may also extend to humans consuming contaminated fish, potentially leading to similar health issues.[59] Previous studies have reported that pharmaceuticals in fish can reach significantly higher concentrations in plasma than in ambient water.[20,60,61] This can be attributed to the fact that the pharmaceuticals can be taken up by fish from the gills, skin or food, leading to enhanced levels of the pollutant in fish tissue.[17,18,62]

Conclusion

The results of the present study provide new information on the concentrations of pharmaceuticals in the muscles and gills of different fish species from Tudor creek for the first time. This study shows that diverse commonly prescribed pharmaceutical compounds are present at detectable, and even quantifiable, concentrations in fish. This is attributed to anthropogenic activities, including direct and indirect sewage discharges into Tudor creek, which contribute to the introduction of pharmaceuticals into the oceanic environment and their accumulation in various edible fish species.

Fish consumption is common among households in Ganahola, Simitini, and Bandarini in Tudor creek, with most residents consuming less than 0.5 kg per day. These households may be at risk of pharmaceutical exposure through fish consumption. Risk assessment based on the calculated THQ indicated that a high THQ value (>5%) suggests potential human health risks from consuming fish from Tudor Creek, particularly due to exposure to trimethoprim, tetracycline, and caffeine. Pharmaceuticals can remain bioavailable to aquatic organisms for extended periods due to pseudo-persistence and may even re-enter the food web over time. Given these potential risks, it is crucial to conduct comprehensive risk assessments and implement strategies to mitigate pharmaceutical contamination in aquatic environments. The exposure to these pharmaceuticals through fish consumption by the households in Ganahola, Simitini, and Bandarini in Tudor creek is a cause of concern, highlighting the need for in-depth investigations, future monitoring and the promotion of proper disposal and management of pharmaceuticals to ensure the safety of local fish consumers. Additionally, a detailed ecological understanding is necessary to comprehend the accumulation and dispersion of pharmaceuticals within aquatic food webs.

There is a necessity to increase public awareness regarding the impact of pharmaceutical discharges into aquatic and marine environments. Additionally, it is imperative to develop and enforce policies and regulations for pharmaceutical disposal to prevent adverse effects on the sustainability of our marine ecosystems and the livelihoods and well-being of people who depend on these environments. Addressing the issue responsibly requires collaboration among governments, industries, communities, and individuals to ensure the long-term health of our oceans and coastal areas.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

VWO Wanjeri: Conceptualization, methodology, validation, formal analysis, writing original draft. E Okuku: Conceptualization, formal analysis, resources, review & editing, supervision. JC Ngila: Writing – review & editing, supervision. E Waiyaki: Methodology, validation, investigation. JK Nyingi: Methodology, validation, investigation, resources. PG Ndungu: Formal analysis, resources, writing – review & editing, supervision, project administration.

Conflicts of interest

There are no conflicts to declare.

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