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Spectrum and environmental risks of residual pharmaceuticals in stream water with emphasis on its relation to epidemic infectious disease and anthropogenic activity in watershed

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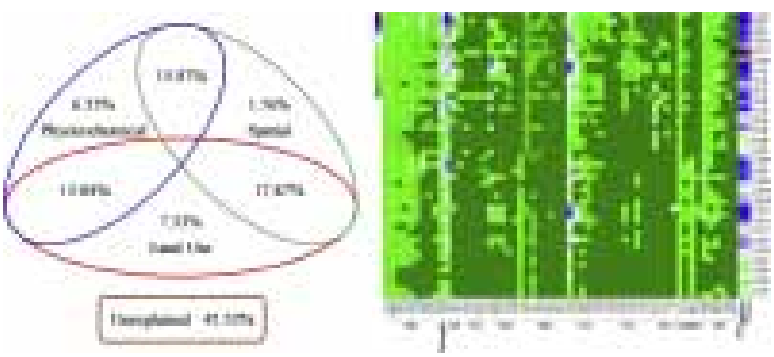
GRAPHICAL ABSTRACT



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ABSTRACT

Pharmaceuticals vastly consumed by modern human for health and food might track anthropogenic impacts on aquatic ecosystem via their wide residual spectrum. This study investigated the spectrum of pharmaceutical residuals in stream water at confluence point of each subwatershed with various land use pattern in Jiulong River watershed, southeastern China. Stream water was sampled in both wet and dry seasons of 2016. Results showed that 59 out of the selected 94 compounds from 6 pharmaceutical categories were quantified among these stream water samples, up to 1488 ng L^{-1} for caffeine (CAF). Antibiotics and central nervous system drugs (CNs) collectively dominated the quantified instream pharmaceutical residuals. Outbreaks of epidemic infectious diseases for human and livestock partially but significantly matched seasonality of instream pharmaceutical residuals. Anthropogenic impact as land use composition of subwatersheds was significant on instream pharmaceutical loadings, especially urban land use. Cocktail risk of instream pharmaceutical residuals to aquatic organisms was assessed ranging from low to medium among the subwatersheds except high risk for the W-01 subwatershed in the dry season. Evidence from this study indicated that seasonality and wide spectrum of instream pharmaceutical residual determination could reveal anthropogenic impacts to aquatic ecosystem, such as epidemic disease and land use.

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1. Introduction

In recent years, pharmaceuticals have been of great concern as emerging contaminants due to their consecutive consumption, elevated occurrence, and possible threats to aquatic environment and human health (Boxall et al., 2012; Daughton, 2004; Daughton and Ternes, 1999). Various kinds of pharmaceuticals, such as antibiotics, endocrine and family planning drugs, non-steroidal anti-inflammatory drugs, central nervous system drugs, cardiovascular drugs, and antiparasitic drugs, have been frequently detected in the aquatic environment (Zhang et al., 2015; Jiang et al., 2013; Kumar et al., 2015; Sim et al., 2011; Chen et al., 2013; Alder et al., 2010; Sim et al., 2013; Bu et al., 2013; Liu and Wong, 2013; Kolpin et al., 2002). Their residues in streams have been proved to relate to natural factors (e.g. precipitation and temperature) and anthropogenic factors (e.g. aquaculture and livestock production, land use pattern, and epidemic diseases outbreaks) (Davis et al., 2006; Luo et al., 2011; Li et al., 2016; Hong et al., 2018; Fisman, 2007). Temporal variations of pharmaceutical residuals (mainly antibiotics) in concentration and composition in stream water were found due to the seasonal rainfall (Jiang et al., 2013; Davis et al., 2006; Luo et al., 2011; Li et al., 2016; Hong et al., 2018) and their spatial heterogeneities were confirmed to relate to the type and intensity of human activity (Bu et al., 2013; Liu and Wong, 2013; Li et al., 2016; Hong et al., 2018). Furthermore, our previous study found that several specific pharmaceuticals (e.g. theophylline cure for asthma and ibuprofen for pain, fever, and inflammation) might be related to seasonal epidemic diseases outbreaks (Hong et al., 2018). However, these studies did not comprehensively explore how the spectrum of pharmaceutical residuals in stream water related to epidemic diseases outbreaks and function of subwatershed development as well, which were critical for tracing the sources of specific pharmaceuticals and understanding urbanization effect on instream pharmaceutical residuals.

Environmental residuals of pharmaceutic compounds posed potential ecosystem impacts on antibiotic resistance, endocrine disruption, and microbial community structure and function (Zhu et al., 2017; Oaks et al., 2004; Xi et al., 2015; Kümmerer, 2008). Due to lack of the spectrum of pharmaceutical residuals in a given analytical sample and the proper approaches for mixture toxicity assessment, environmental risks of pharmaceuticals were still often assessed substance-by-substance and mixture effects were neglected, resulting in risk

