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Contamination patterns and attenuation of pharmaceuticals in a temporary Mediterranean river

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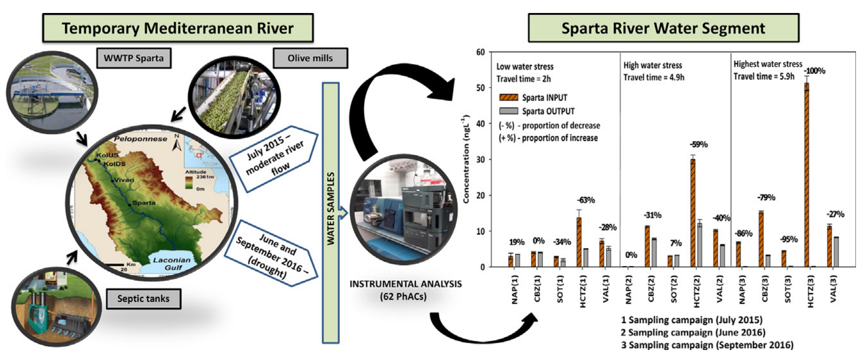
HIGHLIGHTS

- Variation of PhAC and nutrient concentrations relates to river flow variability.
- PhACs and nutrients are considerably higher downstream of the WWTP Sparta.
- Longer residence times accounts for higher in-stream attenuation of most PhACs

GRAPHICAL ABSTRACT



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ABSTRACT

The contamination patterns and fate of pharmaceutically active compounds (PhACs) were investigated in the Evrotas River (Southern Greece). This is a temporary river with differing levels of water stress and water quality impairment in a number of its reaches. Three sampling campaigns were conducted in order to capture different levels of water stress and water quality. Four sampling sites located on the main channel of the Evrotas River were sampled in July 2015 (moderate stream flow), and June and September 2016 (low stream flow). Discharge of urban wastewater has been determined as the main source of pollution, with PhACs, nutrients and other physicochemical parameters considerably increasing downstream the wastewater treatment plant (WWTP) of Sparta city. Due to the pronounced hydrological variation of the Evrotas River, generally, the highest concentrations of PhACs have been detected during low flow conditions. Simultaneously, low flow resulted in an increased water travel time and consequently longer residence time that accounted for the higher attenuation of most PhACs. The average decrease in total concentration of PhACs within the studied waterbody segment (downstream of Sparta city) increased from 22% in July 2015 to 25% in June 2016 and 77% in September 2016. The PhACs with the highest average concentration decrease throughout the sampling campaigns were hydrochlorothiazide, followed by sotalol, carbamazepine, valsartan, and naproxen.

Abbreviations: D.F., average detection frequency; D.O., dissolved oxygen; Dow, octanol-water distribution coefficient; ESI, electrospray ionization; Kow, octanol-water partition coefficient; LOD, limits of detection; LOQ, limits of quantifications; NI, negative electrospray ionization; OTC, over-the-counter; PCA, Principal Component Analysis; PhACs, pharmaceutically active compounds; PI, positive electrospray ionization; r, Pearson's moment correlation factor; SM, Supplementary material; SPE, solid phase extraction; SRM, selected reaction monitoring; UHPLC-QqLIT-MS/MS, ultra-high-performance liquid chromatography coupled to triple quadrupole linear ion trap tandem mass spectrometry; WWTP, wastewater treatment plant.

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1. Introduction

Mediterranean streams and rivers are characterized by inter-annual hydrological variations encompassing floods in spring and autumn and droughts in summer (Sabater et al., 2008), which in turn can cause headwater and middle-order streams to become intermittent, or even to dry out for an extended period (Lake, 2003). Consequently, temporary streams and rivers in the Mediterranean basin are amongst the most complex and dynamic freshwater ecosystems, and at the same time, highly fragile (Larned et al., 2010; Acuña et al., 2014a). These systems are affected by strong hydrological and anthropogenic pressures resulting from extensive water abstraction, river fragmentation and climate change (Larned et al., 2010; Acuña et al., 2014a; Skoulikidis et al., 2017). Water quantity pressures are further accentuated by nutrient enrichment and microcontaminants pollution from urban and industrial wastewaters, and by organic pollution from municipal wastewaters and agricultural activities (Meybeck, 2004; Vörösmarty et al., 2010). Amongst the microcontaminants, the use of pharmaceutically active compounds (PhACs) for both human and veterinary applications results in a vast array of products reaching aquatic environments. PhACs are a group of chemical substances with pharmacologic and physiologic properties and include all prescription, nonprescription, and over-the-counter (OTC) therapeutic drugs, in addition to veterinary drugs (Richardson and Ternes, 2005). Following their administration, PhACs are excreted as a mixture of parent compounds and metabolites that are usually more polar and hydrophilic than the original drug, while large fraction of these substances is discharged into the wastewater in the form of degradation products that are often poorly eliminated in conventional wastewater treatment plants (WWTPs, Gros et al., 2010; Ratola et al., 2012). PhACs are being discharged into the aquatic environment through different sources, i.e. human excretion, disposal of unused and expired drugs, agricultural and livestock practices (Halling-Sørensen et al., 1998; Boxall et al., 2012; Tijani et al., 2016), and reach the environment as treated or untreated wastewater discharges (Heberer, 2002; Vieno et al., 2005). Their continuous discharge into the aquatic environment makes the PhACs pseudo-persistent contaminants (transformation and removal rates are compensated by their continuous discharge into the environment), and as such may cause adverse effects on living organisms and the environment (Daughton and Ternes, 1999; Halling-Sørensen et al., 1998). For example, there is evidence that PhACs, such as antidepressants, psychiatric drugs, hormones, and antihistamines can induce behavioral changes in fish, affecting fish aggression, reproduction and feeding activity, thus, in turn, directly affecting individual fitness and indirectly affecting food webs and ecosystem processes (Schultz et al., 2011; Brodin et al., 2014; Sharifan and Ma, 2017).

