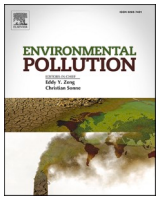
Environmental Pollution 347 (2024) 123668

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol



Ecological and human health risk assessment of pharmaceutical compounds in the Sirsa River of Indian Himalayas☆

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ARTICLE INFO

Handling editor: Da chen

Keywords:
Indian Himalayas
Pharmaceutical micro pollutants
Risk assessment
Hazard quotient
Predicted no-effect concentration

ABSTRACT

The Baddi-Barotiwala-Nalagarh (BBN) region of Indian Himalayas is one of the most important pharmaceutical industrial clusters in Asia. This study investigated the distribution, and ecological and human health risks of four most frequently used pharmaceuticals [ciprofloxacin (CIP), norfloxacin (NOR), cetirizine (CTZ) and citalopram oxalate (ECP)] when co-occurring with metal ions in the Sirsa river water of the BBN region. The concentration range of the selected pharmaceuticals was between 'not detected' to 50 μgL^{-1} with some exception for CIP (50–100 μgL^{-1}) and CTZ (100–150 μgL^{-1}) in locations directly receiving wastewater discharges. A significant correlation was found between the occurrences of NOR and Al ($r^2 = 0.65$; $p = 0.01$), and CTZ and K ($r^2 = 0.50$; $p = 0.01$) and Mg ($r^2 = 0.50$; $p = 0.01$). A high-level ecological risk [risk quotient (RQ) > 1] was observed for algae from all the pharmaceuticals. A medium-level risk (RQ = 0.01–0.1) was observed for *Daphnia* from CIP, NOR and ECP, and a high-level risk from CTZ. A low-level risk was observed for fishes from CIP and NOR, whereas CTZ and ECP posed a high-level risk to fishes. The overall risk to ecological receptors was in the order: CTZ > CIP > ECP > NOR. Samples from the river locations receiving water from municipal drains or situated near landfill and pharmaceutical factories exhibited RQ > 1 for all pharmaceuticals. The average hazard quotient (HQ) values for the compounds followed the order: CTZ (0.18) > ECP (0.15) > NOR (0.001) > CIP (0.0003) for children (0–6 years); ECP (0.49) > CTZ (0.29) > NOR (0.005) > CIP (0.001) for children (7–17 years), and ECP (0.34) > CTZ (0.21) > NOR (0.007) > CIP (0.001) for adults (>17 years). The calculated risk values did not readily confirm the status of water as safe or unsafe because the values of predicted no-effect concentration (PNEC) would depend on various other environmental factors such as quality of the toxicity data, and species sensitivity and distribution, which warrants further research.

1. Introduction

Non-judicious usage and disposal of pharmaceutical compounds result in their increasing concentrations in water and soil, causing harmful effects to ecosystems and thereby raising concerns among researchers, policy makers and environmentalists. Pharmaceutical pollutants can partition in almost every compartment of the natural ecosystem such as water, soil, flora and fauna (Ebele et al., 2017; Patel et al., 2019). Pharmaceuticals can enter water through different transport pathways such as the direct entry through discharges from aquaculture activities or excretion from livestock animals and indirectly through soil-applied sludge as biosolids, manures and composts or

☆ This paper has been recommended for acceptance by Da chen.

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https://doi.org/10.1016/j.envpol.2024.123668
Received 22 November 2023; Received in revised form 26 February 2024; Accepted 26 February 2024
Available online 3 March 2024

leaching from landfills or drift of compounds from manufacturing units (Sharma and Kaushik, 2021; Zhang et al., 2021). Uncontrolled release of poorly treated wastewater into the water bodies without secondary and/or tertiary treatments is identified as one of the major sources of pharmaceuticals (e.g., ofloxacin, tamoxifen, diazepam, erythromycin, carbamazepine) in the environment (Carmona et al., 2014; Tran et al., 2014; Morone et al., 2019). In addition to deteriorating the biodiversity (extremely important in the Himalayan context), the residual concentrations of pharmaceutical and personal care products (PPCPs) in combination with microorganisms in the water environment accelerate the issue of antimicrobial resistance genes and drug resistance and may cause cancer in humans upon consumption of contaminated water over long period (Sharma and Kaushik, 2021; Ghirardini et al., 2021).

Pharmaceutical pollution has been a serious concern for river ecosystems across the globe especially in developing countries like India, China, Brazil, where a mismatch between the application/development of pharmaceuticals and their effective removal strategies exists. In India, the situation is concerning because both in metro cities and rural areas, majority of rivers receive wastewater from domestic and industrial sources often without adequate treatment process. Abundances ($\geq$300 ngL^{-1}) of common PPCPs such as naproxen, ibuprofen, triclosan, estrogen, sulfamethoxazole and gemfribrozil were reported in Indian rivers including Gomti (Malik et al., 2011), Yamuna (Diwan et al., 2018), Kshipra (Philip et al., 2018), Brahmaputra (Kumar et al., 2019), Godavari (Fick et al., 2009) and Sirsa (Bhardwaj et al., 2019; Tribune News, 2022). The Sirsa river of Indian Himalayas before merging into the Satluj river, flows downstream through the Baddi-Barotiwala-Nalagarh (BBN) industrial region (Bhardwaj et al., 2019), spreading over 380 km^2, in the Northwestern Himalayan district of Solan. BBN is one of the largest pharmaceutical manufacturing hubs of South Asia and accounts for $\geq$35% of Asia's total pharmaceuticals production (Bhardwaj et al., 2019; Rajkumar et al., 2020). This region accommodates more than 2000 noteworthy industrial giants and hosts a cluster of plastic, rubber, cement, pulp and paper, dyes, and textile industries that impact the soil and water environments through their untreated discharges (Herojeet et al., 2015, 2016). The region consisting of 229 villages is home to nearly 210,000 people (Chauhan et al., 2013; Bhardwaj et al., 2019). The catchment area of Sirsa river (lower sections) receives a large volume of pharmaceutical wastewater and partially treated or untreated sewage from the BBN region, which was earlier linked to ecological quality deterioration such as sudden death of fishes (Kamaldeep et al., 2011; Asher and Mahar, 2017; SANDRP, 2017). Liquid chemical wastes discharged from the pharmaceutical units flow through drains, canals and rivulets into the Sirsa river, turning the river water occasionally dark in color and creating odor. A few studies previously reported up to 1500 times higher concentrations of ciprofloxacin than the compound's limit of discharge in contaminated hotspots of the Sirsa river water (Balakrishna et al., 2017; Bisht, 2021). However, no study to date has explored the ground-level issues of PPCP contamination (e.g., diversity of PPCP, origin, dissipation) in the rapidly urbanized Indian Himalayan regions, particularly in the semi-urban and rural areas around the BBN hub. The current study is therefore designed for the first time to identify possible hotspots of four pharmaceutical compounds and explore their origin and status of dissipation in and around the BBN region.

The Sirsa river water also contains a heavy load of potentially toxic metal (PTM) ions (Herojeet et al., 2015), which could worsen the contamination situation because pharmaceuticals may form stable coordination complexes with metals, increasing risks to aquatic fauna and flora as well as human health (Andreu et al., 2016). Risk assessment of both PTM and pharmaceuticals thus becomes essential because their monitoring together with risk assessment could provide a thorough understanding of the exposure intensity and help making a suitable management plan for risk mitigation. No studies to date reported the co-contamination status of pharmaceutical and PTM pollutants and assessed risks of pharmaceuticals when co-occurring with PTM in the Indian Himalayan region.

To address these knowledge gaps, this study investigated surface water of the Sirsa river in and around the BBN region to understand the water chemistry along with ecological and human health risks posed by four commonly used pharmaceuticals (contributed by industries located at the river catchment) when co-occurring with metal ions. It was hypothesized that pharmaceutical compounds could appear in hot spots where industrial and household drains and rivulets meet the Sirsa river and varying contamination levels would pose various degrees of risks to ecological receptors belonging to different trophic levels (e.g., algae, *Daphnia*, fishes and humans). The specific objectives were to: (a) monitor and quantify four different groups of targeted pharmaceuticals [e.g., ciprofloxacin (CIP), norfloxacin (NOR), cetirizine (CTZ) and citalopram oxalate (ECP)] along with PTM in the Sirsa river water of the BBN region, (b) estimate relative exposure (ecological and human health risks) from the studied pharmaceuticals and PTM as input pollutants for risk and impact assessment, and (c) prepare a risk map of the studied region based on the pharmaceutical contamination scenario. The monitoring and risk assessment of pharmaceuticals and PTM will provide an understanding of the effects of PPCP pollution on public health and livelihood in the Indian Himalayan region and help developing suitable mitigation strategies.