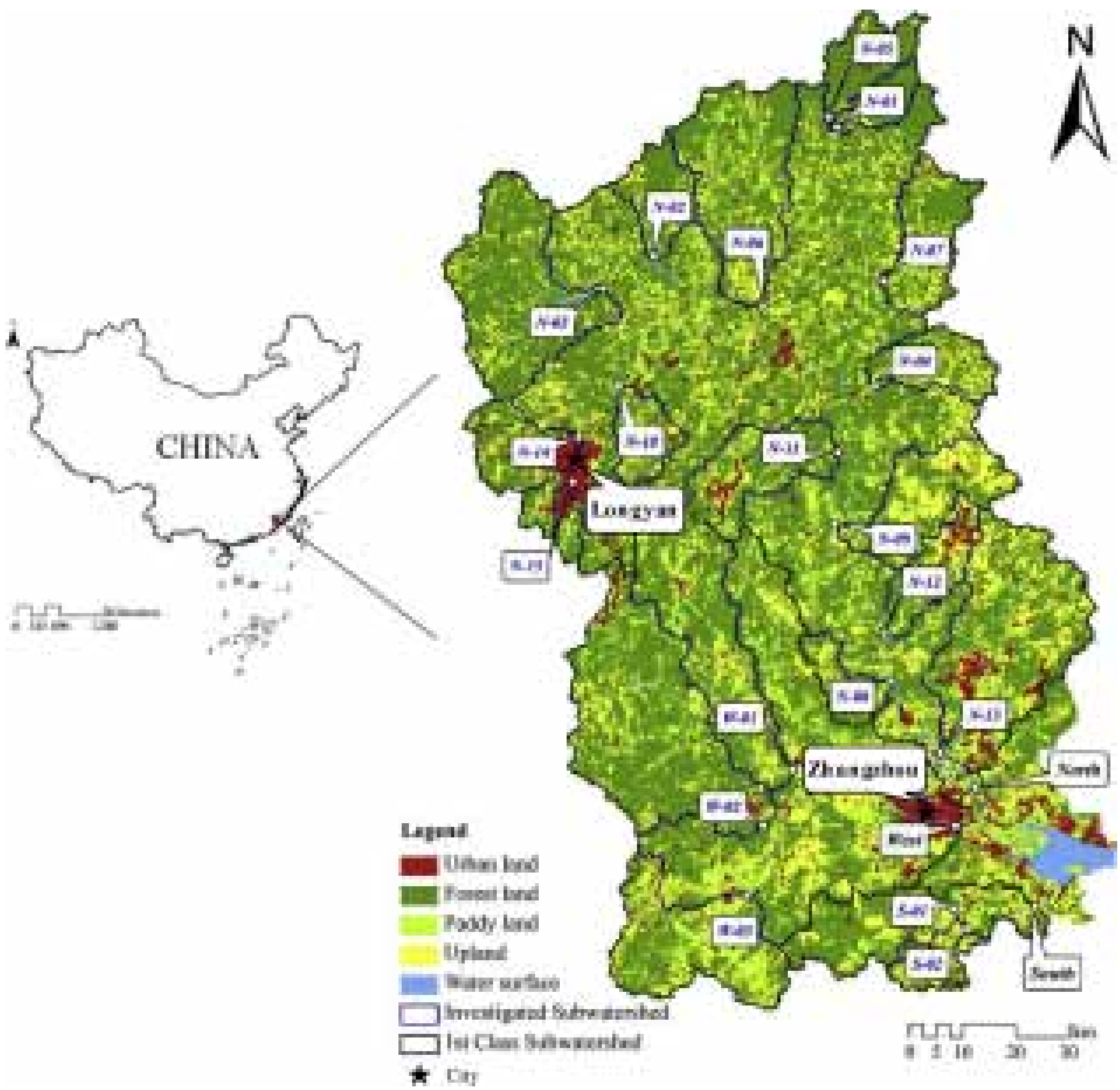

Fig. 1. Locations of the Jiulong River watershed in southeastern China and its three 1st class subwatersheds and twenty functional watersheds with various land use patterns.

underestimations, because analytical monitoring surveys routinely confirmed that organisms in the environment were exposed to complex multicomponent pharmaceutical mixtures (Sanderson et al., 2004; Backhaus and Karlsson, 2014). Recently, (Backhaus and Faust (2012)) used the two well established mixture toxicity concepts (Concentration Addition (CA) and Independent Action (IA)) for providing a tiered outline for environmental hazard and risk assessments of mixtures, and succeed to screening level mixture risk assessment of pharmaceuticals in STP effluents (Backhaus and Karlsson, 2014). However, few studies focused on environmental risks of pharmaceutical residuals' spectrum in stream water and their interactions with outbreaks of epidemic infectious diseases and human activities in watersheds. Actually, these pharmaceutic compounds were designed for epidemic infectious diseases cures, human medication uses in urban areas, and livestock and aquaculture uses in rural areas, while their continuous uses and/or abuses conversely led to environmental risks to aquatic environment where they were directly or indirectly released.

Objectives of this study are to seek the spectrum of pharmaceuticals in stream water and explore its spatiotemporal variation relating to epidemic diseases outbreaks, precipitation, and anthropogenic activity (land use pattern) in watersheds under an urbanization gradient. Based on existing researches, it was hypothesized that concentration and composition of instream pharmaceuticals' spectrum would be associated with land use patterns in subwatersheds relating to human activities, such as human medication uses in urban areas and animal farming uses and agricultural application of pharmaceutical contaminated sludge/composts in rural areas. Epidemic infectious diseases might also differentiate the contribution of instream pharmaceutical in subwatershed due to their seasonal outbreaks (Hong et al., 2018). Environmental risks of pharmaceutical residuals' spectrum in stream water might be underestimated by assessing substance-by-substance and relate to anthropogenic activity (land use pattern) in watersheds. This study employed Jiulong River as the research watershed and selected 20 functional subwatersheds and 3 first-class subwatersheds to generate the anthropogenic activity gradient of urban land use pattern (Fig. 1). Jiulong River, the second longest river in Fujian Province, southeast China, plays a key role in the region's economic growth and ecological environment, while has experienced continuing degradation in water quality in the past two decades (Huang et al., 2014). The incredible number and intensity of pharmaceutical residues were observed in Jiulong River (Jiang et al., 2013; Chen et al., 2013; Hong et al., 2018), indicating that pharmaceutical contamination and its spectrum should be strongly considered here. Therefore, an analytical methodology for the simultaneous determination of a total of 94 pharmaceutical compounds from 6 categories, was developed based on solid phase extraction and high-performance liquid chromatography tandem mass spectrometry and then the spectrum of pharmaceuticals was identified in the Jiulong River at a subwatershed scale along a gradient of anthropogenic impacts in wet (August 2016) and dry (December 2016) seasons.

2. Materials and methods

2.1. Stream water sampling and preparation

Stream water samples were taken above confluence points of three major tributaries and 20 functional subwatersheds of Jiulong River in both wet (August) and dry (December) seasons of 2016 (Figs. 1 and S1). The description of Jiulong River watershed and land-use classification were provided in the Supplementary materials (SM). Three replicates had been conducted cross the stream section at each sampling point. A 2-L stream water was collected at the 30-cm depth below the water surface using a 2.5-L brown glass bottle and a volume of methanol (5%, v/v) was added into the 2-L sample to inhibit microbial activities. All water samples were transported back to laboratory on ice, stored in a dark refrigerator at 4 °C, and processed within 24 h.

2.2. Chemical analysis

The chemicals preparation, extraction procedures, instrumental measurement, and quality assurance/quality control (QA/QC) measures and outcomes were provided in the SM.

2.3. Environmental risk assessment

The classic mixture toxicity concept of Concentration Addition was used to calculate the total expected risk of pharmaceutical residuals' spectrum in stream water of Jiulong River watershed, comparing the expected impact of anthropogenic activity (land use pattern) in each subwatershed and pinpointing the most sensitive group of species. Two approaches for calculating risk quotients for multicomponent pharmaceutical residuals referred to previous studies (Backhaus and Karlsson, 2014; Backhaus and Faust, 2012). The first approach calculated $RQ_{MEC/PNEC}$ on the basis of the sum of MEC/PNEC values, while the second one calculated RQ_{STU} on the basis of the sum of toxic units for the most sensitive trophic level. Since there was a general scarcity of publicly available ecotoxicological data of pharmaceuticals, such as the limited data on the chronic toxicity of most pharmaceuticals as well as the very few data available for in vivo fish toxicity (Sanderson et al., 2004; Backhaus and Karlsson, 2014), we used the Quantitative Structure Activity Relationship (QSAR) estimates for the EC50 values from the Ecological Structure Activity Relationships (ECOSAR) predictive model (US EPA (US Environmental Protection Agency), 2018), assuming a common mode of action of compounds from a similar chemical class. Differences in toxicity between members of a chemical class were then assumed to be caused by differences in lipophilicity-driven uptake rates. Compounds were classified and their EC50 and lipophilicity (Log Kow) were estimated by ECOSAR (vers. 2.00) of the US EPA. Therefore, ecotoxicity estimates (EC50) for algae, daphnid, and fish were shown in the Table S5. The common criteria for interpreting the RQ or MRQ value was applied in this study and considered the following risk levels (European Commission, 2003), i.e. "no risk" with Log_{10} RQ < -2, "low risk" with -2 < Log_{10} RQ < -1, "medium risk" with -1 < Log_{10} RQ < 0, and "high risk" with Log_{10} RQ > 0.

