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Pharmaceutical Residues in Wadi Zomar Catchment Area in Palestine: Screening Assessment

Ala'a Jaddou[1,*], Souad Belkebir [2,*], Saed Khayat[3],
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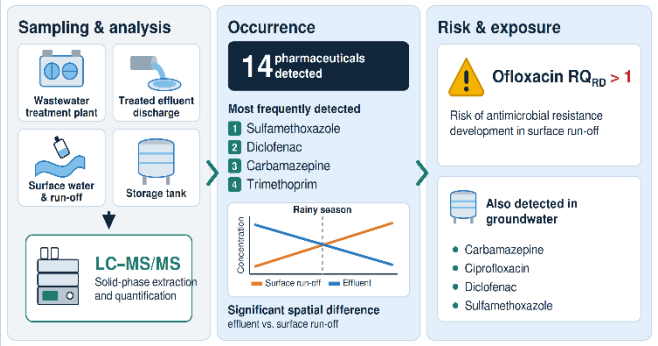
Abstract: The presence of antimicrobials in wastewater treatment plant discharges, among other pharmaceutical compounds (PhCs), raises concerns regarding their contribution to health and aquatic ecological implications, including antimicrobial resistance (AMR). Two campaigns of grab wastewater samples were collected, and one sample of drinking water was collected. Water samples were analyzed using LC-MS/MS. Risk Quotients (RQ_{RD}) were calculated for the detected antibiotics as risk assessments for AMR. Sulfamethoxazole (SMX), trimethoprim (TMP), diclofenac (DIC), and carbamazepine (CBZ) were the most frequently analytically measured pharmaceuticals in all water samples. West Nablus WWTP delivered variable removal efficiency in both campaigns. However, it was noticed that there was a significant spatial difference between the WWTP effluent discharge point and the Anabta-Zomar point of sampling directly after the rainy season. Ofloxacin (OFX) had an RQ_{RD} > 1 in WWTP effluent discharges and surface run-offs along the sampling point and is found to pose a risk for AMR development. Drinking water is found to be polluted with carbamazepine (CBZ), diclofenac (DIC), ciprofloxacin (CIP), and Sulfamethoxazole (SMX). The above findings are in line with the worldwide aquatic context concerning pharmaceutical contaminants. Additionally, they highlight the necessity for comprehensive assessments of the ecological risks posed by pharmaceutical residues and their possible role in promoting antimicrobial resistance, especially regarding the antibiotics identified in this research.



Keywords: WWTP, Pharmaceutical compounds, antibiotics, environment, wastewater, sustainability.

Introduction

Pharmaceutical (PhC) residues in the environment are considered "emergent pollutants" requiring close attention [1,2]. Numerous studies reported anticonvulsants, hormones, anti-inflammatory medications, and antibiotics as the most detected pollutants in aquatic compartments emphasizing the inability of conventional WWTPs to partially or fully remove such PhCs before effluents are discharged [3,4], with the possibility of leaching and reaching groundwater and drinking water as it has been found in China, Kenya, India, the Middle East and North Africa (MENA) region, and the United States of America (USA) as well as in Europe [2,5–9].

The key physicochemical features of PhC compounds contribute to their stability and resistance to degradation, which has led to their frequent identification. [10,11]. The aggregate intake in the human and veterinary sectors also increases the predicted load in water compartments and its reach to groundwater and drinking water [12,13]. In China, one of the leading countries in pharmaceutical consumption [14,15], antibiotics were detected in filtered tap water with a total average of 0.182 µg/L[16]. The MENA region research portion of PhCs' detection in finished drinking water is limited compared globally [9,17]. Few studies have identified the presence of PhCs in finished drinking water in Iran, Algeria, Iraq, Saudi Arabia, and Egypt [18–22]. In Palestine, no data on PhC residues in drinking water were available. Only one study reported the detection of trace residues of hormones in raw wastewater [23], and another study reported antibiotics and herbicide residues in small-scale, off-grid greywater treatment systems [24].