Once released into the aquatic environment, PhACs undergo different in-stream attenuation processes (i.e. biotransformation, photolysis, sorption, volatilization). These processes are related to the specific characteristics of the PhACs, the physicochemical and biological parameters of the river (Gurr and Reinhard, 2006; Kunkel and Radke, 2008), and to the specific dilution capacity and water travel time within the study reach or waterbody (Rueda et al., 2006; Keller et al., 2014). There is, however, limited knowledge regarding the fate, behavior, and transport of PhACs in Mediterranean aquatic ecosystems, compared to other pollutants (Halling-Sørensen et al., 1998; Kolpin et al., 2002; Golet et al., 2002; Moldovan, 2006; Acuña et al., 2014b), while the functioning of in-stream attenuation mechanisms is not completely understood (Kunkel and Radke, 2011), particularly in the Mediterranean river systems (Al Aukidy et al., 2012; López-Serna et al., 2012; Stasinakis et al., 2012; Stamatis et al., 2013; Nannou et al., 2015). Also, few studies have detailed the fate and in-stream attenuation of PhACs during different seasons (Pal et al., 2010), especially together with the other organic micropollutants (Biales et al., 2015; Fairbairn et al., 2016; Garrido et al., 2016) and during heavy rainfall and floods (Pailler et al., 2009). However, concentration levels of PhACs in the Mediterranean streams and rivers depend as well on numerous factors such as the land uses and the hydrometeorological conditions. Therefore, reduced dilution capacity of Mediterranean streams and rivers during dry periods may result with the increased concentration levels of PhACs and other organic micropollutants (Almeida et al., 2014; Sabater et al., 2016), while due to an increased rainfall and subsequent dilution capacity during wet periods, generally lower concentration levels of PhACs may be expected (Kasprzyk-Hordern et al., 2009; Lacey et al., 2012; Papageorgiou et al., 2016). Though, during heavy rainfall events in the Mediterranean, flow augmentation, sediments resuspension, combined sewer overflows resuspension, and reduced hydraulic retention time in the WWTPs, leads to a particularly increased in-stream concentration levels of PhACs (Cowling et al., 2005; Sui et al., 2011; Osorio et al., 2012; Osorio et al., 2014; Corada-Fernández et al., 2017; Reoyo-Prats et al., 2018). Therefore, determining the PhACs concentrations and their fate mechanisms in the Mediterranean aquatic environment is important in order to assess their environmental risk (Boxall et al., 2012), particularly during drought and heavy rainfall events.

The main objectives of this study were to i) determine the concentration patterns of PhACs in a temporary Mediterranean river affected by agricultural and urban pollution; ii) estimate the recovery potential (natural in-stream attenuation of contaminants) in the water bodies studied, and iii) define the joint effects of hydrological (river flow) and chemical stressors (urban and agricultural pollution) on the occurrence and distribution of PhACs in this Mediterranean river.

2. Materials and methods

2.1. Study area

The study was conducted at the Evrotas River, a biogeographically isolated basin in the southernmost Balkan Peninsula, in Southern Peloponnese, Greece (Fig. 1). The Evrotas River is a large (2418 km^2), mid-altitude Mediterranean basin, with the river flowing unobstructed between the mountain ranges of Taygetos (2407 m a.s.l.) and Parnon (1904 m a.s.l.), and entering after 90 km into the Lakonian Gulf. Along the course of the Evrotas, numerous permanent and temporary karstic springs contribute to river runoff (Vardakas et al., 2015). The mountainous area of the basin is mostly formed by Mesozoic-Palaeogene limestone and impermeable rocks (schists and flysch), while the lower parts of the river basin are formed of extensive alluvial aquifers (Pliocene and Quaternary sediments, Skoulikidis et al., 2011). The Evrotas River Basin has an average annual temperature of 16 °C and a mean annual precipitation of 803 mm (2000–2008), with wet and cool winters and warm and dry summers (Nikolaidis et al., 2009). The combined effects of water abstraction and natural drought result in the partial desiccation of the river in late summer-early autumn (Skoulikidis et al., 2011).

The main sources of municipal sewage in the study area is the city of Sparta (population of 16,239), which has a sewage collection system (with not all of the households, however, connected to it) and WWTP that discharges treated effluents into the Evrotas River. The smaller communities upstream are served by septic tanks and cesspools. The Evrotas River, therefore, receives the treated sewage of Sparta and untreated wastewaters from nearby communities. However, during the dry period, the WWTP may not operate sufficiently and/or cesspool waste dumping may occur, as evident by the zero dissolved oxygen (D.O.) values recorded repeatedly and for periods of several days downstream the WWTP effluent discharge point (Lampou et al., 2015). These add to the disposal of agro-industrial wastes and agrochemical pollution (oil mill wastes, wastes from orange juice production, Markantonatos et al., 1996; Skoulikidis et al., 2011).