2.4. Data process and statistical analysis

The heat map of risk quotients in stream water of Jiulong River watershed were generated using the R (version 3.3.3). All statistical analyses were conducted using SAS 9.2 for Windows® (SAS Institute Inc., Cary, USA). Details of multi-categories statistical analyses (i.e. one-way analysis of variance, two-sample paired t-test, principal component analysis, pearson correlation analysis, partial redundancy analysis, canonical correlation analysis coupling a redundancy analysis, and multiple linear regressions) were provided in the SM.

3. Results

3.1. Spectrum of pharmaceuticals

This study investigated the spectrum of pharmaceuticals in the Jiulong River at a subwatershed scale along a gradient of anthropogenic impacts in wet (August 2016) and dry (December 2016) seasons. Finally, 59 out of 94 pharmaceutical compounds from 6 categories, including 31 of 37 antibiotics, 9 of 16 CNs, 5 of 14 cardiovascular drugs (CVs), 4 of 12 endocrine and family planning drugs (EFs), 4 of 7 nonsteroidal anti-inflammatory drugs (NSAIDs), and 6 of 8 antiparasitic drugs (APs), were quantified in stream water from three 1st class subwatersheds and twenty subwatersheds of Jiulong River watershed (Table S1 and Fig. S2). Summed concentrations of quantified pharmaceutical compounds in stream water ranged from 40.4 to 2650 ng L^{-1} with a median of 328 ng L^{-1} (Fig. 2). Instream pharmaceutical residuals were dominated by antibiotics and CNs, collectively accounting for

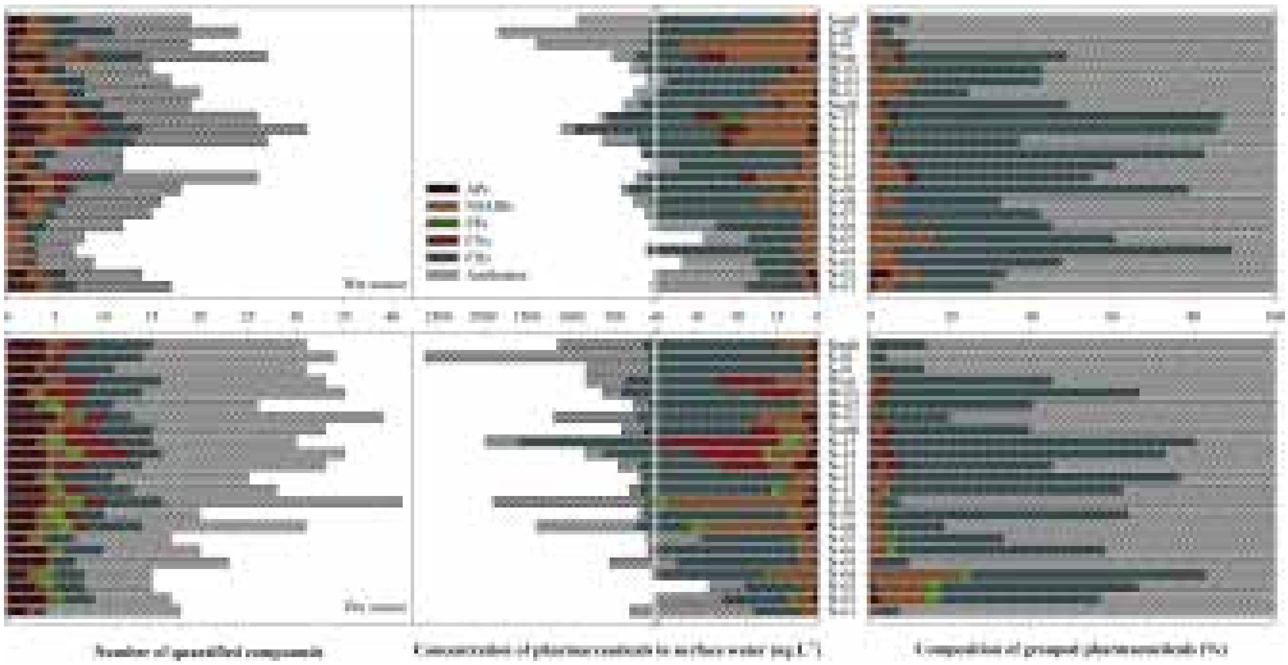

Fig. 2. Patterns of grouped pharmaceuticals in number (left), concentration (middle), and composition (right) in stream water of Jiulong River watershed during wet (August 2016) and dry (December 2016) seasons.

contributions of 75–100%, followed by NSAIDs (0.1–22%) and the rest 3 groups of APs, CVs, and EFs, collectively accounting for 0–6.4% (Fig. 2).

3.2. Spatiotemporal distribution

The number of quantified pharmaceutical compounds in stream water was lower in the wet season than that in the dry season (Fig. 2), as well as the number of quantified antibiotics (Fig. S3). Only SMX and CAF were detected in each subwatershed in both the wet and dry seasons. Except ETM, LIM, TTC, FFC, CFC, MFA, NPX, DCF, SCA, VST, and E1, quantified pharmaceutical compounds had lower frequencies in the wet season than the dry season (Fig. S2). Lower pharmaceutical residuals were observed in the wet season samples, ranging from 42.7 to 1824 ng L^{-1} with a median of 274 ng L^{-1}. Dry season sample residuals ranged from 40.4 to 2650 ng L^{-1} with a median of 461 ng L^{-1} ($p < 0.01$, Fig. 2). However, their compositions were similar and collectively dominated by antibiotics and CNs, accounting for contributions of 83–99% and 75–100% in the wet and dry seasons, respectively (Fig. 2).

Except for LCM and FBD in the wet season, residual concentrations of individual and grouped pharmaceuticals in stream water of both the wet and dry seasons showed significant differences among twenty-three subwatersheds from Jiulong River watershed, respectively ($p < 0.01$, Figs. 2,3, and S3). The highest summed concentrations of quantified pharmaceuticals in the wet and dry seasons were all found in S-02 of South stream (1824 and 2650 ng L^{-1}), as well as their dominant antibiotics (1723 and 2544 ng L^{-1}) with a dominant composition of SAs (80% and 76%) (Figs. 2 and S3). Compared to the domination of antibiotics and CNs in North stream and West stream, higher percentages of antibiotics (> 86%) were found in South stream (Fig. 2). In addition, the residual concentration of individual pharmaceutical compound in stream water of the wet and dry seasons well discriminated twenty-three subwatersheds using principal component analysis, explaining 26% and 19% of variations by component 1 and 2, respectively (Fig. S4). In both the wet and dry seasons, residual concentrations of most human only pharmaceuticals significantly drove the separation of N-14 and N-15, while concentrations of all veterinary only pharmaceuticals led the separation of S-01, S-02, and South (Table S6 and Fig. S4).