The potential toxicological impacts on both natural environmental inhabitants and human health have been subject to scrutiny [25]. Trace residues of PhCs are sufficient for varying toxicity effects, as documented by researchers, depending on the settings in which they are discovered [4,26]. For example, carbamazepine (CBZ) toxicity in inhibiting the growth rate of *P.*

[1] Department of Medicine, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine. E-mail: alaa.jadoo@najah.edu
[2] Department of Family and Community Medicine, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine. E-mail: souadbelkebir@najah.edu
[3] College of Agricultural Sciences and Technology, Palestine Technical University Kadoorie, Tulkarm, Palestine. E-mail: s.khayat@ptuk.edu.ps
* Corresponding author: alaa.jadoo@najah.edu
ORCID iD (Ala'a Jaddou): 0009-0006-5961-6485
*Corresponding author: souadbelkebir@najah.edu
ORCID iD (Souad Belkebir): 0000-0002-4788-7900

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subcapitata is observed at a concentration of 10.4 mg/L, while 6 mg/L of diclofenac (DIC) is sufficient for the same effect [27]. Environmental antibiotic detection worries about antimicrobial resistance (AMR) selection pressure and its potential impact on human public health. The minimal selection concentration (MSC) of an antibiotic creates selection pressure in wild susceptible and resistant microorganisms. Resistant bacteria can prevail, but vulnerable natural populations are quickly eradicated [28,29]. *Gullberg et al.* reported a MSC for ciprofloxacin (CIP) of 0.1 µg/L in *Escherichia coli* — approximately 1/230 of the minimum inhibitory concentration (MIC) of the susceptible strain [28]. Notably, the concentration of ciprofloxacin in the environment has been observed to exceed the MSC value defined by *Gullberg et al.* [4]. The vast majority of reported toxic values are based on acute toxicity effects and/or under laboratory conditions, eliminating complex matrix effects (antagonistic/synergistic effects) [27,30–32]. Furthermore, as a result of the wide detection of various PhC residues in environmental compartments, some countries integrated PhC residue surveillance systems as a response measure to evaluate any ecotoxicity (e.g., the European Union (EU) watch list [33], The drinking Water Contaminant Candidate List in the U.S. [34], Australian Guidelines for Water Recycling [35], and as proposed by *Y. Li et al.* for the Chinese aquatic environment [36]). Pharmaceutical manufacturing industries related to biotechnology, research, and diagnostics have collaborated and formed the AMR Industry Alliance to curb AMR in the environment. They have endorsed antimicrobial predicted no-effect concentration (PNEC) values reported by scientific research as cut-off points regulating their effluents before discharge [37]. On a higher level, the World Health Organization (WHO), the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the United Nations Environment Programme (UNEP) all have endorsed the One Health approach, which considers the complex interconnections between human, animal, and environmental health. Within this scope, environmental surveillance is becoming well recognized as a fundamental component in AMR mitigation strategies and protection of public health [38,39].

In northern Palestine, a WWTP was established in West Nablus (2015) to enhance the ecological and well-being settings in the upper portion of Wadi Zomar (previously used as a sewage drainage). The main focus of the West Nablus WWTP is to preserve the integrity of both surface and groundwater by preventing contamination and the utilization of reclaimed wastewater for irrigation. Wadi Zomar is currently being used as an environmental discharge compartment for West Nablus WWTP treated wastewater [40]. Previous research found trace residues of hormones in raw wastewater before it entered West Nablus WWTP. Despite high removal estimates, trace hormone effluents are released into Wadi Zomar [23]. This makes Wadi Zomar an interesting case study for investigating the occurrence of emerging pharmaceutical contaminants.

To the best of our knowledge, no study has examined different pharmaceutical residues in Palestinian aquatic matrices. Therefore, we aim to study PhC residues in wastewater before and after treatment by West Nablus WWTP, as well as in drinking water. To compare hospital antibiotic dispensing patterns with the occurrence of selected antibiotics in the Wadi Zomar catchment area and to conduct a screening-level risk assessment in antimicrobial resistance development.

Materials and Methods

Study Area

West Nablus WWTP

Nablus city is located in the north of Palestine and 681 m above sea level. The WWTP is located west of Nablus and is 305 m above sea level. It receives sewage (domestic and industrial) from the West Nablus catchment area alongside 5 surrounding villages (Zawata, Beit Eba, Dair Sharaf, Beit Wazan, and Qusin), with an approximate population of 120,000 (Figure 1a). The plant has been in service since 2015 and operates as a secondary treatment facility [41].