2.2. Sampling sites and collection

Three sampling campaigns were conducted by scientists of the Hellenic Centre for Marine Research in order to capture different levels of

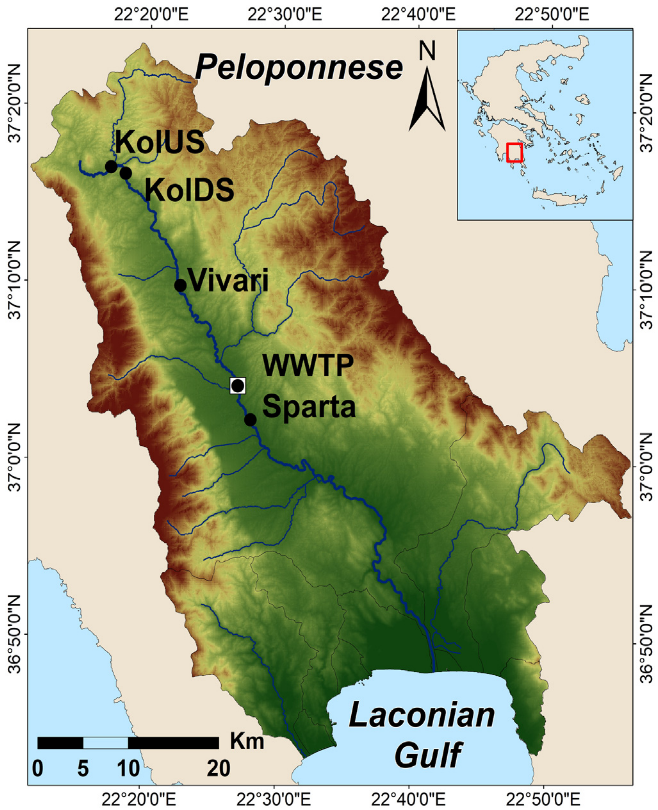

Fig. 1. The Evrotas River catchment and the four sampling sites. The upper right inset shows the location of the Evrotas River Basin within Greece.

water stress and water quality. Four sampling sites located on the main channel of the Evrotas River were sampled in July 2015 (moderate stream flow), and June and September 2016 (low stream flow) (Fig. 1). Composite water samples for the analysis of PhACs were collected from surface waters in the left, center and right river side of the stream channel (20–30 cm below the water surface), and then mixed and transferred to 1 L polyethylene bottles. Samples were transported in refrigerated isothermal containers (dry ice) and stored at −20 °C until extraction by scientists of the Catalan Institute for Water Research. The two upstream sampling sites (KolUS and KolDS) are respectively located in a perennial river section with relatively undisturbed characteristics (KolUS) and in an intermittent river section which dries up partially during late summer, due to natural and artificial desiccation (KolDS, Fig. 1, Table 1). The Vivari and Sparta sampling sites are located in the middle section of the Evrotas River (Fig. 1). Both sites have overall higher river discharge and wider active channel than the upstream sampling sites. Vivari is a relatively undisturbed perennial site with dense riparian woodlands, fed by several karstic springs. The Sparta sampling site is located 20 km further downstream and is a degraded intermittent reach with diffuse pollution from agriculture and point-source pollution from the nearby WWTP, together with pollution from cesspool waste dumping, and olive mill and orange juice processing wastewaters (Lampou et al., 2015; Kalogianni et al., 2017; Karaouzas et al., 2017). The main characteristics of the treatment process, population served and average monthly WWTP outflows of the Sparta WWTP for the sampling periods of July 2015, June and September 2016 were retrieved from the dataset provided by YPEKA (http://astikalimata.ypeka.gr). The measured average monthly outflows from the WWTP located 4603 m upstream of the sampling site 'Sparta' ranged respectively between 3662 m^3d^{-1} and 4163 m^3d^{-1} (Table 1S of the Supplementary material, SM) during the sampling periods. The WWTP serves a population of approximately 20,000 inhabitants with sewage and sludge treatment lines. Resident population data were retrieved from the dataset provided by the Hellenic Statistical Authority (http://www.statistics.gr) (Table 1).

2.3. Environmental data collection and nutrient analyses

Water flow data were obtained in the field using a Water Flow meter OTT C20. Several point measurements of water flow were taken at cross sections and then integrated in order to calculate average river flow. Daily average river flow ($m^3\ s^{-1}$) was calculated for the sampling periods and for periods of 14 and 28 days prior to each sampling date for each sampling site (Fig. 2). Due to the lack of long-term daily measurements in the study area, calculations were estimates based on the SWAT model (Neitsch et al., 2011) developed by Gamvroudis (2016) for the Evrotas River Basin. In order to additionally explore the natural in-stream attenuation of PhACs, we have applied a Lagrangian sampling design to the sampling sites. This design follows the same parcel of water as it moves downstream (Zuellig et al., 2006). Preliminary dye tests (NaCl) were used to determine water travel time between the sample-collection sites (input and output of each waterbody segments) (Kilpatrick and Cobb, 1985). For this study, travel time was defined as "the amount of elapsed time for the dye peak to travel between two monitoring sites" (Zuellig et al., 2006). The distance between the input and output of each waterbody segment, together with the corresponding water travel time in each of the sampling campaigns, are presented in Table 2S, in SM. However, in this manuscript, we have decided to graphically show the in-stream attenuation only at the Sparta waterbody segment, due to a fact that in the other sampling sites a much lower number of PhACs has been detected, while site KolDS was dry in the second and third sampling campaign. The land uses classes distribution of the sites was based on CORINE 2012 database (European Environmental Agency, 2012) (Table 3S, SM). The type of agricultural land uses and livestock units per sampling site are shown in Table 4S, in SM.

Physicochemical variables such as D.O. concentration (mgL^{-1}), pH, water temperature (°C) and conductivity ($\mu S\ cm^{-1}$) were measured in situ (Table 5S, SM) using a Portable multiparameter Aquaprobe AP-

Table 1
Overview of the sampling sites along the Evrotas River Basin.

Sampling site	Catchment	Coordinates		Resident population	Distance from Skortinou springs (m)	Comment
		Latitude (φ)	Longitude (λ)			
KOL US	Evrotas	37°15′ 5.83″N	22°15′ 54.00″E	1203	3165	Low agricultural activities, sparse human settlement, almost pristine riparian forest.
KOL DS	Evrotas	37°16′ 6.90″N	22°18′ 15.16″E	1540	8555	In summer, reduced to scattered deep pools. Then dries up completely, due to natural and artificial desiccation.
VIVARI	Evrotas	37°9′ 51.85″N	22°22′ 30.00″E	3876	24,252	Active river channel with a discharge much higher compared to upstream reaches. Fed by several karstic springs. Dense riparian woodlands and aquatic macrophytes locally.
SPARTA	Evrotas	37°2′ 20.69″N	22°27′ 50.78″E	32,404	45,194	Diffuse pollution from agriculture. Point source pollution (effluents of Sparta WWTP/olive oil mill wastes). Hydromorphological modification (water abstraction/river bank modifications).