3.3. Correlations between instream pharmaceutical residues and anthropogenic, spatial, and environmental factors

Except for TCs, FQs, and EFs, pharmaceutical concentrations were negatively correlated with forest land use percentage in the investigated subwatersheds, regardless of season ($p < 0.05$, Table 1). Instream concentrations of CNs, CVs, and EFs showed exclusively and significantly positive correlations with urban land use percentage for both seasons ($p < 0.01$, Table 1). The percentages of rural land use and water surface in the subwatersheds had similar and positive correlations with instream concentrations of SAs, TMP, CPs, MLs, and NSAIDs, but higher in the wet season ($p < 0.01$) than the dry season ($p < 0.05$, Table 1). Furthermore, pharmaceutical concentrations in both the wet and dry seasons were significantly related to physicochemical properties of stream water with positively relating to specific conductance, salinity, and chlorophyll *a*, but negatively to turbidity and luminescent dissolved oxygen ($p < 0.05$, Table 1). The spatial factor of elevation showed significantly negative correlations with instream concentrations of SAs, TMP, CPs, TCs, and APs, but positive correlations with MLs, FQs, CNs, CVs, and EFs ($p < 0.05$, Table 1).

Results of partial redundancy analysis (pRDA) showed that over 50% of the observed variation in pharmaceutical residues was explained by selected factors, and anthropogenic factor (i.e. land use composition) was the most important contributor to the variance of pharmaceutical residues (Fig. 4). Environmental and spatial factors contributed 37.46 and 35.50% of the total variance, respectively. Moreover, anthropogenic factor contributed 7.33% alone and 32.91% together with its interactions with environmental and spatial factors of the total variance in pharmaceutical residues (Fig. 4). Consequently, anthropogenic activity appeared to be the major driver of spectrum and distribution of pharmaceutical residues in the investigated watersheds of Jiulong River. However, 45.52% variation in pharmaceutical residual profiles was unexplained.

3.4. Environmental risk assessment

Due to the unavailable toxicology data for LCM, only 58 quantified pharmaceutical compounds were calculated for risk quotients (RQs). A

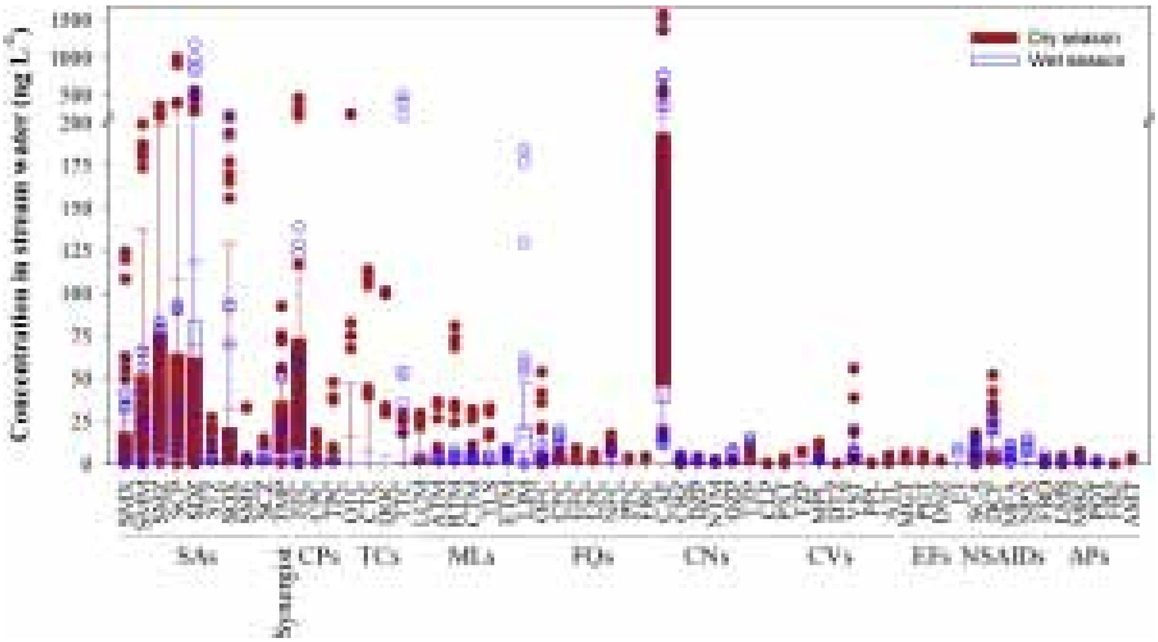

Fig. 3. Spatiotemporal distribution of fifty-nine quantified pharmaceutical compounds in stream water of Jiulong River watershed during wet (blue) and dry (red) seasons of 2016. The boxplot showed the median, 10th, 25th, 75th, and 90th percentiles as vertical boxes with error bars and each outlier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

majority of quantified instream pharmaceutical compounds had Log_{10} RQ < -2, suggesting no risk to aquatic organisms regardless of the dry and wet season sampling events (Fig. 5). The high risk was only found in West stream (W-01) of Jiulong River in the dry season, with the highest RQ of AMT up to 2.64 (Fig. 5). FFC and CAF might pose medium risks to aquatic organisms while SQX, TMP, CPC, TPC, ATM, RTM, CTM, CBZ, PXT, MFT, E1, PBD, and MBZ posed low risks (Fig. 5). It was obvious that, toxic unit values (TU, MEC/EC50) of most pharmaceuticals were larger for algae than dophnid and fish, revealing algae consistently being the most sensitive trophic level to pharmaceutical residues (Fig. S5). The ratio between the $MRQ_{MEC/PNEC}$ and MRQ_{STU} values never exceeded 1.35 in all subwatersheds. The Maximum Cumulative Ratio (MCR), which was the ratio between the most risky compound and the total mixture risk, varied between 1.02 and 6.71, depending on the actual scenario and species group under consideration (Fig. S5). The ratio STU/median (TU), i.e. the ratio between the risk of an median mixture component and the complete mixture, easily exceeded a factor of 1000 (Fig. S5), emphasizing the importance of systematically analyzing the overall risk of pharmaceuticals' spectrum in the Jiulong River watershed in order to end up with a realistic risk estimate. Furthermore, except for West stream (W-01) in the dry season, the base-10 logarithm of mixture risk quotients generally exceeded −2, but were below 0 (Fig. 5), indicating a potential but no high risk for each subwatershed in the Jiulong River.