2. Materials and method

2.1. Chemicals and reagents

All chemicals used in this study were of High-Performance Liquid Chromatography (HPLC; 98% purity) and Analytical Reagent (AR) grade. Pharmaceutical standards (two antibiotics – CIP and NOR, and salt of one each of two anti-depressant (ECP in oxalate form) and anti-allergic (CTZ in hydrochloride form) drugs were purchased from Sigma-Aldrich, USA. Ultrapure water (FisherScientific™, USA) was used for preparing the analytical standards. Acetonitrile (99.8%) and methanol (99.9) were purchased from Fisher Scientific, whereas potassium dihydrogen orthophosphate (99.5% pure), phosphoric acid (85% pure) and formic acid (98% pure) were purchased from Lobachemie, India.

2.2. Sampling procedure

Sampling was conducted in the month of July and August in 2021. Description of the geo-morphological and climatic background of the sampling area and details of the sampling procedure are provided in Supplementary Information (SI) (SI.1 and SI.2). A map of the study area indicating all sampling locations is shown in Fig. S1. Different types of water samples (surface water, drainage water, groundwater, civil supply water) were collected during the sampling campaign across the Sirsa river and from nearby places [details are provided in SI (Tables S1–S2)]. In total, 134 surface water samples (main samples) were collected in July (n = 61) and August (n = 73). Other representative samples (ORS), i.e., samples from groundwater (GW), civil supply water (CS) and effluent/drain (DR), located within 5 km diameter of the river basin were also collected in July (n = 13) and August (n = 30). These months were selected for water sampling representing pre-monsoon and post-monsoon periods when most of the local industries release effluents into the river and its tributaries. Field photographs showing information about the sampling points and surrounding areas are provided in SI (Fig. S2).

2.3. Analytical measurements

Instrumentation: The pH, total dissolved solid (TDS) and dissolved oxygen (DO) were recorded on site using a handheld Hanna pH meter (HI98107P), TDS meter (HI98301P) and a portable digital DO meter (model no. MT-121), respectively. The biological oxygen demand (BOD) and chemical oxygen demand (COD) were analyzed (by open reflux

method) using the guidelines of APHA (APHA, 2005). Reagent blanks were analyzed at each step to check the accuracy and precision of the measurements (APHA, 2005). The PPCPs, namely CIP, NOR, CTZ and ECP, were selected based on their widespread production, usage and frequent detection/occurrence under Indian conditions and potential eco-toxicological effects of the drugs (Bade et al., 2015; Pereira et al., 2020a). Physico-chemical properties of the selected pharmaceuticals are given in SI (Table S3). A DionexUltra-High-Performance Liquid Chromatography (UHPLC) system (UltiMate3000, Thermo Scientific, USA) coupled with Dionex UHPLC UltiMate3000 Autosampler and Dionex UHPLC UltiMate3000 Diode Array Detector (DAD) was used for the analysis. A Zorbax Eclipse Plus C18 column (4.6 × 100 mm, 3.5-μm pore size; Agilent Technologies, USA) was used in isocratic condition. The concentration of metallic elements in the water samples was analyzed using inductively coupled plasma optical emission spectroscopy (ICP-OES) (iCAP™ 7000 Series, Thermo Scientific™, USA).

Methods: For pharmaceuticals analysis, modified analytical methods of Gezahegn et al. (2019), Diwan et al. (2009), Fick et al. (2009) and Bhimanadhuni et al. (2012) were adopted as described in Supplementary Material Table S4. CIP and NOR were analyzed in the same run. To prepare stock solutions, 1 mg of CIP and NOR was dissolved in 10 mL formic acid-acetonitrile (84:16 v/v),1 mg CTZ in 10 mL acetonitrile, and 1 mg ECP in 10 mL methanol. Each stock solution was sonicated (Digital ultrasonic cleaner-LMUC-6) for 20 min, vortexed and filtered using 0.45 μm membrane filters. The pH of the mobile phase (potassium dihydrogen phosphate solution) was adjusted to 3.0 ± 0.05 using dilute orthophosphoric acid and sonicated for degassing (Table S4). The mobile phases were filtered through Whatman no. 1 filter paper. The details of methods and different parameters of HPLC (mobile phase, flow rate of mobile phase, time of run, wavelength, column temperature and analyte volume) for the analysis of PPCPs are provided in Table S4. Working standards of trace elements were prepared following serial dilution of a Multi-Element Plasma Standard Solution (Specpure™, Thermo Scientific™, USA) using Milli-Q water (Milli-Q® Type 1 Ultrapure Water Purification System) and analyzed. Details of the water quality index calculation are provided in SI (SI.3, Table S5).

2.4. Risk assessment

2.4.1. Ecological and human health risk of target pharmaceuticals

The risk quotient (RQ) method was adopted (USEPA, 2004; Liu et al., 2020) to assess the potential ecological risks of target pharmaceuticals on the aquatic ecosystem (Eq. (1)).

$$RQ_{eco} = \frac{C}{PNEC_{eco}} \quad \text{(Eq. 1)}$$

where, C is the concentration of pharmaceuticals in water (ngL^{-1}), RQ_{eco} is the risk quotient for ecological risks and $PNEC_{eco}$ is the predicted no-effect concentration for ecological risk in water. The $PNEC_{eco}$ is defined as the maximum pharmaceutical concentration (ngL^{-1}) that would not have an adverse effect on the environment under the existing conditions. The $PNEC_{eco}$ values were obtained from the literature and their associated parameters are listed in Table 1. In these literature, the $PNEC_{eco}$ was calculated using the half lethal concentration (LC_{50}) and half-maximum effect concentration (EC_{50}) (ngL^{-1}) (Eq. (2)):

$$PNEC_{eco} = \frac{(LC_{50} \text{ X } EC_{50})}{AF} \quad \text{(Eq. 2)}$$

where, AF is the evaluation factor value which is recommended as 1000 by the European Water Framework Directive (European Union, 2015b).

The ecological risk from antibiotics is low when the RQ value ranges from 0.01 to 0.1, medium when RQ ranges from 0.1 to 1, and high when RQ is more than or equal to 1 (Gopal et al., 2021).

Human health risk was estimated using Eq. (3) (Gopal et al., 2021).

Table 1
Predicted no-effect concentrations (PNEC) for fish, *Daphnia*, and algae (adopted from literature) for ecological risk assessment of target PPCPs.

S. No.	Pharmaceutical	PNEC [a] (μgL^{-1})		
		Algae	*Daphnia*	Fish
1	CIP	0.0067[a]	653[a]	13131.4[a]*
2	NOR	10.4[a]	298.8[a]	20081[a]*
3	CTZ	0.41[c]	398[c]	153[c]*
4	ECP	96.9[b]	14[b]	100[b]*
a =	Pereira et al. (2015)			
b =	Pereira et al., 2020a,2020b			
c =				
*	LC_{50} was estimated with ECOSAR			
AF	1000			

[a] PNEC is calculated by dividing LC_{50} by an assessment factor (AF) of 1000 for fish, *Daphnia*, and algae.

$$RQ_{hr} = \frac{MEC}{PNEC_{hr}} \quad \text{(Eq. 3)}$$

where, MEC is the measured environmental concentration of a pharmaceutical in the water sample, $PNEC_{hr}$ is the predicted no effect concentration equivalent to drinking water for health risk, and RQ_{hr} is the risk quotient for human health risk. $RQ_{hr} > 1$ indicates the possibility of risk to human health, values between $1 > RQ_{hr} > 0.2$ warrants further investigation on the toxicity effect, and $RQ_{hr} < 0.2$ displays no appreciable concern to human health (Yang et al., 2017; Sharma et al., 2019). $PNEC_{hr}$ was calculated using Eq. (4):

$$PNEC_{hr} = \frac{1000 \text{ X } BW \text{ X } AT \text{ X } ADI}{IR \text{ X } EF \text{ X } ED} \quad \text{(Eq. 4)}$$

where, BW is the median body weight (kg) of age specific groups (given in Table 2), AT is average time (day), ADI is acceptable daily intake ($\mu gkg^{-1}day^{-1}$), IR is water ingestion rate ($Lperson^{-1}day^{-1}$), EF is frequency of exposure ($dayyear^{-1}$), and ED is exposure duration (year) (from SI Table S6).