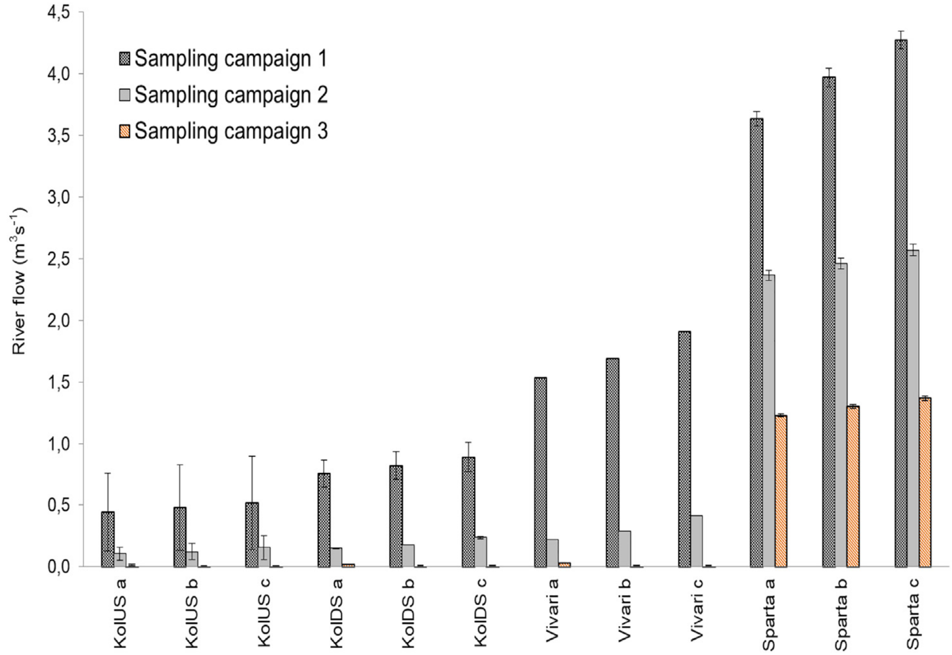

Fig. 2. Daily average river flow ($m^3\ s^{-1}$) during the sampling days (a) and for periods of 14 (b) and 28 (c) days prior to each sampling date for each sampling site (simulated with the SWAT model, Neitsch et al., 2011). Numbers 1–3 in the legend indicate the three sampling periods: 1 (July 2015), 2 (June 2016), 3 (September 2016), while error bars show standard deviation.

200 with a GPS Aquameter (Aquaread AP 2000). Water samples for nutrient analysis were transferred at laboratories of the Hellenic Centre for Marine Research and filtered through 0.45 μm cellulose ester membrane filters (Whatman, U.K.). Nitrite (NO_2^-, mgL^{-1}), and orthophosphate (PO_4^{3-}, mgL^{-1}) concentrations were determined by a Skalar San++ Continuous Flow Analyzer (Boltz and Mellon, 1948; Navone, 1964). Nitrate (NO_3^-, mgL^{-1}) concentrations were determined using both Ion Chromatography and a Skalar Automatic Analyzer, while the concentration of the ammonium (NH_4^+, mgL^{-1}) was determined using a Skalar Automatic Analyzer.

2.4. Sample preparation and analysis

Chemical standards used in this research are listed in Table 6S in the SM. Following the preparation, standards were stored at −20 °C. Fresh stock antibiotic solutions were prepared every month due to their limited stability, while the stock solutions for the rest of the substances were renewed every three months.

2.4.1. Analytical method

The PhACs analysis of water samples was conducted at laboratories of the Catalan Institute for Water Research following the method developed by Gros et al. (2012). The analyses were carried out with an off-line solid phase extraction (SPE), followed by ultra-high-performance liquid chromatography coupled to triple quadrupole linear ion trap tandem mass spectrometry (UHPLC-QqLIT-MS/MS). Prior to the SPE, water samples were filtered through 1 μm glass fiber filters and by 0.45 μm nylon membrane filters (Whatman, U.K.). Later on, filtered and previously spiked water samples were extracted by SPE using Oasis HLB (60 mg, 3 mL) cartridges, while extracts were evaporated under a gentle stream of nitrogen and reconstituted to a final volume of 1 mL. Reconstituted water samples were then fortified with 10 μL of a 1 ng/μL standard mixture containing all isotopically labeled standards. Chromatographic separations were carried out with a Waters Acquity Ultra-Performance™ liquid chromatography system, coupled to a 5500 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer (Applied Biosystems, Foster City, CA, USA) with a turbo Ion Spray source. The separation was achieved with two binary pump systems (Milford, MA, USA), using an Acquity HSS T_3 column (50 mm × 2.1 mm i.d., 1.8 μm particle size) for the compounds analyzed under positive electrospray ionization (PI) and an Acquity BEH C_{18} column (50 mm × 2.1 mm i.d., 1.7 μm particle size) for the ones analyzed under negative electrospray ionization (NI), both purchased from Waters Corporation. For the analysis in the (PI) mode, methanol and 10 mM formic acid/ammonium formate (pH 3.2) were used as a mobile phase at the flow rate of 0.5 mL/min. However, for the analysis in the (NI) mode, acetonitrile and 5 mM ammonium acetate/ammonia (pH = 8) were used as a mobile phase at the flow rate of 0.6 mL/min. The sample volume injected was 5 μL for both modes. Electrospray ionization (ESI) and selected reaction monitoring (SRM) modes were selected for the MS^2 detection. Finally, all data were acquired and processed using Analyst 1.5.1 software, while quantification was carried out by isotope dilution. Method performance parameters of target compounds including limits of detections (LODs), limits of quantifications (LOQs) and recovery rates are summarized in Table 7S (SM).