West Nablus WWTP uses activated sludge with mechanical treatment, biological treatment, and sludge treatment steps with gas utilization [41]. Wastewater is first screened for coarse and fine debris before entering the WWTP. Screened wastewater is then moved to gravity sedimentation tanks, where more than 50% of organic suspended solids are removed, forming the primary sludge (pumped to the primary thickener tank). Afterward, the remaining suspended solids are removed in the aeration tanks, using activated sludge, where excess sludge is formed. The activated sludge employed consists of a high concentration of special aerobic bacteria and other microorganisms, which were activated in the aeration tanks under a high concentration of oxygen. The excess sludge was pumped to belt thickeners to increase the thickness to 6%. Thickened primary sludge and thickened excess sludge are mixed before being pumped into the anaerobic digester. The solids retention period in the digester is 21 days, during which optimal circumstances for anaerobic bacteria are sustained (temperature, pH, and solid content). The biogas produced from the digester normally contains 33% carbon dioxide and 66% methane, which is in turn used to produce the electrical and thermal power required to run the plant. The location of the plant is displayed in Figure 1a. The loading rate is estimated to be 14,000 m^3/day according to the initial design. In 2022, it received an average of 12,591 m^3/day, and the effluent averaged 484 m^3/hr in the same year [41].

Palestine is located in the Mediterranean region and has a moderate climate. The period of rainfall occurs from November to April, and the period of little or no rainfall occurs from June to September. To investigate the impact of seasonal variations and temporal factors on targeted PhC residues, two sampling campaigns were conducted: one during the wet season (spring) and one during the dry season (autumn) [42].

Wadi Zomar

Wadi Zomar is a hydrological stream that originates from the mountains in Nablus towards the east and flows through historical Palestine until it reaches its outlet on the western Mediterranean (Figure 2). The area covers around 44 kilometers in length and 5 kilometers in width, with depths ranging from 0.2 meters to 8 meters (Figure 2). Wadi Zomar has been heavily contaminated for many years due to the presence of industrial facilities, domestic wastewater, stone mills, and olive mills. These activities have significantly changed the water quality in the stream, with contaminated stream water infiltrating the mountain aquifers [42].

The investigated area of Wadi Zomar in this study comprises 5 km and lies between West Nablus WWTP and Anabta village. Wadi Zomar passes through the village and is surrounded by groundwater wells (natural aquifers extending more than 300 m