4. Discussion

Seasonality has played a much broader role in general population dynamics and its strength and mechanism can alter the spread and persistence of infectious diseases (Altizer et al., 2006). The seasonality of epidemic infectious diseases (e.g. influenza) has been assumed to determine the amount and type of anti-infection medicine usages, resulting in seasonal pharmaceutical residues in the environment (Hong et al., 2018; Fisman, 2007). In the dry season (December 2016), human beings frequently suffered from natural focal and insect-borne infectious diseases (e.g. Black fever (HBF), Echinococcosis (HEC), and Epidemic hemorrhagic fever (HHF)) (Fig. 6) and widely selected the symptomatic antiparasitic drugs (APs) to cure these diseases. Interestingly, APs had significant elevations of residual concentrations ($p <$ 0.01, Fig. 2) and correlations with rural and urban land use percentages ($p < 0.05$, Table 1) in stream water of the dry season than those in the wet season, as well as fluoroquinolones (FQs) curing the secondary infection of human respiratory infectious diseases (H7N9 Avian influenza (HHN) and Avian influenza (HAI)) (Table 1 and Figs. S3 and 6). Bethony et al. (2006) pointed out that the benzimidazole anthelmintics, mebendazole (MBZ) and albendazole (ABZ), were commonly used for large-scale prevention of morbidity in children living in endemic areas. Sim et al. (2013) found that human sanitary waste was one of principal sources of anthelmintics to aquatic environment with albendazole and flubendazole (FBZ) being the most dominant in the human sanitary waste, sewage, and hospital wastewater treatment plants. In this study, MBZ and FBZ also had significant elevations of residual concentrations and detection frequencies in stream water of the dry season that those in the wet season in Jiulong River watershed (Figs. S2 and 3). Polgreen et al. (2011) showed that outpatient use of respiratory fluoroquinolones was extremely seasonal and strongly associated with influenza activity.

On the other hand, in the wet season (August 2016), macrolides (MLs, e.g. LCM, CTM, RTM, ATM, and ETM) were widely used to cure human infectious diseases of natural focal and insect-borne (e.g. Anthrax (HAT)), blood-borne and sexually transmitted (e.g. Syphilis (HSP) and Gonorrhoea (HGR)), intestinal (e.g. Bacterial and amoebic dysentery (HAD)), and respiratory infectious diseases (e.g. Pertussis (HPT)), accounting for higher percentages and significantly relating to rural and urban land use percentages ($p < 0.01$, Table 1 and Figs. S3 and 6). Hansen et al. (2002) suggested that macrolides were a valuable class of antimicrobial agents and played an important role in the management of infectious diseases. Furthermore, compounds from sulfonamides (SAs, e.g. SMZ, SMX, SDZ, SCP, and SMM) and their synergist (TMP), and chloramphenicols (CPs, e.g. TPC and FFC), wide uses for veterinary and aquaculture (Table S6), had significant elevations of correlations with rural land use percentage in the wet season when livestock diseases (e.g. Brucellosis (SBL) and Avian cholera (CAC)) break out and with water surface when fish diseases (e.g. bleeding, fin rotting, enteritis, and red skin disease) mostly take place ($p <$ 0.01, Table 1 and Fig. 6). The sulfonamides have been used

Table 1
Correlations between instream concentrations of grouped pharmaceuticals and anthropogenic, environmental, and spatial factors in the subwatersheds during the wet (August 2016) and dry (December 2016) seasons in the Jiulong River watershed, southeast China, explored by Pearson Correlation Analysis (N = 69).

Compound	Wet season									
	Land use composition (%)				Physicochemical property					Spatiality
	Forest land	Rural land	Urban land	Water surface	Specific conductance	Salinity	Chlorophyll *a*	Turbidity	Luminescent dissolved oxygen	Elevation
SAs	-**	**		***	***	***	***	-***	-***	-**
synergist	-***	***		***	***	***	***	-***	-***	-**
CPs	-**	**		***	***	***	***	-*	-***	-***
TCs								-*		-*
MLs	-***	**	**	***	***	**	***		-***	
FQs	**	-***			-*	-**		**		**
CNs	-*		***							
CVs	-*		***		***	***				
EFs			***							**
NSAIDs	-***	**	**	**	**	**		-**		-*
APs				**	*	**	**			

Compound	Dry season									
	Land use composition (%)				Physicochemical property					Spatiality
	Forest land	Rural land	Urban land	Water surface	Specific conductance	Salinity	Chlorophyll a	Turbidity	Luminescent dissolved oxygen	Elevation
SAs	-*	*		**	***	***	***	-***	-***	-**
synergist	-*						*	-**	-***	
CPs	-**	*		***	**	**	***	-***	-***	-**
TCs					***	***				
MLs	-*		***		***	***			-*	*
FQs			***		***	***			-**	*
CNs	-**		***							*
CVs	-**		***							*
EFs			**	-***				**		**
NSAIDs					***	***				
APs	-*	*	*		***	***	*		-**	

*, **, and *** represented significance levels of $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively; “-” represented “negative correlation.

extensively in veterinary medicine both for prophylaxis and therapy of livestock infectious disease (Riviere et al., 1991). Similarly to our previous study (Hong et al., 2018), NSAIDs had a significant elevation of concentrations in the wet season sampling event in comparison to that in the dry season ($p < 0.01$, Fig. 2), and were also significantly correlated to rural and urban land uses of the subwatersheds during the wet season ($p < 0.01$, Table 1), most likely due to more frequent outbreaks of influenza and fever in the wet season. Additionally, most epidemic infectious diseases were highly correlated to the canonical variables of instream individual pharmaceutical compound in the dry and wet seasons, while individual pharmaceutical compound showed quite low relations to epidemic infectious diseases (Table S7), indicating that epidemic infectious diseases didn't dominate the sources of instream pharmaceuticals in the Jiulong River watershed, because seasonal epidemic infectious diseases couldn't play more roles than other common diseases or anthropogenic activities (e.g. aquaculture and livestock production, and land use pattern). Therefore, these findings were in agreement to the hypothesis, i.e. outbreaks of epidemic infectious diseases for human and livestock partially but significantly matched seasonality of the instream pharmaceutical residuals.

Besides the seasonal effect by epidemic infectious diseases, we have also observed the seasonal dilution effect by rainfall on pharmaceutical residues in number of quantified compounds, detection frequency, residual concentration and composition in stream water, i.e. generally significant lower in the wet season than the dry season ($p < 0.05$, Figs. 2,3, S2, and S3), which were similar to those found in wastewater (Yu et al., 2013), stream water (Hong et al., 2018), reclaimed wastewater and even drinking water (Loraine and Pettigrove, 2006).