2.5. Statistical analysis

The variables were checked for normal distribution using the Shapiro-Wilk test. Pearson's moment correlation factor (r) was performed between the candidate variables, and those strongly correlated (correlation coefficient was >0.8) were unselected from further statistical analysis to avoid multicollinearity. PhACs with undetected values and values <LOQ were replaced by the corresponding values equal to one-half of LOD and one-half of LOQ (Farnham et al., 2002). Two separate Principal Component Analysis (PCA) were performed in order to explore the variability of i) nutrients and physicochemical variables and ii) PhACs concentrations of each family of compounds. The relationships between the score values of the physicochemical PCA and of the PhACs PCA, as well as with land uses were explored with a Pearson correlation analysis. The score values were normalized by subtracting the mean and dividing it by the standard deviation before the analysis. Additionally, Pearson correlation was used to explore the relationship between the proportion of PhACs decrease within the Sparta waterbody segment and the corresponding water travel time and temperature throughout the sampling campaigns. All analyses were performed with SPSS (version 17.0, SPSS Inc., Chicago, U.S.A.).

3. Results

3.1. Hydrological characterization

Water flow in the Evrotas River ranged from 0.008 $m^3\ s^{-1}$ to 4.28 $m^3\ s^{-1}$ (Fig. 2). In all sampling campaigns, water flow was generally higher downstream than in the upstream sampling sites due to vertical and lateral inputs. The hydrology of the river showed a large variability between sampling periods; water flow during July 2015 was 1.6 times higher than June 2016 and 3.13 times higher than September 2016. Consequently, water travel time between the input and output of the Sparta waterbody segment (3.7 km) increased from 2 h (July 2015) to 4.9 h and 5.9 h respectively in June and September 2016 (Table 2S, SM).

3.2. Chemical variables

Potassium and nitrite concentrations were not considered for further analysis, due to multicollinearity with other chemical variables. Throughout the sampling campaigns, the Sparta sampling site was the most polluted site as indicated by high concentrations (median, minimum-maximum) of NO_3^- (0.61 mgL^{-1}, 0.30 mgL^{-1}–1.6 mgL^{-1}), NH_4^+ (0.01 mgL^{-1}, 0.01 mgL^{-1}–0.25 mgL^{-1}), K^+ (0.76 mgL^{-1}, 0.62 mgL^{-1}–2.4 mgL^{-1}), Cl^-(11 mgL^{-1}, 7.1 mgL^{-1}–18 mgL^{-1}), PO_4^{3-}(0.002 mgL^{-1}, 0.0004 mgL^{-1}–0.052 mgL^{-1}) and of conductivity (492 $\mu ScmL^{-1}$, 139 $\mu ScmL^{-1}$–651 $\mu ScmL^{-1}$) (Table 5S, SM). Concentration levels of D.O. in this site were similar to the other sites in July 2015, but they were much lower in both June and September 2016. In all sampling sites, higher concentrations levels of studied variables were observed during periods with the lower stream flow (June and September 2016), whereas NO_3^- and PO_4^{3-} levels were higher during higher flow conditions (July 2015). River water temperature ranged between 16.6 °C and 25.5 °C throughout the sampling campaigns, while generally higher temperatures in the Sparta sampling site were recorded during June and September 2016 reaching 25.5 °C and 23.4 °C, respectively (Table 5S, SM). The PCA using physicochemical variables (Fig. 1S, SM) explained 48.8% variability in the first axis and 25.6% variability in the second axis. The scores of the first component were significantly correlated with urban land uses ($r = 0.89$, $p < 0.001$).

3.3. PhACs concentrations

Eleven (11) different PhACs out of the 62 monitored were detected (Table 8S, SM), nine of them in at least two of the three sampling campaigns, and two in only one campaign. Additionally, two PhACs were detected with concentration levels <LOQ. The total concentrations of detected PhACs (sum of all compounds per each sampling site) were generally higher during low stream flow (June and September 2016) than during high stream flow (July 2015, Figs. 2 and 3). The diuretics and the analgesics/anti-inflammatory class were the most abundant, followed by antihypertensives, psychiatric drugs, β-blocking agents and antibiotics (Fig. 3). The concentration levels ranged from 0.31 ngL^{-1} up to 51 ngL^{-1}, while the highest number and individual concentration levels of PhACs were predominantly detected during low flow periods (June and September 2016). The diuretic hydrochlorothiazide (average detection frequency, D.F. 50%) and the analgesic/anti-inflammatory ketoprofen (D.F. 17%) were those with the highest concentrations detected in all sampling campaigns, reaching up to 51 ngL^{-1} and 45 ngL^{-1}, respectively. The antihypertensive valsartan was the most frequently detected PhAC (D.F. 67%) reaching concentrations up to 9.8 ngL^{-1} in the period with the lowest flow (Table 8S, SM). The analgesics/anti-inflammatory naproxen, the psychiatric drugs carbamazepine and 10.11-epoxycarbamazepine and the β-blocking agent sotalol were detected in 25%–33% of all samples analyzed, with concentrations ranging between 2.3 ngL^{-1} and 9.5 ngL^{-1}. The total PhACs concentrations (sum of all compounds) in sampling sites situated upstream of Sparta ranged between 0.84 ngL^{-1} and 9.1 ngL^{-1}, respectively (Fig. 3). The highest total concentration of PhACs occurred in the Sparta sampling site, where total PhACs concentration (sum of all compounds in each family of compounds) in September 2016 was 1.3 times higher than the total concentration in June 2016 and 4.4 times higher than in July 2015 (Fig. 3). The first axis of the PCA performed with the PhACs (Fig. 2S, SM) accounted for 79.1% of the total variability, with psychiatric drugs, β-blocking agents, diuretics and the analgesics/anti-inflammatories being the variables that contributed most. The variability of the first component was significantly correlated with urban land uses ($r = 0.96$, $p < 0.001$).