ADI was derived from toxicological, microbiological and therapeutic approaches using either lethal dose (LD_{50}) or lethal concentration (LC_{50}) or no-observable-adverse-effect level (NOAEL) value as point of discharge (POD) (Schwab et al., 2005; Wen et al., 2014) (Eq. (5)):

$$ADI = \frac{POD \times 1000}{UF1 \times UF2 \times UF3 \times UF4 \times UF5} \quad \text{(Eq. 5)}$$

where, UF was taken as a unit less uncertainty or modifying factor, as defined in Schwab et al. (2005). Several reported studies were screened for the calculation of PNEC and ADI value for the studied analytes (Bu et al., 2013; Mathur et al., 2021; Bisht, 2021; Madhav et al., 2018). ADI value was available only for CIP and NOR but not for CTZ and ECP. Hence, to keep a similarity in calculation, an attempt was made to calculate ADI value for CIP and NOR using the maximum recommended average daily dosage value of these analytes (Schwab et al., 2005). The value and consideration for each uncertainty factor were adopted according to the recommendations of the United States Environmental Protection Agency (USEPA, 2002). The average of maximum recommended daily dosage in adults (>17 years) and children (0–6 and 7–17 years) was taken as the point of discharge (POD). The ADI and POD values for $PNEC_{hr}$ calculation are given in Table 2.

2.4.2. Ecological and human health risk of PTM

Ecological risk from PTM in the studied water samples was calculated using a previously reported method (Håkanson, 1980; Ojekunle et al., 2016; Dixit and Siddaiah, 2021). The risk was calculated in three steps. The first step calculated the single contamination coefficient (C_f) using Eq. (6):

Table 2
Parameters used for the estimation of Acceptable Daily Intake (ADI) for health risk assessment from target PPCPs.

Analyte	POD	UF1	UF2	UF3	UF4	UF5	ADI	Critical effect and basis for POD	Ref.
CIP	(mg/kg/day)						μg/kg/day		
	33.33	3	1	1	10	1	1111.0	Therapeutic effect. POD	1
	16.3						543.3	* 500 mg/day = 33.33 mg/kg/day	
	10.71						357.0	** 750 mg/day = 16.30 mg/kg/day	2
								*** 750 mg/day = 10.71 mg/kg/day	
NOR	26.67	3	1	1	10	1	889.0	Therapeutic effect. POD	3
	8.6						286.7	* 400 mg/day = 26.67 mg/kg/day	2
	5.7						190.0	** 400 mg/day = 8.6 mg/kg/day)	
								*** 400 mg/day = 5.7 mg/kg/day	
CTZ	0.167	3	1	1	10	1	5.6	Therapeutic effect. POD	4
	0.108						3.6	*2.5 mg/day = 0.167 mg/kg/day	5
	0.142						4.7	** 5 mg/day = 0.108 mg/kg/day	2
								*** 10 mg/day = 0.142 mg/kg/day	
ECP	0.667	3	1	1	10	1	22.2	Therapeutic effect. POD	
	0.217						7.2	* 10 mg/day = 0.667 mg/kg/day	2
	0.285						9.5	** 10 mg/day = 0.217 mg/kg/day	6
								*** 20 mg/day = 0.285 mg/kg/day	

*POD (Point of Discharge) is the average of maximum recommended average daily dose in adults and children (0–6 and 7–17) and adult (>17 years) in mg/kg/day.
*children (0–6 years) - average wt 15-kg.
**children (7–17 years) - average wt 46-kg.
***adult(>17 years) - average wt 70-kg).
1https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/019537s057,020780s019lbl.pdf.
2Schwab et al., 2005.
3https://www.rxlist.com/noroxin-drug.htm#side_effects.
4https://link.springer.com/article/10.2165/00003495-199346060-00008.
5https://www.ncbi.nlm.nih.gov/books/NBK549776/.
6https://link.springer.com/article/10.2165/00023210-200317050-00004.

$$C_f = \frac{C_m}{C_b} \quad \text{(Eq. 6)}$$

where, C_m is the concentration of a PTM in water sample, and C_b is the established standard or permissible limit of that PTM. The C_b values were derived from the WHO guidelines (Dixit et al., 2021).

The second step calculated the risk posed by individual PTM using Eq. (7):

$$E_r = T_r \times C_f \quad \text{(Eq. 7)}$$

where, E_r is the potential risk of individual PTM, and T_r is the toxic response factor or toxic coefficient for potentially toxic PTM. The T_r values for Cr ($T_r = 2$), Ni ($T_r = 5$), Pb ($T_r = 5$), Cu ($T_r = 5$) and Zn ($T_r = 1$) were adopted from Dixit and Siddaiah (2021).

The third step calculated the potential ecological risk index (RI) which was the sum of the potential risk of all PTM (Eq. (8)):

$$RI = \sum_{i=1}^{n} Er \quad \text{(Eq. 8)}$$

Health risk from PTM to adults and children was calculated according to the method of USEPA (USEPA, 2004). The PTM selected as the target pollutants in this study included Cr, Cu, Fe, Ni, Mn, Pb and Zn, and these were used for non-carcinogenic risk assessment. According to the USEPA framework, the non-carcinogenic health risk was calculated following three steps (Eqs. (9)–(11)).

$$CDI_{ing\text{-}nc} = \frac{[C_m \times IR \times EF \times ED]}{[BW \times AT_{nc}]} \quad \text{(Eq. 9)}$$

where, CDI is the chronic daily intake or average daily dose (ADD) (μg $kg^{-1}day^{-1}$), C_m is the concentration of PTM for individual metal in water (μgL^{-1}), IR is the water ingestion rate (m^3year^{-1}), EF is the exposure frequency (day $year^{-1}$), ED is the exposure duration (year), BW is the average body weight (kg), AT_{nc} is the averaging time for non-carcinogenic effects (day). The values of variables used for the assessment of risks and their detailed description are given in SI (Table S6). Finally, hazard quotient (HQ) (Eq. (10)) and hazard index (HI) (Eq. (11)) were calculated using the equation below:

$$HQ = \frac{CDI}{R_f D} \quad \text{(Eq. 10)}$$

where, R_f D ($\mu gkg^{-1}day^{-1}$)is the reference dose for ingestion and is usually different for every PTM. A HQ value > 1 reflects possible adverse health effects, whereas value < 1 means no adverse health effects.

$$HI = \sum_{i=1}^{n} \Sigma HQ \quad \text{(Eq. 11)}$$

A summation of HQ values of all the PTMs provides the HI, which indicates potential health and safety hazards related to the human health. The value of HI ≤ 1 indicates no significant risk of non-carcinogenic effects, whereas HI > 1 indicates probability of non-carcinogenic effects.

2.5. Quality assurance/quality control and statistical analysis

The pharmaceutical analysis involved repeated injections of working standards (continuous calibration verification standards (CCVs), blanks and mobile phase after every 10 samples. The results obtained were in the range of <25% relative standard deviation (RSD) for mean precision. The coefficient of determination (R^2) values were >0.98 for all the analytes. The spiked concentrations of samples ranged from 5 μgL^{-1} to 500 μgL^{-1} for different analytes, and the recoveries were 72.4–99.3%. The retention time, limit of detection and limit of quantification of the four analytes are given in supplementary table (Table S7). The analysis of PTM was done using appropriate working standards prepared from a Multi-Element Plasma Standard Solution (Specpure™) supplied by Thermo Scientific™, USA. Standard calibration curves were prepared for each metal with $R^2 > 0.98$. After every 20 samples, standard solutions of PTM were run to check the accuracy of the measurement. The RSD for standards and sample replicates was recorded within the range of ≤5% throughout the study. Pearson's correlation was carried out using SPSS (16.0). Geochemical distribution maps for selected PPCPs were generated by using inverse distance weighting (IDW) interpolation method using GIS (Arc Map 10.2). The concentration maps were

prepared using ArcGIS (10.3) software. Concentrations were divided into 5 categories to better visualize the quantification and distribution of contaminants in the region. Based on the sampling points, coordinates were projected in the study region.

3. Results and discussion

3.1. Chemical characteristics of water samples

The average values of selected chemical parameters (pH, TDS, DO, BOD, COD) and permissible limits of these parameters in water are given in Table S8. The individual values of these parameters for all the samples are given in SI (Tables S1 and S2). The box plots shown in Fig. 1 (a) - (c) represent variations and ranges in values of these parameters. The pH was in the range of 6.1–9.7 in the surface water samples and 7.3–9.1 in other representative samples (CS, GW and DR) throughout the sampling period. Of the river water samples, 11% and 44% samples were above the acceptable range of pH according to the WHO guidelines (pH range: 6.5–8.5; WHO, 2017) in July and August, respectively. In other representative samples, ~10% samples from civil supply and ~8% samples from groundwater were above the acceptable pH range. Alkaline nature of surface water in the BBN region was also reported in previous studies (Herojeet et al., 2016, 2020; Rana et al., 2016), where the pH rise of water was attributed to consumption/neutralization of dissolved CO_2 by pharmaceutical effluents released into the water bodies. It was reported that pharmaceutical compounds increased photosynthetic algal activities which remove CO_2 from water as a part of photosynthetic activities, hence decreased dissolved CO_2, reducing acid formation, and hence increasing pH of water (Ramola and Singh, 2013; Chander et al., 2016).