Anthropogenic activities, including population explosion, urbanization, industrialization, and land management policy, motivated land use change to meet the need of food, water, and land resources (Foley et al., 2005; Martinuzzi et al., 2014). Particularly, land use patterns could represent the diversity and intensity of anthropogenic activities, such as urbanization referred to urban land uses, agriculture and livestock production involved rural land uses, and aquaculture related to water surface. They have been successfully used as anthropogenic factors in combination with multivariate statistics in source identification of pharmaceuticals (Li et al., 2016; Hong et al., 2018). Our data suggested that anthropogenic activities might act strongly on the spectrum and distribution of pharmaceutical residues in the Jiulong River watershed (Table 1 and Fig. 4). The increase of human activity and intensity in the investigated subwatersheds of Jiulong River from low to high urban land uses in the North stream and high rural land uses in the South stream might be an important reason for the increasing elevations of characteristics human and veterinary pharmaceutical residues in stream water, respectively (Fig. 7). Furthermore, physicochemical factors had an influence on pharmaceutical residues (Table 1 and Fig. 4) due to the fact that pharmaceuticals described a large class of chemical contaminants with large variations in physicochemical properties (e.g. pKa, Kow, and water solubility). These physicochemical factors of stream water (e.g. pH, organic matter, and salinity) had been proved to affect the occurrence (Nakada et al., 2008), sorption (Oh et al., 2016), and gradation (Oliveira et al., 2019) of pharmaceutical residues in aquatic environment. In addition, it should be noted that the large variation (45.52%) in pharmaceutical residual profiles cannot be explained by pRDA. We assumed that this high proportion of unexplained variation could be related to the selection of unavailable socio-economic parameters (e.g. population, GDP, livestock and aquaculture production, and pharmaceuticals usages) in this study.

In the present study, concentrations (up to 61 and 95 times) and contributions (up to 3 and 18 times) of characteristic human only pharmaceuticals generally increased in stream water of the wet and dry seasons from North stream (N-01 - N-15) except for N-05, N-07, N-08, and N-10 along an increasing gradient of urban land use in the subwatershed (Fig. 7), and residual concentrations of most human only pharmaceuticals, such as RTM, CPC, CAF, MPL, and CBZ, significantly

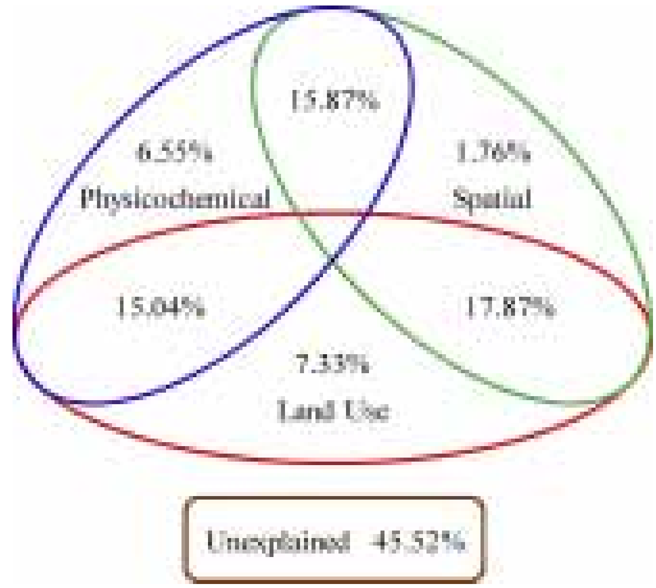

Fig. 4. Partial redundancy analysis (pRDA) differentiating the effects of anthropogenic (land use composition), spatial (elevation, PCNM1, and PCNM4), and environmental factors (specific conductance, salinity, turbidity, and luminescent dissolved oxygen) on pharmaceutical residues in stream water of Jiulong River watershed.

drove the separation of N-14 and N-15 (high percentages of urban land, namely Longyan urban areas) (Table S6 and Figs. 1 and S4), indicating that human only pharmaceuticals served as the major contributor of instream pharmaceuticals in urbanized areas, which have been identified from anthropogenic sources in urbanized regions (Arlos et al., 2014; Fairbairn et al., 2016). It could be explained by the fact that urban land use showed the highest correlations with instream pharmaceuticals' concentration and composition (i.e. EFs, CVs, CNs, MLs, and FQs) ($p < 0.01$, Tables 2) and had positive parameter estimates and high contributions to R^2 (50% and 64%) for human only pharmaceuticals in the multiple linear regression models of the wet and dry seasons (Table S8), resembling the patterns of 3 categories (i.e. antibiotics, non-steroidal anti-inflammatory drugs, and respiratory system drugs) in our previous study (Hong et al., 2018). Hanamoto et al. (2018) has succeeded in predicting the instream loadings of 12 WWTPs-derived pharmaceuticals by human population in a Japanese watershed.

On the other hand, high contributions of characteristic veterinary only pharmaceuticals increased from 9.5% to 24.1% and 38.3% to 59.5% in stream water of the wet and dry seasons in South stream with the increasing gradients of rural land uses (Fig. 7), and concentrations of all veterinary only pharmaceuticals (i.e. TLS, FFC, SCP, SQX, SCZ, EFC, FBZ, FBD, and AMT) led the separation of S-01, S-02, and South (high percentages of water surface and rural land, namely Zhangzhou aquaculture and cropping areas) (Table S6 and Figs. 1 and S4), revealing veterinary only pharmaceuticals were rural characteristics due to frequent human activities, such as cropping, aquaculture and livestock production, occurred in rural areas. It could also be explained by the results that water surface and rural land had positive parameter estimates and relatively greater contributions to R^2 for veterinary only and aquaculture pharmaceuticals (Table S8). There were significantly positive correlations among residues of SAs, CPs, and APs (including many veterinary only pharmaceuticals) in stream water ($p < 0.05$), but not with CVs, CNs, and EFs (including most human only pharmaceuticals) (Tables S6 and S9), suggesting the unconformity of pharmaceuticals' sources. Hanamoto et al. (2018) observed that instream loadings of two veterinary drugs (sulfamonomethoxine (SMM) and lincomycin) were positively correlated with swine population in the