3.4. Natural attenuation of PhACs (Sparta)

The in-stream attenuation at the Sparta river segment was highly variable amongst the PhACs detected and the different sampling periods (Fig. 4; the physicochemical properties of individual PhACs are shown in Table 2). Overall, the average proportion of decrease for PhACs increased from 22% in July 2015 up to 25% and 77% in June and September 2016 respectively. The PhACs with the highest average concentration decrease throughout the sampling campaigns was hydrochlorothiazide, followed by sotalol, carbamazepine, valsartan, and naproxen. Additionally, the proportion of PhACs decrease within the Sparta waterbody segment was positively and significantly correlated with the water travel time in each of the sampling campaigns ($r = 0.50$, $p < 0.005$). Consequently, PhACs detected within the Sparta river segment in conditions of longer water travel time in June and September 2016 showed higher elimination rates. However, no significant correlation was detected between water temperature and the proportion of PhACs decrease ($p > 0.005$).

4. Discussion

Urban wastewaters were the main source of pollution from PhACs in the Evrotas River. This was indicated by the significant correlations between the score values of each first principal component (physicochemical variables and PhACs families) and urban land use proportions. The lower concentration range of PhACs in the Evrotas River can be attributed to the small resident population in the basin, in comparison with other basins in Greece (Stasinakis et al., 2012; Stamatis et al., 2013), since concentrations of PhACs were comparable with those detected in small rivers in rural regions with relatively small resident populations (Kasprzyk-Hordern et al., 2008; Bartelt-Hunt et al., 2009; Morasch, 2013; Chiffre et al., 2016). However, concentrations increased downstream reaching the highest values in the “Sparta” site, located 20 km downstream of the local WWTP. This pattern suggests that the WWTP was the main point source of PhACs and nutrients, as similar studies indicate (Gros et al., 2007; Vieno et al., 2005; Gros et al., 2007; Conley et al., 2008). However, some PhACs such as analgesics/anti-inflammatories, antibiotics, and antihypertensives were also frequently detected in the upstream sampling sites, possibly from untreated wastewaters of the small local settlements.

Fluctuations in river flow influenced the water chemistry of the river. Water regime and weather conditions (Kasprzyk-Hordern et al., 2008) influenced the concentrations of target analytes, nutrients, and physicochemical parameters, which were higher during lower flows (June and September 2016) and were reduced considerably during higher water flows (July 2015). Lower river flows and associated lower dilution accounted for the overall higher total concentrations of detected PhACs and nutrients in 2016. Similarly, high concentrations and high detection frequencies of PhACs as a result of low-flow conditions have also been reported elsewhere (Gros et al., 2007; Fernández et al., 2010; Osorio et al., 2012; Osorio et al., 2016).

Pharmaceutical product concentrations attenuated within the river segment. In-stream attenuation mechanisms are still incompletely understood (Kunkel and Radke, 2011) and could not be clearly established