TDS in the water samples fall in the range of 214–1150 mgL^{-1} and 150–5075 mgL^{-1} during July and August, respectively (Table S8). Of the surface water samples, 16 and 5% samples in July and August, respectively, were above the acceptable TDS limit in water (1000 mgL^{-1}) (WHO, 2011). Samples from two locations (R24 and R43) had TDS above 5000 mgL^{-1} SI (Table S2), which indicated direct mixing of effluents or sewage into the river water at these points, as also reported by

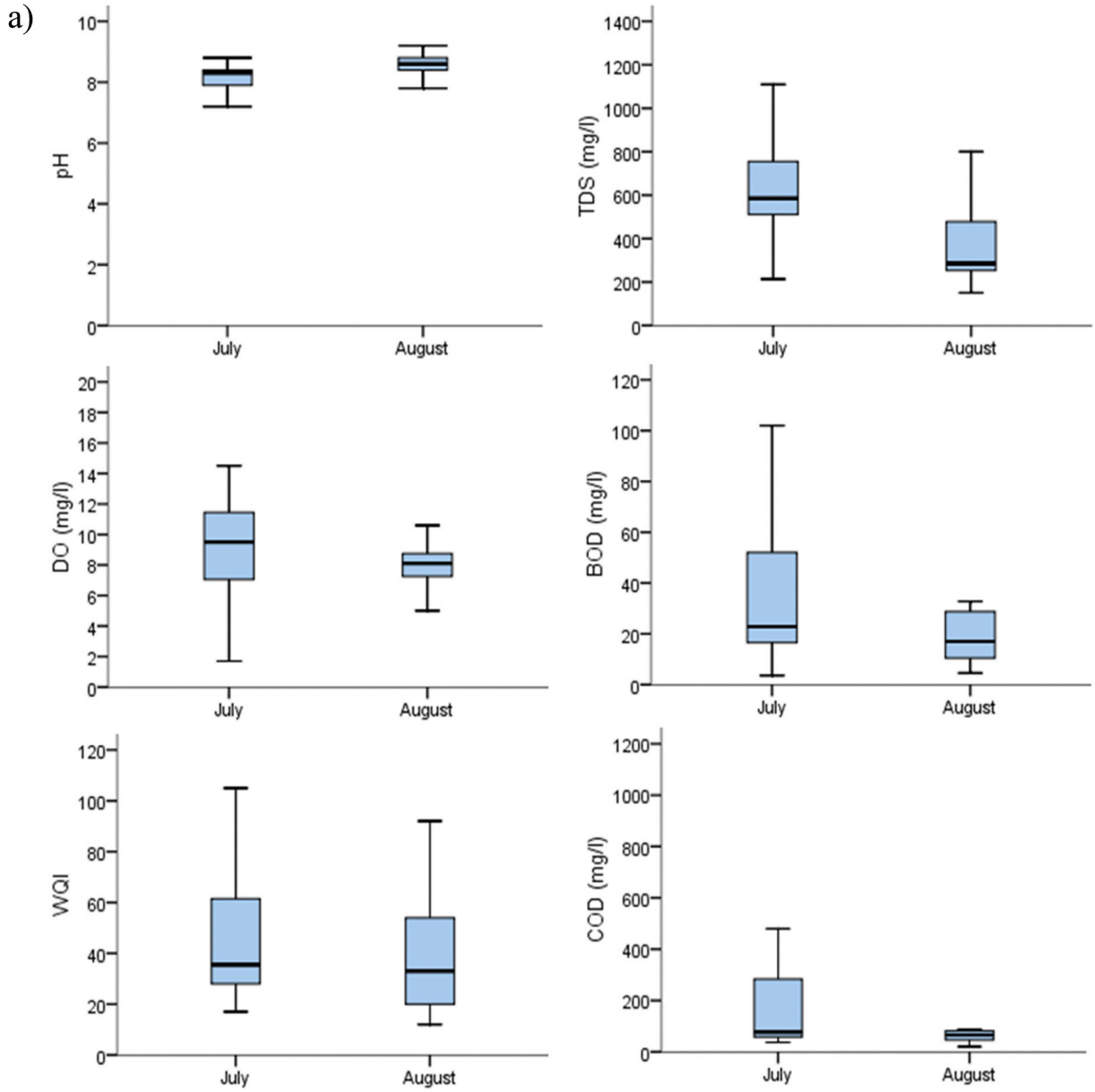

Fig. 1. Box plots depicting (a) concentration and variations of pH, TDS, DO, BOD, COD, and WQI; (b) concentration of major elements (Na, K, Mg, Ca); and (c) PTMs (Cr, Cu, Ni, Pb, Fe, Mn, Al) in different sampling campaigns in the Sirsa river water.

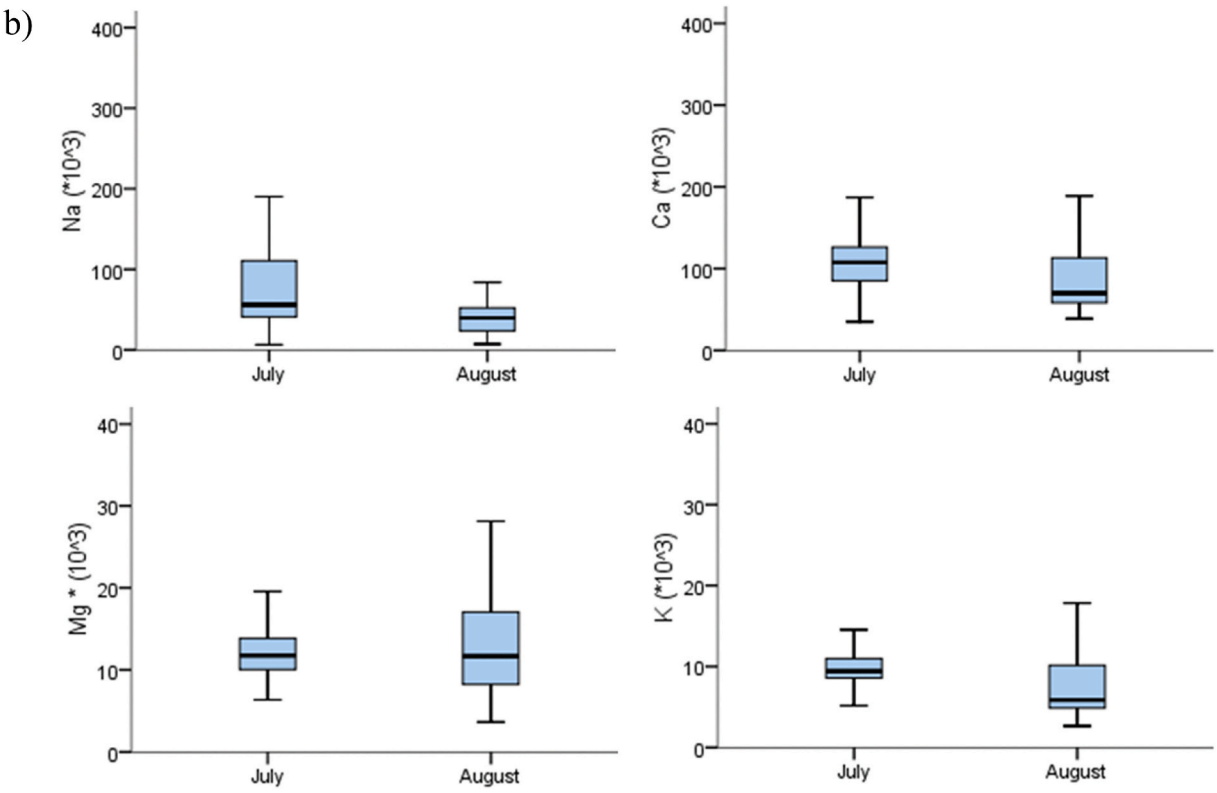

Fig. 1. (*continued*).

Herojeet et al. (2015).

DO is one of the most important factors in determining the health of a river ecosystem. In the month of July, DO in river water was in the range of 1.7–28 mgL^{-1}, and in August it ranged from 2.9 to 18.1 mgL^{-1}. Overall, 1 and 5% of the surface water samples in July and August, respectively, were below the acceptable DO limit prescribed (5 mgL^{-1}) by WHO (Table S8) (WHO, 2011). A high variation in BOD, from 3.6 to 180 mgL^{-1} (July) and 4.6–120 mgL^{-1} (August), alongside variation in COD values, from 37 to 1044 mgL^{-1} (July) and 20–448 mgL^{-1} (August), was found in the water samples. This could be attributed to the discharge of poorly treated industrial effluents containing large amount of dissolved organic matter into the river water from the industrial cluster in the BBN region. A decrease in average value of DO, BOD and COD from July to August was likely due to the dilution of effluents with rainwater. These results corroborated with findings of prior studies in the region (Herojeet et al., 2015).