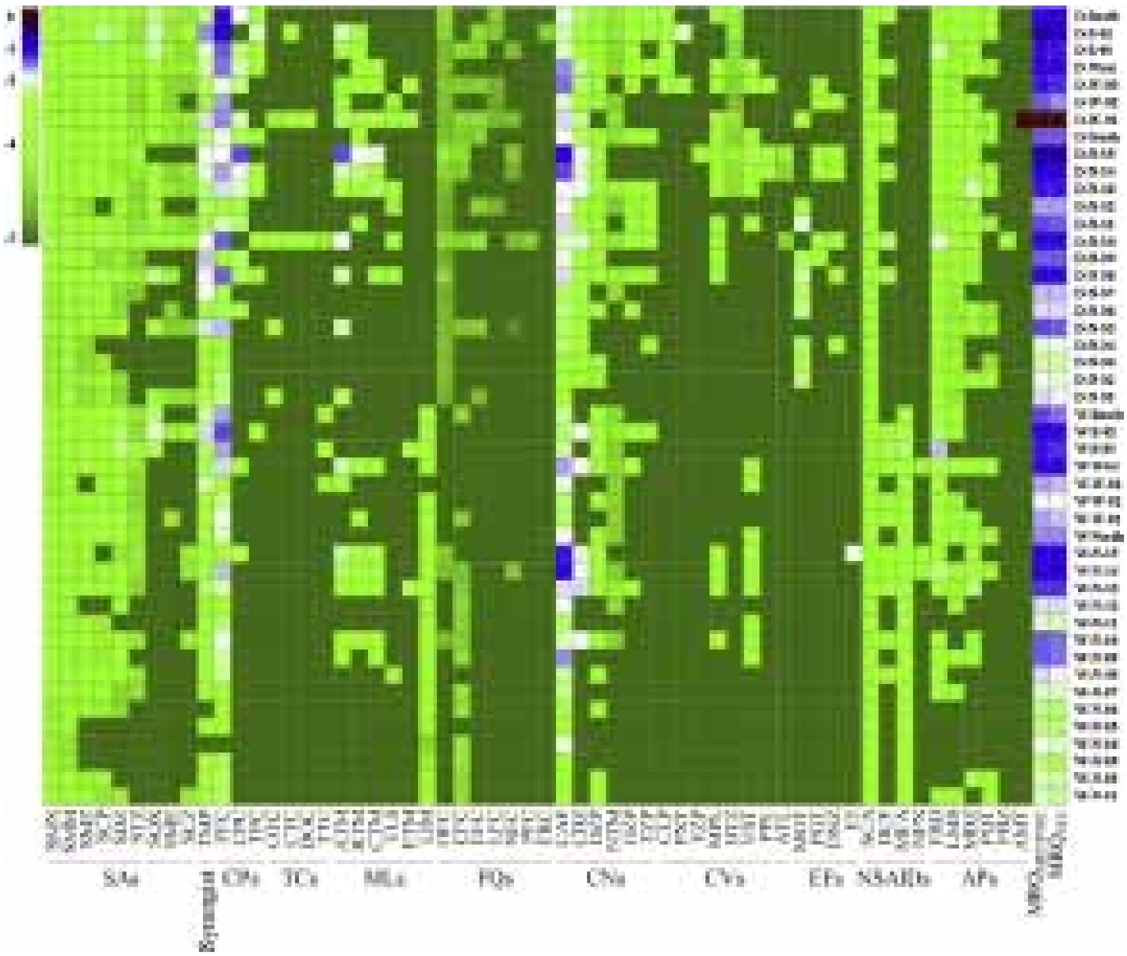

Fig. 5. Risk quotients (RQs) of 58 quantified pharmaceutical compounds and their mixture risk quotients (MRQs) in stream water of Jiulong River watershed during wet (with the capital W before the subwatershed logs along the Y axis) and dry (with the capital D) seasons of 2016. The legend denoted corresponding fold change values at a log scale.

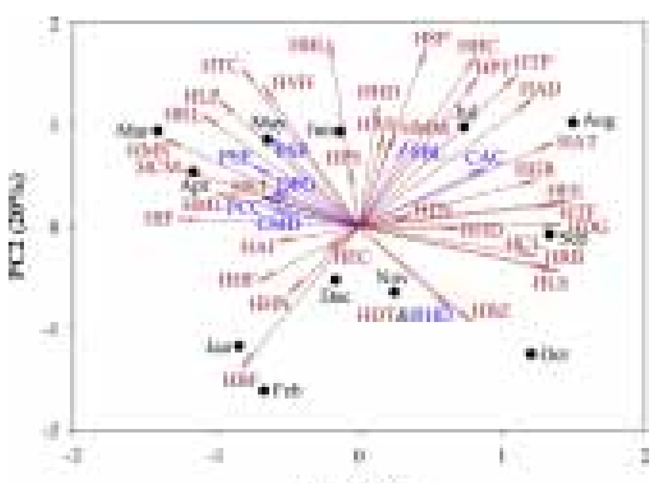

Fig. 6. Patterns of thirty-six human (red) and eight livestock (blue) infectious diseases outbreaks from January (shortened as Jan) to December (Dec) of 2016 in China, explored by Principal component analysis (PCA). Abbreviations of human and livestock infectious diseases referred to Table S7. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

watershed. Li et al. (2016) also found antibiotics discharges from aquacultural ponds via flooding or drainage to the Tiaoxi watershed, China during the wet season as well as in the Hai River watershed, northern China (Luo et al., 2011). Therefore, these findings were contributed significantly to confirm the hypothesis that anthropogenic activities (land use patterns) in the subwatersheds determined the spectrum and distribution of instream pharmaceuticals in concentration and composition.

In the present study, the spectrum of instream pharmaceutical residuals was quantified in functional subwatersheds of the Jiulong River watershed under anthropogenic impacts (Tables 2 and S8, and Figs. 2,3, S2, and S3). Residual concentrations of instream pharmaceutical compounds ranged from below the detection limits to ng L^{-1} (Fig. 3), which were lower than or comparable to those reported in other watersheds of China and the globe (Bu et al., 2013; Kolpin et al., 2002; Luo et al., 2011; Singh et al., 2019). The highest concentration of quantified pharmaceutical compound was found in stream water of the dry season at N-15 with the concentration of CAF up to 1488 ng L^{-1} (Fig. 3), which was similar to that found in the effluents but 1–2 orders of magnitude lower than that in the influents from municipal wastewater treatment plants, hospitals, and pharmaceutical manufactures (Sim et al., 2011). CAF was detected in stream water of both wet and dry seasons in all subwatersheds most likely due to popular tea drinking in the region, which had also been reported worldwide with high occurrence and was proposed as the biomarker for anthropogenic input into the aquatic environment (Kolpin et al., 2002; Wu et al., 2014). Considering its extensive detection, considerable residues, and potential toxicological

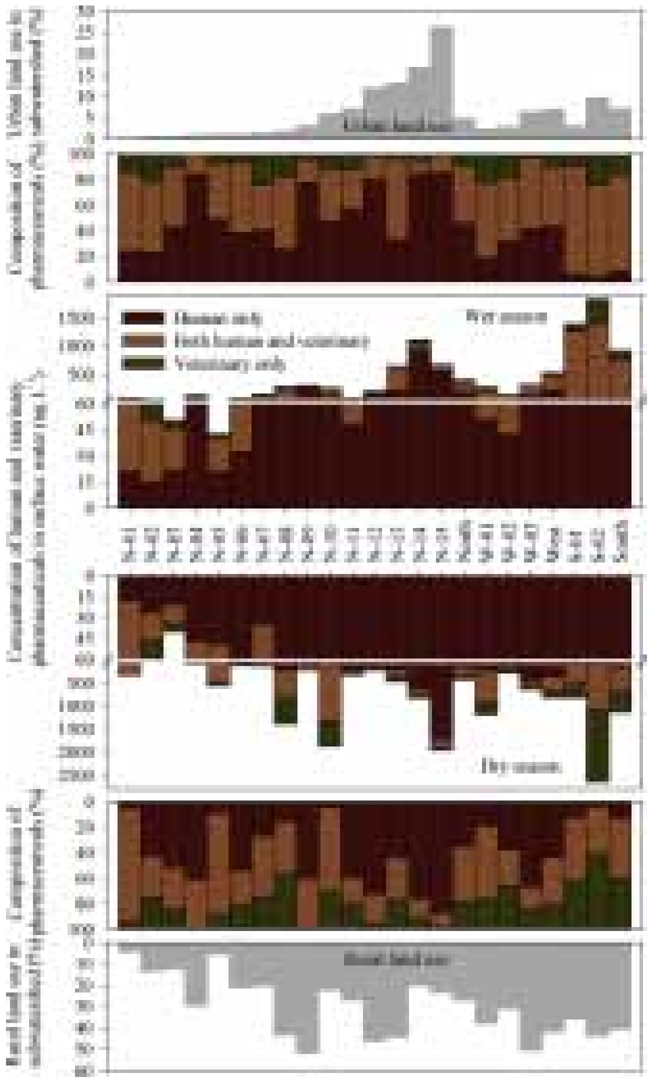

Fig. 7. Contributions of pharmaceuticals classified by human only, veterinary only, and both human and veterinary uses in stream water of Jiulong River watershed during wet and dry seasons of 2016.