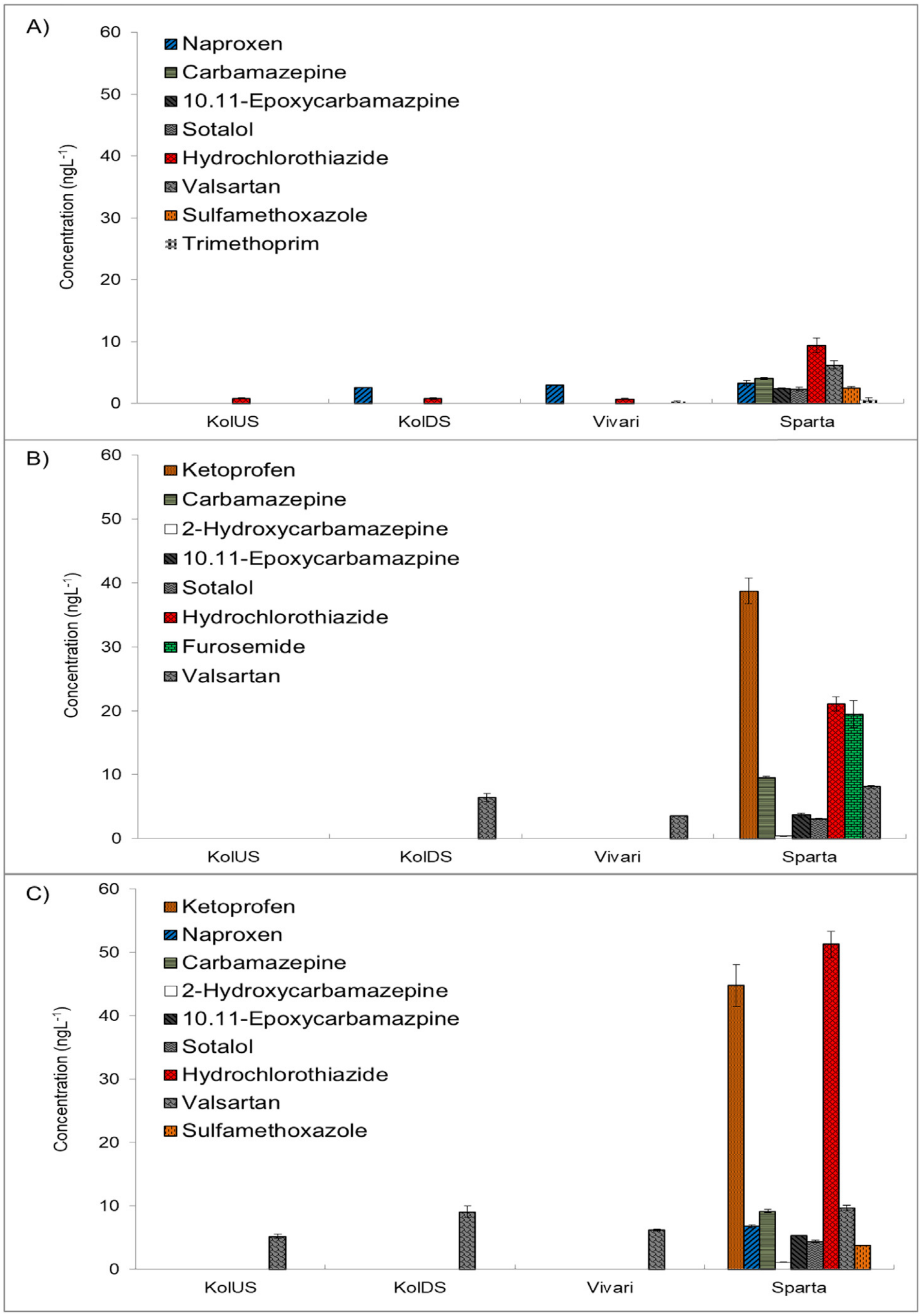

Fig. 3. Spatio-temporal distribution of individual PhACs concentrations (input-output average concentration) in each waterbody segment: A) 1st sampling campaign (July 2015-high stream flow) B) 2nd sampling campaign (June 2016-low stream flow), C) 3rd sampling campaign (September 2016-lowest stream flow). The error bars show standard deviation.

with our approach. However, our results show that increased water travel time (and consequently longer residence time) during dry periods may account for the higher attenuation of most PhACs, and that other factors related to the chemical structure, environmental conditions (e.g. temperature, light intensity, sediment type, turbidity, humic substances, nitrate), and biotic and abiotic processes, such as biodegradation, photodegradation, volatilization and sorption (Vieno et al., 2005; Osorio et al., 2012; Osorio et al., 2016), could also contribute to the attenuation of PhACs. Though, amongst these, environmental conditions such as the seasonal variability of the river flow has shown to be a critical factor affecting the in-stream PhACs concentrations in the Evrotas River (Johnson, 2010; Matamoros and Rodríguez, 2017; Hanamoto et al., 2018). Dilution of surface water can be due to the input of small creeks and/or inputs of groundwater into the river. The different in-stream chemical-biological attenuation processes of the contaminants can also be related to the water travel time within the river segment (Lindqvist et al., 2005; Vieno et al., 2005; Kunkel and Radke, 2012); longer travel times in June and September 2016 within the Sparta River segment resulted in generally higher elimination rates of PhACs. The decrease of PhACs within a water segment, such as the Sparta segment, depends on the rates at which the natural in-stream attenuation processes operate, as well as on the chemical structure and physicochemical properties of the PhACs and their distribution in the various compartments of the environment (Petrovic and Barcelo, 2007). So far, octanol-water partition coefficient (Kow) and octanol-water distribution coefficient (Dow) have been used in order to evaluate the tendency of a substance to stay in the water phase. However, the pH at which measurements are made for evaluating Kow is also a

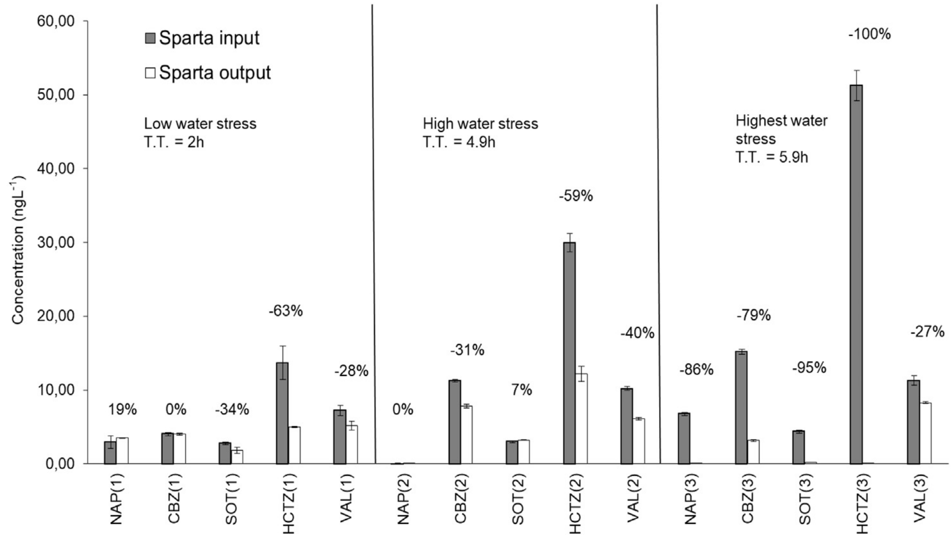

Fig. 4. Natural attenuation of individual PhAC concentrations at the Sparta waterbody segment (input-output) with the corresponding water travel time (T.T./h) in each sampling campaign: 1) July 2015 (low water stress), 2) June 2016 (high water stress) and 3) September 2016 (highest water stress). Note: NAP (Naproxen), CBZ (Carbamazepine), SOT (Sotalol), HCTZ (Hydrochlorothiazide) and VAL (Valsartan). Percentages are depicting the proportion of increase (positive values) or decrease (negative values) of each PhACs per sampling period, while error bars show standard deviation.