3.2. Concentration of pharmaceutical compounds in water samples

The concentration of PPCP in water depends on multiple factors such as, PPCP consumption pattern, their release from industries, removal efficiencies of wastewater treatment plants (WWTPs), prevailing temperature, rate of degradation of PPCP and dilution of PPCP in the receiving water (Jin et al., 2014). The large pharmaceutical industrial setup in the BBN region is located in the catchment area of the Sirsa River. Poorly treated effluents from these industries and common effluent treatment plants (CETPs) have emerged as the major sources of pollution in addition to household drains and agricultural runoff. Previous studies reported high concentrations of CIP in CETP discharges which resulted in the mortality of aquatic species (Koshy, 2018; Gaonkar, 2022).

A statistical summary of targeted PPCP concentrations in the analyzed samples is provided in Table S8 and their variations are shown through box plots in Fig. 2. The concentration of different PPCPs in each sample collected across the river is shown in SI (Fig. S3), for a better understanding. The concentrations of CIP, NOR, CTZ and ECP in the Sirsa river water were in the range 'not detected' (n.d.) to 203 μgL^{-1}, n. d. to 277 μgL^{-1}, n. d. to 52 μgL^{-1} and n. d. to 207 μgL^{-1}, respectively, for the samples collected in the month of July. For samples collected in the month of August the concentrations of studied PPCPs were n. d. to 143 μgL^{-1}, n. d. to 324 μgL^{-1}, n. d. to 234 μgL^{-1} and n. d., respectively. The detected concentrations of the studied pharmaceuticals in the Sirsa river water were nearly similar to the concentrations reported by Fick et al. (2009) in surface water of Isakavagu-Nakkavagu river near a pharmaceutical industry (Patancheru Enviro Tech Ltd) in Hyderabad, India. They reported a concentration range of 10–250 μgL^{-1}, n. d. to 5 μgL^{-1}, 5 to 530 μgL^{-1}, and n. d. to 76 μgL^{-1} for CIP, NOR, CTZ and ECP, respectively, which is quite comparable to the results of this study. Studied PPCPs and their concentration in the present study at certain points are also similar to the PPCP concentrations found in the wastewater of a pharmaceutical manufacture company in Patancheru, Hyderabad (Larsson et al., 2007). The points having high concentrations (>100 μgL^{-1}) are: S53, S54 for CIP; S37, S68 for NOR and S27, S34, S61, S63 for ECP in the month of July and R19, R58 for CIP, R80 for NOR and R24, R26 for CTZ in the month of August. These PPCPs are normally found at a concentration below 1 μgL^{-1} in sewage drains, and in few cases, slightly higher than that such as hospital effluents (Kümmerer et al., 2004; Larsson et al., 2007). The above studies observed a high concentration of pharmaceuticals (>200 μgL^{-1}) in samples collected from proximity of industrial effluent discharge sites, which was the case in our present study too. Out of total samples collected, majority of them were observed for the presence of CIP (32% in July and 40 % in August), followed by CTZ (42 % in July and 9% in August). The concentration of CIP in the present study is much higher than the EC_{50} toxicity values published in Robinson et al. (2005) for *Microcystis aeruginosa* (17 gL^{-1}) and *Lemna minor* (203 gL^{-1}). Sarafraz et al. (2020) reported a significant increase in CIP concentration in Indian river waters over a period. These rivers include Yamuna in Delhi (Mutiyar and Mittal, 2014), Musa in

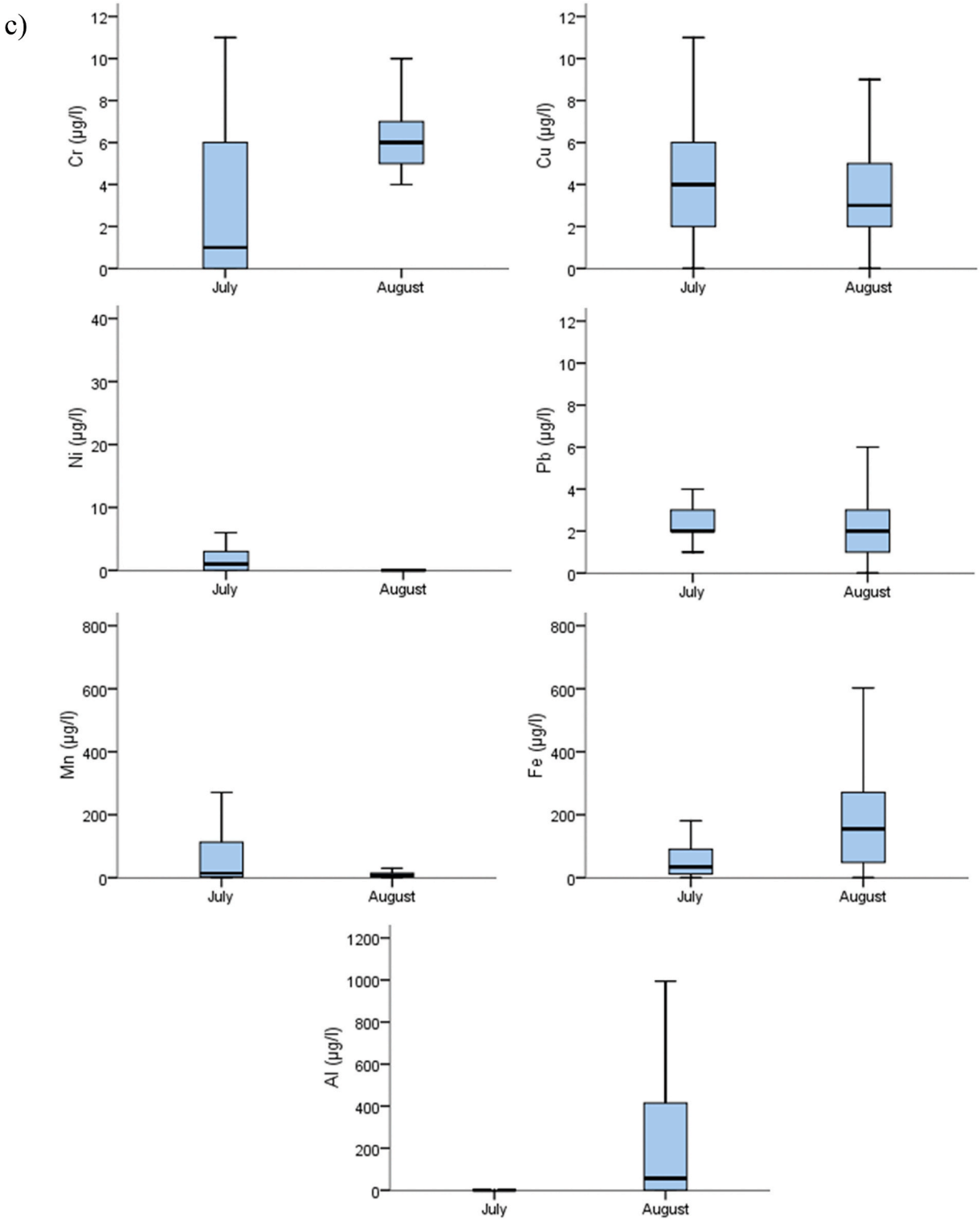

Fig. 1. (*continued*).

Hyderabad (Gothwal and Thatikonda, 2017), and Nag river and Pili river in Nagpur (Archana et al., 2016). The concentration of CIP in the Ganges (Singh and Suthar, 2021) and Yamuna (Mutiyar and Mittal, 2014) river of India was observed in the range of 2–27 μgL^{-1}, which was one order of magnitude lower than the CIP concentration in the Sirsa River water. The river water concentration of CIP in other parts of the world was reported to be 0.03 μgL^{-1} in USA (Kolpin et al., 2002), 0.036 μgL^{-1} in Finland (Vieno et al., 2007), up to 0.5 μgL^{-1} in Italy (Castiglioni et al., 2008) and up to 1.3 μgL^{-1} in Australia (Watkinson et al., 2009). High concentrations of PPCPs in surface water attributed to sewage or direct addition of wastewater or inefficiently treated water to rivers were observed in many developing countries such as China, Brazil and Russia (Luo et al., 2011; Li et al., 2015). Unlike CIP, a good comparison of NOR, CTZ and ECP concentrations found in the current study with previous reports was difficult due to non-availability of data in India rivers for these PPCPs. Majority of the studies (Larsson et al., 2007,