effects, CAF was considered to pose low to medium risks to aquatic organisms in the Jiulong River watershed (Fig. 5). Interestingly, abamectin (AMT) was only found in stream water of the dry season with low detection frequency (4%) and residual concentration (3.30 ng L^{-1} at W-01), and estimated to pose high risk to aquatic organisms in the Jiulong River watershed (Figs. S2 and 5), which could be explained by the fact that AMT was highly toxic to aquatic invertebrates ($EC50 = 1.5\,\mu g\ L^{-1}$) and was rapidly biodegraded and photodegraded and even adsorbed by sediments (Ansara-Ross et al., 2008).

On the other hand, the remarkable positive correlation between $MRQ_{MEC/PNEC}$ and MRQ_{STU} values ($R^2 = 0.995$ and 0.999, $p < 0.001$) of multicomponent pharmaceutical residues in the Jiulong River watershed and their ratios, ranging from 1.02 to 1.35 and 1.00 to 1.32 in the wet and dry seasons, respectively (Fig. 5), were similar to those found in the downstream rivers of five sewage treatment plants in Nanjing, China ($R^2 = 0.9995$, $p < 0.0001$, and a ratio < 1.2) (Liu et al., 2015) and in seven European STP effluents (a ratio < 1.3) (Backhaus and Karlsson, 2014), which could be explained by the fact that the pharmaceuticals dominating the mixtures had a quite similar ecotoxicological profile, with algae consistently being the most sensitive trophic level (Backhaus and Karlsson, 2014). Therefore, using the mixture risk quotient (MRQ) expressed by $MRQ_{MEC/PNEC}$ and MRQ_{STU} was a practicable method to assess cocktail risks of pharmaceutical residuals in the environment if the toxicity profiles of the mixture compounds were similar, or if even all species had average similar sensitivities to the mixture components (Backhaus and Faust, 2012). According to Backhaus and Karlsson (2014), ignoring Independent Action or even using the sum of individual risk quotients instead of STUs as a rough approximation of Concentration Addition did not make a major difference for the final risk estimate. Additionally, even though a majority of quantified instream pharmaceutical compounds posed no risks, their mixture risks reached the levels ranging from low to medium in most subwatersheds of the Jiulong River (Fig. 5), indicating that environmental risks assessed substance-by-substance were remarkably underestimated, especially multicomponent pharmaceutical residuals occurred in subwatersheds. A similar result was observed in seven European STP effluents that the risk quotient of a randomly selected pharmaceutical was often more than a factor of 1000 lower than the total risk of the mixture (Backhaus and Karlsson, 2014). Noteworthily, as shown in Fig. 5, higher environmental risks (i.e. RQ for individual pharmaceutical compound and MRQs for multicomponent pharmaceuticals) were observed in the regions impacted by extensive human activities, such as Longyan urban areas (higher urban land percentages of N-14 and N-15) and Zhangzhou aquaculture and cropping areas (higher water surface and rural land percentages of S-01, S-02, and South), revealing that human activities released various pharmaceutical components directly or indirectly into the receiving environments and whereafter posed potential threats to aquatic organisms and even affected human health. Therefore, these findings were in agreement to the hypothesis, i.e. environmental risks of pharmaceutical residuals' spectrum in stream water were underestimated by assessing substance-by-substance and related to anthropogenic activity (land use pattern) in watersheds.

5. Conclusion

A wide spectrum and seasonality of instream pharmaceutical residuals were explored in the urbanizing watershed, southeastern China in the current study. Its spatial distribution of the instream pharmaceutical residuals along the urbanization gradient consisting of the subwatersheds was clearly associated to land use pattern, especially the urban land percentage. The seasonal matching between outbreak of human and livestock epidemics and specific pharmaceutical residuals in stream water, integrating the land use pattern, illustrates anthropogenic impacts on aquatic ecosystem in the studied watershed. Meanwhile, variations of the spectrum of instream pharmaceutical residuals among the subwatersheds also hint medication discrimination of human and livestock, routine living consumption (e.g. CAF) and abuse. Along the gradient of subwatershed urban land percentage in the North branch of the Jiulong River, non-significant linear increase of the instream human-use-only pharmaceutical residuals suggests that more considerations of anthropogenic factors should be taken, such as consumption, wealth, and population as well as more geographic and climate factors besides land use. To reveal more accurate interactions might require county-level data of epidemics and pharmaceutical consumption for further studies.

Declaration of Competing Interests

The authors declare that they have no known competing financial

Table 2
Explanations between anthropogenic land use patterns and grouped pharmaceutical concentrations in stream water of the wet (August 2016) and dry (December 2016) seasons in the Jiulong River watershed, southeast China, revealed by Canonical Redundancy Analysis (Proc CANCORR).

	Standardized Variance of the Land uses Explained by			Standardized First Variance of the Pharmaceuticals Explained by		
	Their Own Canonical Variables Proportion	R^2	The Opposite Canonical Variables Proportion	Their Own Canonical Variables Proportion	R^2	The Opposite Canonical Variables Proportion
Wet season	0.316	0.803	0.254	0.186	0.803	0.149
Dry season	0.378	0.863	0.326	0.244	0.863	0.210

Squared Multiple Correlations between the Land uses and the First M Canonical Variables of the Pharmaceuticals			Squared Multiple Correlations between the Pharmaceuticals and the First M Canonical Variables of the Land uses		
Land use	M1		Pharmaceutical group	M1	
	Wet season	Dry season		Wet season	Dry season
Urban land	0.756	0.824	Endocrine and family planning drugs	0.546	0.068
Rural land	0.005	0.026	Central nervous system drugs	0.499	0.619
Water surface	0.001	0.127	Cardiovascular drugs	0.413	0.656
			Non-steroidal anti-inflammatory drugs	0.089	0.017
			Macrolides	0.038	0.400
			Tetracyclines	0.020	0.007
			Antiparasitic drugs	0.017	0.071
			Fluoroquinolones	0.012	0.375
			Trimethoprim	0.004	0.029
			Chloramphenicols	0.003	0.065
			Sulfonamides	0.002	0.006

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 material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2019.121594.

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