crucial parameter. Wells (2006) reported that Kow does not properly describe environmental partitioning and dynamic in the environment of polar and ionizable compounds, such as PhACs, and that for them the coefficient Dow is more adequate, as it is pKa dependent at the pH of the environment. High Kow (or Dow) (Log Kow > 4) values mean that PhACs tend to sorb onto suspended particles and end up in the sediment, whereas compounds with low Kow (Log Kow < 2.5) and high water solubility are expected to remain in the water phase. Therefore, due to its moderate hydrophilic character (Dow > 2.5), low water solubility (17.7 mg L^{-1}) and poor biodegradability (Kbiol ˂ 0.1 L gSS^{-1} d^{-1}), the overall sorption tendency is fairly considerable for carbamazepine. Acuña et al. (2014b) also reported that sorption, rather than biotransformation and photodegradation processes, was the main mechanism driving the in-stream attenuation of carbamazepine. In contrast, hydrophilic compounds with low Dow (˂2.5) and high water solubility (>100 mg L^{-1}) are expected to remain in the aqueous phase and, therefore, to undergo different in-stream attenuation processes, such as biodegradation and photodegradation (Acuña et al., 2014b; Kunkel and Radke, 2011). Consequently, high attenuation rates of sotalol and especially hydrochlorothiazide, in the present study, in comparison with other analytes could be explained by their overall low Dow (˂2.5) and high water solubility (>700 mg L^{-1}), while the increase of their attenuation rates, especially in June and September 2016 at low flows could be attributed to their tendency for photodegradation (Kunkel and Radke, 2012; Li et al., 2016; Baena-Nogueras et al., 2017). On the other hand, naproxen and valsartan with their generally low Dow (˂2.5) may be considered as moderately biodegradable PhACs (0.5 < Kbiol < 1 L gSS^{-1} d^{-1}). Though, in the case of naproxen, direct phototransformation resulting in short half-lives (˂3 h) has been also proposed as another potential in-stream attenuation pathway beside biodegradation (Lin and Reinhard, 2005; Fono et al., 2006; Lin et al., 2010). Variation in environmental conditions (i.e. temperature, UV radiation) may also affect the in-stream dynamics and fate of PhACs (Osorio et al., 2012). For example, increased water temperatures may decrease sorption, while simultaneously increasing biodegradation (Hulscher and Cornelissen, 1996). However, in the case of the Sparta waterbody segment, the small temperature differences between the sampling periods did not allow finding statistically significant relationships (p > 0.005) between water temperature and the in-stream decrease of the PhACs.

Finally, since PhACs do not occur as single compounds in the environment but as a mixture of different transformation products, active substances, and their metabolites, their effects on the aquatic organisms might be stronger than those corresponding to single compounds (Cleuvers, 2003). Also, during drought, when the highest concentration levels of PhACs occur, aquatic biota of temporary rivers are jointly exposed to pollution and water stress, characterized by habitat shrinkage, water quality deterioration and increased competition for limited resources, which in turn can result in severe deleterious effects (Arenas-Sánchez et al., 2016; Karaouzas et al., 2017).

Table 2
Physicochemical properties of individual PhACs.

Analyte	*Water solubility (mg L^{-1})	**Charge at pH 7	*pK_{a1}	*pK_{a2}	*Log K_{ow}	Log D_{ow} at pH 7.4	K_{biol} (L gSS^{-1} d^{-1})	Photolysis rate constant (h^{-1})
Naproxen	15,9	Negative	4,2	n.a.	3,18	−0.16[d]	<0,2–9[a]; 1,0–1,9, 0,4-0,8; 0,08–0,4[c]	0,49[f]
Carbamazepine	17,7	Neutral	13,9	n.a.	2,45	2.77[d]	≤0,1[b]; <0,03–<0,06[a]; <0,005–, <0,008[c]	0,02–0,08[g]
Sotalol	137,000	Positive	9,4	10,7	0,24	−1.62[d]	0,40–0,43[b]	n.a.
Hydrochlorothiazide	722	Negative	7,9	9,8	−0,07	−0.58[d]	n.a.	1,61[h]
Valsartan	23,4	Pos./Neut.	4,4	7,4	5,8**	−0.89[e]	n.a.	n.a.

Notes: D_{ow} – octanol/water distribution ratio; K_{ow} – octanol/water partition coefficient; pK_a – acid dissociation constant; K_{biol} – biodegradation rate constant; (*) data obtained from (Acuña et al., 2014b); ** values were obtained with Marving software (Chemaxon Ltd.); ([a]) data obtained from (Suarez et al., 2009); ([b]) data obtained from (Wick et al., 2009); ([c]) data obtained from (Abegglen et al., 2009); ([d]) data obtained from (Li et al., 2016); ([e]) data obtained from ChemSpider (www.chemspider.com); ([f]) data obtained from (Lin and Reinhard, 2005); ([g]) data obtained from (Matamoros et al., 2009); ([h]) data obtained from (Baena-Nogueras et al., 2017); n.a. – not available.

5. Concluding remarks

Concentrations of PhACs, nutrients and physicochemical parameters were considerably higher downstream the WWTP of Sparta city. These concentrations were the highest during low flow conditions in June and September 2016, when increased water travel time accounted for the higher attenuation of most PhACs in the Sparta waterboy segment. The average proportion of decrease for PhACs increased from 22% in July 2015 up to 25% and 77% in June and September 2016. However, the PhACs with the highest average concentration decrease throughout the sampling campaigns was hydrochlorothiazide, followed by sotalol, carbamazepine, valsartan, and naproxen. Our results emphasize that in rivers submitted to strong hydrological stress, such as the Evrotas River, in-stream attenuation mechanisms represent an important contributing factor to the reduced rates of PhACs.

Conflicts of interest

We declare no conflicts of interest. The submitted manuscript contains original data and it is not under review in any other scientific journal. All the authors and relevant institutions have read the submitted version of the manuscript, accept responsibility for it, declare no competing financial interest, and approve its submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2018.07.308.

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