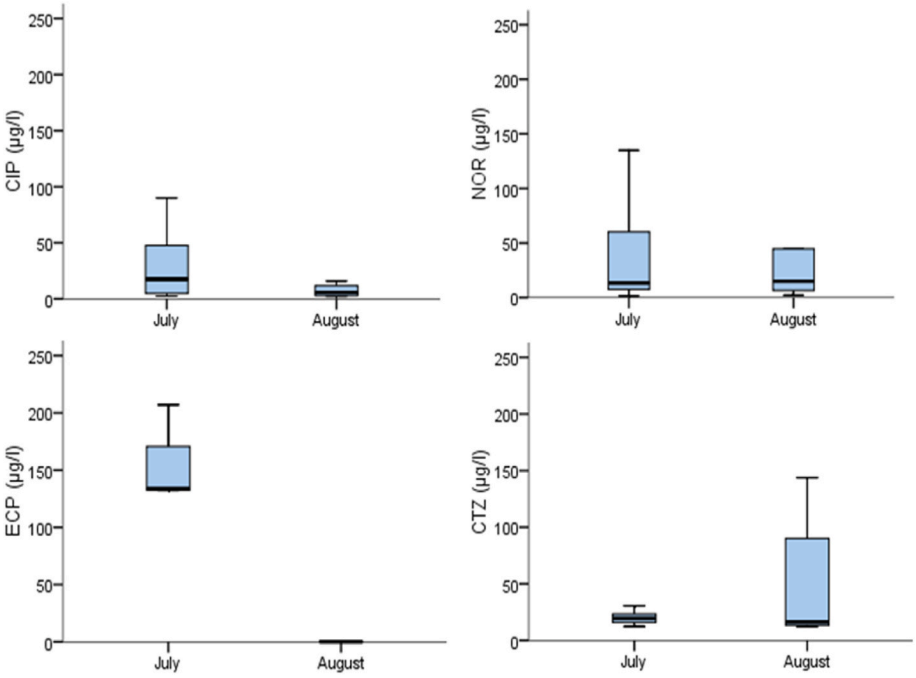

Fig. 2. Box plots representing variation in concentration of PPCPs in studied water samples.

Mutiyar and Mittal, 2014; Gani and Kazmi, 2017) focused on these PPCPs in India had dealt with municipal sewage or treated - untreated wastewater. However, the latter three PPCPs emerged as contaminants of concern in the current study and require constant monitoring in Indian rivers. The maximum number of samples containing CTZ was observed during July sampling event (before the rainy season started). Most of the samples had high concentrations of total PPCP in July than August, which could be attributed to the dilution effect after rainfall events. Similar findings were reported by Padhye et al. (2014) and Sui et al. (2015) where the presence of antibiotics from 47 groundwater sites with a detection frequency of >70% was found. According to the reports from Meteorological Centre, Shimla, Himachal Pradesh, the average monthly rainfall in the month of July and August in the region was 304 mm and 204 mm, respectively.

Among other representative water samples, GW samples had NOR concentration below the detection limit, while the concentration of CIP, CTZ and ECP was in the range of n. d. to 90 μgL^{-1}, n. d. to 16 μgL^{-1} and n. d. to 193 μgL^{-1}, respectively. A similar concentration of these PPCPs in GW was observed by Fick et al. (2009) in Hyderabad. In CS samples, CIP, CTZ and ECP were in the range of n. d. to 3 μgL^{-1}, n. d. to 18 μgL^{-1} and n. d. to 131 μgL^{-1}, respectively, whereas NOR was below the detection limit (n.d.). In DR samples, the CIP, NOR, CTZ and ECP concentration ranged from n. d. to 84 μgL^{-1}, n. d. to 211 μgL^{-1}, n. d. to 23 μgL^{-1} and n. d. to 132 μgL^{-1}, respectively. A similar range of CIP and NOR concentration (8–236 μgL^{-1} and 6–22 μgL^{-1}) in the effluent of two hospitals in Ujjain, India, was reported earlier (Diwan et al., 2010). Fick et al. (2009) reported CIP, ECP and NOR concentrations in pharmaceutical effluents of Patancheru, Hyderabad, India, in the range of 28,000–31,000 μgL^{-1}, 390–420 μgL^{-1} and 150–160 μgL^{-1}, respectively. Macrolides, sulfonamides, β-lactams, fluoroquinolones and tetracycline classes of antibiotics were detected in major rivers/water bodies in South Asia such as Kaveri, Velar and Tamiraparani Rivers, and in the Pichavaram mangrove waste (Di Poi et al., 2018; Sathe et al., 2022). Triclosan was detected in two Tamiraparani River sample locations at higher levels (13–1000 $\mu g\ L^{-1}$) compared to other surface water samples (Jagini et al., 2019). Effluent discharges from industries, domestic areas and mixed untreated wastewater (e.g., from home, hospitals, textile and laundry units) were considered as major sources of PPCP exposure to general population. A wide variety of PPCPs (≥160 compounds) were found in aquatic systems at extremely low quantities ranging from ngL^{-1} to μgL^{-1} (García-Galán et al., 2021). Our research findings corroborate all these previously reported data.

3.3. Water quality index calculation and analysis of metals

The metal concentrations and their variations in Sirsa river water in the months of July and August have been summarized in Table S8 and shown in Fig. 1c. Weathering of parent materials and leaching are the primary sources of metals entering into water bodies (Gao et al., 2016; Wu et al., 2020). Secondary sources include anthropogenic sources, i.e., effluents from industries like automobiles, textile, tannery, electroplating, waste dumping and release of effluents directly from metal industries (abundantly present in the region) results in the addition of large amount of metals in the river water (Tao et al., 2012; Wang et al., 2015). Pharmaceuticals industries also serve as the sources of metals in water (Nessa et al., 2016; Rana et al., 2016). Concentration of Al in water ranged from n. d. – 193 μgL^{-1} in July and n. d. – 1500 μgL^{-1} in August respectively. No sample (collected in July) was found above the permissible limit (WHO, 2017) of Al concentration, but 39% samples were above these limits which were collected in August. This can be attributed to the release of large quantities of effluents from the nearby industries. In ORS, high concentrations of Al above the permissible limit were also observed in groundwater and drain water samples stemming from the sewage treatment plants. This is due to the fact that nearby Al industries and wastewater treatment plants effluents released high concentrations of Al due to wide usages of aluminum salts as coagulants in treatment plants to reduce color, turbidity, and organic matter to treat water (Kajjumba et al., 2021; Tony, 2022). Concentrations of Cr (n.d. −13 μgL^{-1}), Cu (n.d. – 11 μgL^{-1}), Pb (n.d. – 9 $\mu gL\text{-}^{1}$) and Zn (n.d. – 365 μgL^{-1}) in surface water for both July and August were within the permissible limits (Table S8). Concentrations of Fe were in the range from n. d. – 948 and n. d. – 671 μgL^{-1}, whereas Mn was found from n. d. – 1069 and n. d. – 1685 $\mu gL^{-1.}$ in July and August, respectively. Among all the collected samples, 10% samples in July and 39% samples in August indicated high concentrations of Fe above the permissible limits. Similar observations were also found for Mn and Ni. Large variations in

the average concentrations of Na (95,444 and 57,439 μgL^{-1}) and Ca (114,770 and 89,869 μgL^{-1}) were observed in the months of July and August, respectively although the effect was non-significant in August Fig. 1b. This might be attributed to the dilution effect with increase in the amount of rainfall. In general, high concentrations ($\geq$100 μgL^{-1}) of metals (Al, Fe, Mn, Ni, and Zn) are found in the river water during rainfall event due to the industrial discharges which are stabilized in the catchment of the river in the post-monsoon period (Herojeet et al., 2016, 2020).

Quality of water as determined from water quality index classification (Singh and Hussian, 2016) indicates excellent for majority (70 %) of the samples in July and August (Table 3). 16 % and 27 % samples fell in the good category, whereas 8 % and 3% samples were in poor category. Samples of R24, R26 in July and S34 in August fell in unsuitable category which was possibly due to the vicinity of multiple small drains, which contributed towards high BOD, COD and TDS values. Among ORS, samples R27 and R89 (groundwater) and R47 (civil supply) fell in the good category.

3.4. Correlation analysis

The relationships between water quality parameters and the studied PPCPs have been shown in Table 4. From the two sampling campaigns, Pearson correlations were calculated and it was observed that among the four targeted PPCPs, NOR had the best relationship with Al. In the river water samples, Al had a significant positive relationship with NOR (R^2= 0.65, n = 23, $p < 0.01$). Also, CTZ had moderate correlation with Mg (R^2= 0.50, n = 121, $p < 0.01$) and K (R^2= 0.50, n = 124, $p < 0.01$). Moderately strong correlation of Ni was observed with Mn ($R^2 = 0.68$ at $p < 0.01$); whereas poor correlations were observed for Mg ($R^2 = 0.47$ at $p < 0.01$) and Fe with Al ($R^2 = 0.54$ at $p < 0.01$). As both Fe and Al are abundantly found in the water samples of the BBN region, therefore their dominant sources might be attributed to the industrial discharges as discussed in the previous section. The correlations among the studied parameters were improved when they were calculated separately from two different sampling events.

3.5. Health risks assessment

3.5.1. Ecological and human health risks from targeted pharmaceuticals

Pharmaceuticals released into the river system through industrial and domestic effluents or waste dumping may pose severe ecological risks (Kookana et al., 2011; Mutiyar and Mittal, 2014). Health risks described through hazard quotient (HQ) indicate risks if its value > 1, as discussed in the above section. Less discharge/controlled release of effluents from industrial plants and low risks were observed in Korean rivers by Choi et al. (2008). On the other hand, Agunbiade and Moodley (2014) and Sarafraz et al. (2020) had observed HQ values between 1 and 10 due to the occurrence of CIP in South African and Indian rivers, thus people are at adverse health risks of CIP contamination encountering this river water system. This is due to the high discharge concentrations of these pharmaceuticals in the environment.

RQ values in the studies of Gothwal and Thatikonda (2017) and Mutiyar and Mittal (2014) were in the ranges between 0.1 and 1, which indicated probable adverse ecological risks of CIP in the surface water (Sarafraz et al., 2020). Among the targeted PPCPs in the Sirsa river, CTZ followed by CIP exhibited noticeably high RQ values for algae (Fig. 3a). Also in this study, high PPCP concentrations were observed for CIP and CTZ in July and August (Fig. 2). Halling-Sørensen (2000) have also reported adverse effects and toxicity of CIP on green algae. Although, there are much less reports available related to the toxic effects of CTZ and ECP, high RQ values related to the ECP was observed in the present study for *Daphnia* (11) and fish (1.5) (Fig. 3a).

HQ values related to the human health risks stemming from PPCPs are depicted in Fig. 3b. HQs <1 are assumed to present no appreciable risks to human health after consumption of these PPCPs whereas, HQs >1 requires additional assessments methods to assess potential risks. According to the methods used for studying health risks in the present study, average HQ values for four analytes followed the order: ECP > CTZ > CIP > NOR for children (0–6 yr); ECP > CTZ > NOR > CIP for children (7–17 yr) and ECP > CTZ > NOR > CIP for adult (>17 yr). HQ values for CIP, NOR, CTZ and ECP were 0.0005, 0.001, 0.106 and 0.135 for children of the age (0–6) year, whereas, values were 0.001, 0.005, 0.179 and 0.451 respectively, for children of the age (7–17) year. For adults (>17 year), HQ values were 0.001, 0.007, 0.127 and 0.315, for CIP, NOR, CTZ and ECP, respectively. Highest HQ was observed for ECP followed by CTZ, NOR and CIP. Among the collected samples, only one sample (R26) with HQ > 1 was observed which implied health risk (Table S9). The risk was associated with adults and children (7–17 years) from CTZ concentration as the HQ was >1. This might be due to the addition of household sewage at this point. All other samples were observed for studied analytes at no health risks level (HQ < 1). This does not confirm the status of water as safe as values of PNEC depends upon various factors used for calculation.

Few samples showed HQ values between 1 and 0.2 for ECP and CTZ. These samples included those points that were joining drains (S11, S26, S27), near landfill (S34), or near pharmaceuticals industries hub (S57, S61, S63) (Table S9). These samples warrant further investigation on the toxicity effects. Others with HQ < 0.2 displayed no appreciable concern to human health according to the classification provided in the studies of Yang et al. (2017) and Sharma et al. (2019).

3.5.2. Ecological and human health risks from PTM

The average degree of contamination for heavy metals and the corresponding evaluation standards for potential ecological risk index (RI) are given in Table 5. Based on single contamination coefficient (C_f) values of all the metals, 100% samples of July and August were found under the low contamination category. The comprehensive contamination factor (C_d) and potential risks of individual metals (Er) classification showed low contamination in the Sirsa river. Also, low potential ecological risk index was observed from the calculated risks values. Hence the ecological risk assessment values from the studied potentially toxic metals suggested low ecological risks during both seasons (July and August) (Table 5).

The average HQ and HI values for health risks from metals are presented in Table S10 and evaluates a comprehensive risk assessment in

Table 3
Water quality index categorization for samples in Sirsa river water and other representative samples (calculated according to Singh and Hussian, 2016).

		No. of samples falling under the category					
	Sample type	Excellent <50	Good 50–100	Poor 100–200	Very Poor 200–300	Unsuitable >300	Total samples
July	SW	43	10	5	2	1	61
August	SW	51	20	2	0	1	73
ORS	DR	0	0	2	0	0	8
	CS	0	1	0	0	0	10
	GW	0	1	0	0	0	25

SW: surface water; GW: ground water; DR: drain water: CS: civil supply: GW groundwater.

Table 4
Correlation analysis of studied parameters in the Sirsa river samples.

	pH	TDS	DO	BOD	COD	CIP	NOR	CTZ	ECP	Cr	Cu	Zn	Mn	Fe	Pb	Ni	Al	Na	Mg	Ca
pH	1.00																			
TDS	−0.17	1.00																		
DO	0.16	−0.05	1.00																	
BOD	−0.32	−0.07	−0.14	1.00																
COD	**0.52**[a]	0.02	−0.16	0.52	1.00															
CIP	−0.01	−0.02	0.36	−0.15	−0.22	1.00														
NOR	0.25	−0.15	−0.12	0.03	−0.19	0.08	1.00													
CTZ	−0.11	0.34	−0.05	0.00	0.18	0.01	−0.26	1.00												
ECP	−0.08	0.08	−0.03	−0.06	0.37	0.04	−0.24	0.03	1.00											
Cr	0.23	0.04	0.13	0.07	−0.23	−0.23	0.04	0.12	−0.23	1.00										
Cu	−0.19	−0.02	−0.10	0.17	0.25	0.08	−0.12	0.01	0.00	−0.21	1.00									
Zn	0.00	0.10	−0.02	0.03	−0.10	−0.07	−0.17	−0.04	−0.03	0.13	−0.04	1.00								
Mn	−0.21	**0.58**[b]	0.05	−0.03	0.00	−0.03	−0.14	0.27	0.12	0.10	−0.02	0.10	1.00							
Fe	0.05	0.14	−0.02	0.02	−0.05	−0.12	−0.13	0.16	0.04	0.27	0.07	−0.05	0.42	1.00						
Pb	−0.14	0.12	−0.02	0.18	0.29	−0.01	−0.29	0.46	0.09	−0.06	0.27	0.09	0.22	0.14	1.00					
Ni	−0.07	**0.85**[b]	0.08	−0.15	−0.05	−0.01	0.19	0.26	0.04	0.14	−0.01	0.15	**0.68**[b]	0.24	0.01	1.00				
Al	0.23	−0.24	−0.06	−0.05	−0.32	−0.14	**0.65**[b]	−0.12	−0.09	0.26	0.01	−0.09	−0.19	**0.54**[b]	−0.26	−0.11	1.00			
Na	−0.24	0.37	0.29	−0.06	−0.01	−0.05	−0.02	0.18	0.05	−0.06	0.43	−0.04	0.30	0.09	0.20	0.40	−0.18	1.00		
Mg	−0.10	**0.61**[b]	−0.10	0.22	0.13	−0.05	0.12	**0.50**[b]	0.04	0.15	−0.02	0.15	0.36	0.13	0.28	**0.47**[a]	−0.14	0.25	1.00	
Ca	−0.09	0.10	0.30	0.04	0.16	−0.03	−0.17	0.25	0.03	−0.18	0.06	−0.05	0.08	0.10	0.33	−0.09	−0.23	0.33	0.39	1.00
K	−0.13	**0.46**[a]	0.00	0.16	0.14	0.00	0.15	**0.50**[b]	−0.03	0.12	0.19	−0.06	0.25	0.16	0.27	0.31	−0.19	0.45	**0.71**[b]	0.28

a. Cannot be computed because at least one of the variables is constant.
[a] Correlation is significant at the 0.05 level (2-tailed).
[b] Correlation is significant at the 0.01 level (2-tailed).

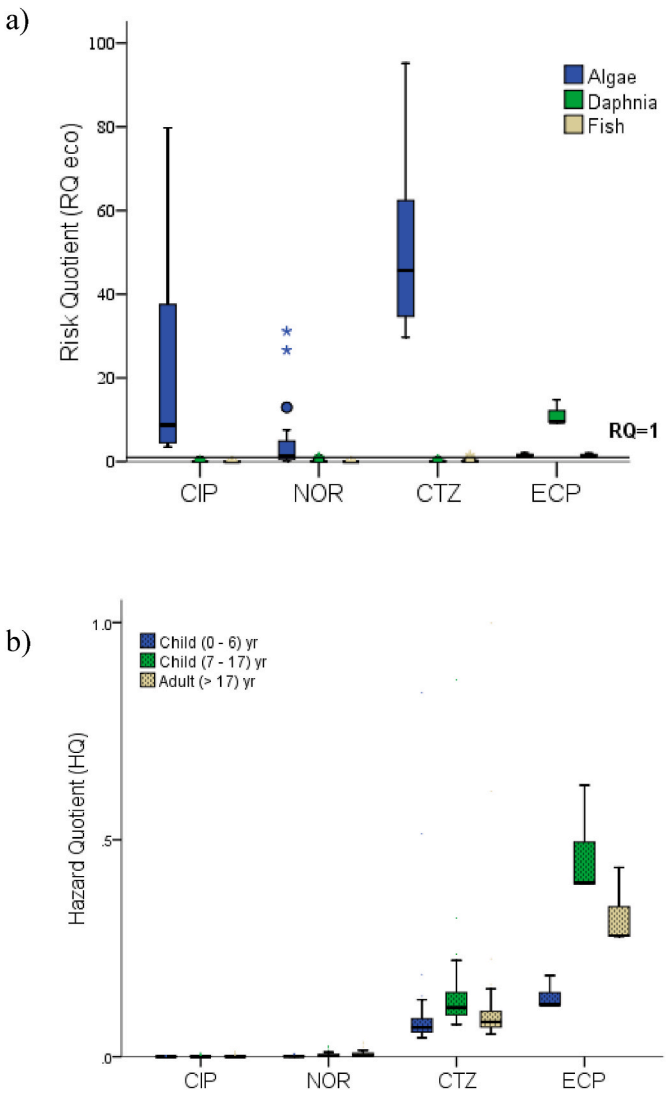

Fig. 3. Box plots depicting (a) risk quotient values for ecological risk of pharmaceuticals (RQ_{eco}) to species algae, *Daphnia* and fishes in Sirsa river water; (b) variations in hazard quotient (HQ) values for four selected pharmaceuticals in human health risk assessment in the Sirsa river water.

Sirsa river from various toxic metals. The average hazard quotient (HQ) values for ingestion concerning adults and children were <1 for all the metals. But for individual sites, 19% samples in July and 11% samples in August seasons had HQ values > 1 for adults. Similar results were obtained for children for 19% and 7% samples during July and August. This suggests significant risks from ingestion of water at certain sites. But average HI values were below 1 both for adult (0.60 in July and 0.55 in August) and children (0.52 in July and 0.47 in August), indicating no significant risks from metals from ingestion of river water. The prevalence of metal ions and the interaction between metal ions and pharmaceuticals may result in the formation of toxic coordination complexes and give synergistic/antagonistic interactions among the pollutants. This may also induce the growth of antibiotic-resistant (and/or multi-resistant) bacteria and genotoxicity, which can pose a threat to human as well as environmental health (Andreu et al., 2016). A detailed investigation of the interaction between metal ions and pharmaceuticals is out of scope of the present study and should be pursued in the future.

3.6. Concentration maps for pharmaceuticals

The concentration maps (Fig. 4) were plotted to check the

Table 5
Average degree of contamination of selected heavy metals and corresponding evaluation standards for potential ecological risk index (RI).

Wetland		C_d	Contamination	E_r					RI	Contamination
			based on C_d	Cr	Cu	Ni	Zn	Pb		based on RI
July	Min	0.02		0.00	0.00	0.00	0.00	0.00	0.05	
	Max	0.81		0.44	0.03	1.07	0.00	2.50	3.37	
	Avg	0.34	Low	0.12	0.01	0.17	0.00	1.23	1.54	Low
August	Min	0.08		0.16	0.00	0.00	0.00	0.00	0.17	
	Max	1.64		0.52	0.03	6.93	0.12	4.50	7.71	
	Avg	0.35	Low	0.25	0.01	0.16	0.00	0.93	1.36	Low

Cf < 1: Non contamination, ≥1 - <2: Light, ≥2 - <3: Moderate, ≥3: Heavy.
Cd < 8: Low, ≥8 - <16: moderate, ≥16 - <32: relatively high, ≥32: very high.
Ef < 40: Low, ≥40 - <80: moderate, ≥80 - <100: strong, ≥32: extremely high.
RI < 150: Low, ≥150 - <300: moderate, ≥300 - <600: strong, ≥600: extremely high.

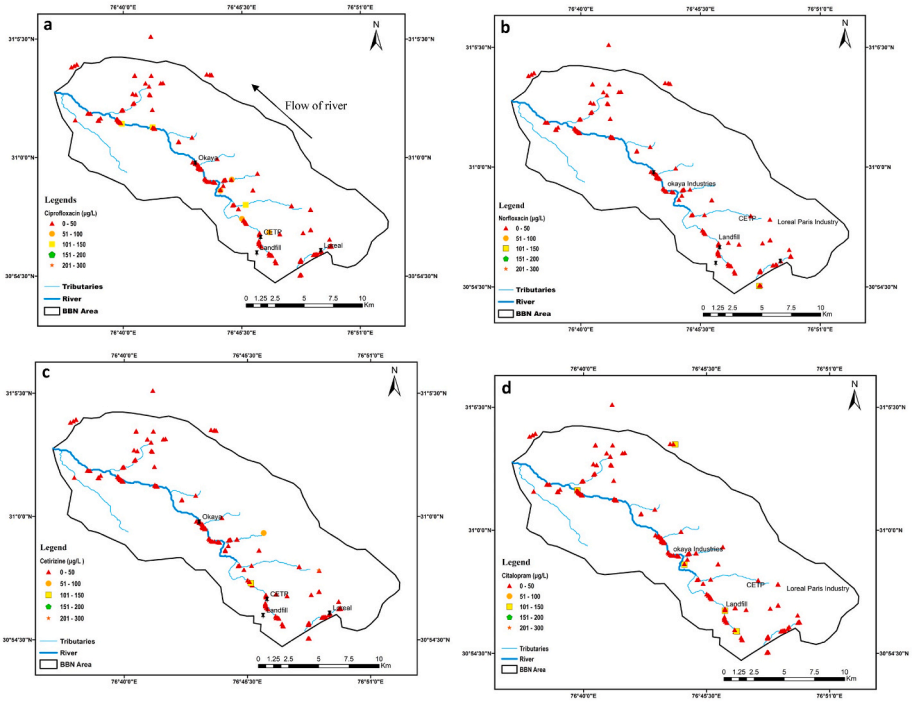

Fig. 4. Concentration maps depicting variations of (a) CIP; (b) NOR; (c) CTZ; (d) ECP, in the Sirsa river water.

distribution of concentrations of studied pharmaceuticals in the river. Through these maps regions for high concentrations of studied pharmaceuticals were identified and explained. The concentration maps indicated that majority of samples fell in the concentration ranges between 0 and 50 μgL^{-1} for all four pharmaceuticals along the stretch of the river. Concentration of CIP increased in the industrial cluster zones and in regions receiving discharges from WWTP. The CIP and CTZ concentrations in these regions fell in the ranges of 50–100 μgL^{-1} and 100–150 μgL^{-1}.

4. Conclusions

The present study was conducted to monitor and quantify selected pharmaceuticals in the Sirsa river water to check metals and pharmaceuticals occurrence and to estimate related exposure (ecological and health) risks. Among the studied metals, Cr, Cu, Pb, and Zn were found within the permissible limits of WHO, whereas values of Al, Fe, Ni and Mn remained above these limits in 10–40% samples due to the addition of Al and Fe coagulants during water treatment. Concentrations of pharmaceuticals were found higher (≥320 μgL^{-1} for NOR in the month of August) in the Sirsa river water as compared to other Indian rivers such as the Yamuna and Ganga. Risk assessment of pharmaceuticals with RQ > 1 indicated high ecological risks to algae from CIP, NOR and CTZ. ECP indicated risks to aquatic species such as *Daphnia* and fish. Future studies should focus on PPCPs' interaction with microbial community, monitoring of antimicrobial resistance genes in the polluted water and human health risk arising from other antibiotics in the studied region.

CRediT authorship contribution statement

Arohi Dixit: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Himanshu Pandey:** Investigation, Data curation. **Rajiv Rana:** Investigation. **Anil Kumar:** Resources, Methodology, Formal analysis. **Rajkumar Herojeet:** Writing – review & editing, Validation. **Renu Lata:** Writing – review & editing, Validation. **Raj Mukhopadhyay:** Writing – review & editing, Validation, Data curation. **Santanu Mukherjee:** Writing – review & editing, Supervision, Resources, Project administration. **Binoy Sarkar:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

This study was supported by the Lancaster University-Global Challenge Research Funding Scheme (Grant No. GCRF/2021-02-UTB1000XS22). Authors are also thankful to Shoolini University for providing administrative and technical support during the project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.123668.

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