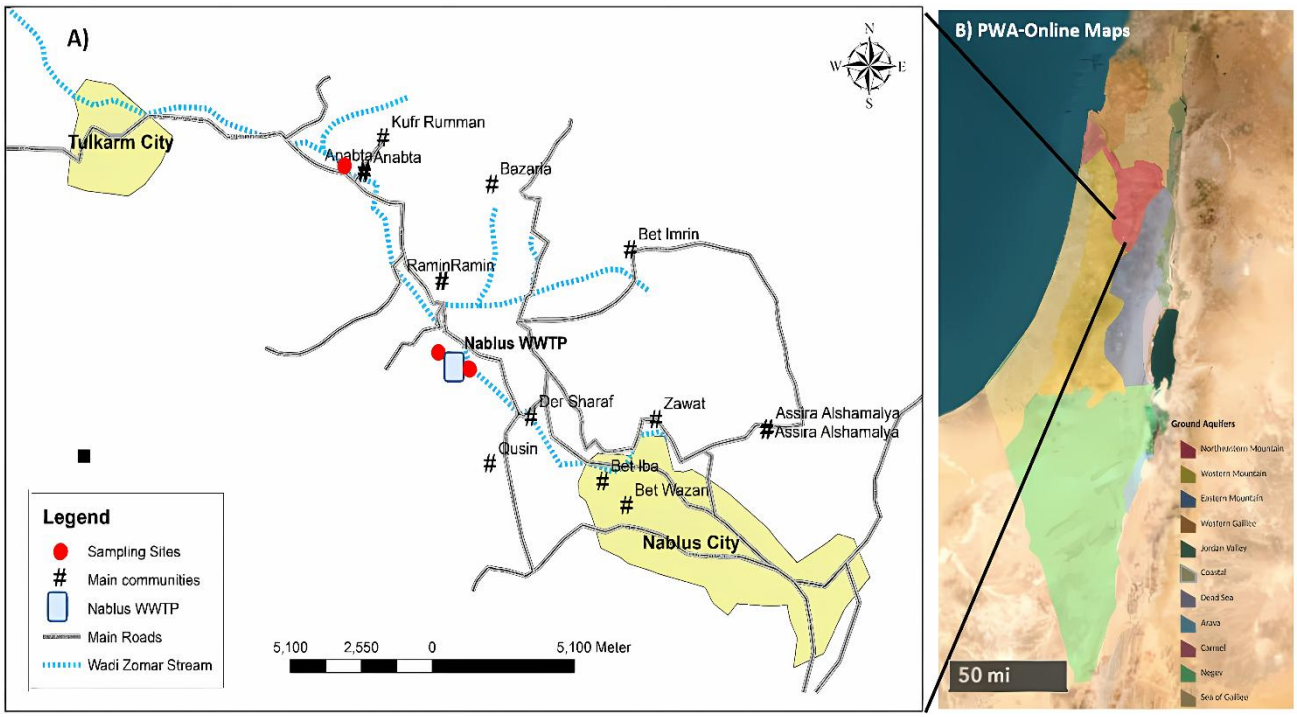

Figure (1) Location of West-Nablus WWTP and sampling points. (A) The geographical locations of sampling points (red circles) at the inlet of the West Nablus WWTP (blue rectangle), the outlet point, and Wadi Zomar-Anabta (red circle). Wastewater at Wadi Zomar has many tributaries (from Bet Imren, Bazaria, and Kufr Rumman) along its natural path as displayed here. (B) Palestine/West Bank ground aquifers water supply map adopted from the Palestine Water Authority (PWA) website, Accessed from: https://www.arcgis.com/apps/instant/sidebar/index.html?appid=98e6f48832f54d218cb81a53b6970a88

in depth). Most of these wells are municipal wells used for regular human consumption, and some are agricultural wells [43]. The western and northeastern water basins are the main aquifers for northern West Bank, Palestine. These aquifers are surrounded by layers of Jerusalem-Turonian rock formation. The shallow layer of the uppermost Jerusalem-Turonian aquifer permits pollutants to move directly to the absorption zone of the major aquifers below or near the Wadi Zomar stagnant area, where most groundwater wells are dug [44].

Water Sample Collection

Wastewater Sample Collection

The first sampling location for the West Nablus WWTP was selected at the entrance point, as it serves as the central point where all untreated sewage from nearby communities is eventually discharged. Therefore, we anticipate that there is an increased probability of detecting targeted PhCs in our study.

The second sampling location was the West Nablus WWTP effluent exit point before discharge into Wadi Zomar. This point was selected to investigate the presence/absence of PhCs in treated wastewater and the removal efficiency of West Nablus WWTP before discharge into the receiving environment, Wadi Zomar.

This Wadi passes through Anabta village, Tulkarem city (63 m above sea level), historical Palestine, and finally into the Mediterranean Sea. The third sampling point was collected from Wadi Zomar in Anabta village to further evaluate the fate of targeted PhCs as treated surface wastewater travels along Wadi Zomar for a distance of about 5 km. This point was also chosen to investigate the potential for PhC residues to leach from Wadi Zomar into the underlying groundwater aquifers, given the unique hydrogeological features of the earth layers in Anabta village and Wadi Zomar [45,46].

Three samples per sampling campaign were collected. At the WWTP entrance, exit, and a 20-foot wadi at mid-depth from the bridge, where water was well mixed, samples were gathered. Grab sampling is low-cost and well-suited to budget constraints and cross-border laboratory access. However, a grab sampling in two sampling campaigns may not capture variability or provide a valid removal efficiency assessment; it's considered adequate for the study's scope [47].

Six 1 L grab wastewater samples were collected in amber glass bottles and divided into two campaigns (spring and autumn). Each campaign consisted of three grab samples as follows: one collected from the West Nablus WWTP inlet, one from the West Nablus WWTP outlet, and one from treated surface wastewater from Wadi Zomar in Anabta village. Amber glass bottles were previously rinsed with LC-grade methanol (Sigma-Aldrich, St. Louis, MO, USA), then washed with double deionized water (Chromasolv™ Plus, for HPLC-gradient obtained from Honeywell Riedel-de Haën, Muskegon, MI, USA). Samples were immediately stored in ice bags and refrigerated at 4-8 °C until shipment to the analyzing laboratory (Royal Scientific Society, Amman, Jordan) within 48 hours of collection. The analyzing laboratory is internationally accredited (ISO 9001, ISO 17020, ISO 17025, UKAS, and JAS).

An additional two grab samples were collected from Wadi Zomar at the Anabta sampling point in each campaign, stored on ice bags, and tested for wastewater quality parameters at West Nablus WWTP Lab. Those parameters include Chemical Oxygen Demand (COD), Biological Oxygen Demand (BOD), Total Suspended Solids (TSS), conductivity, and pH.

Groundwater Sampling

A Passive Organic Chemical Integrative Sampler (POCIS) (Environmental Sampling Technologies, EST Inc., St. Joseph, MO, USA) was used for groundwater sampling. Two POCIS with

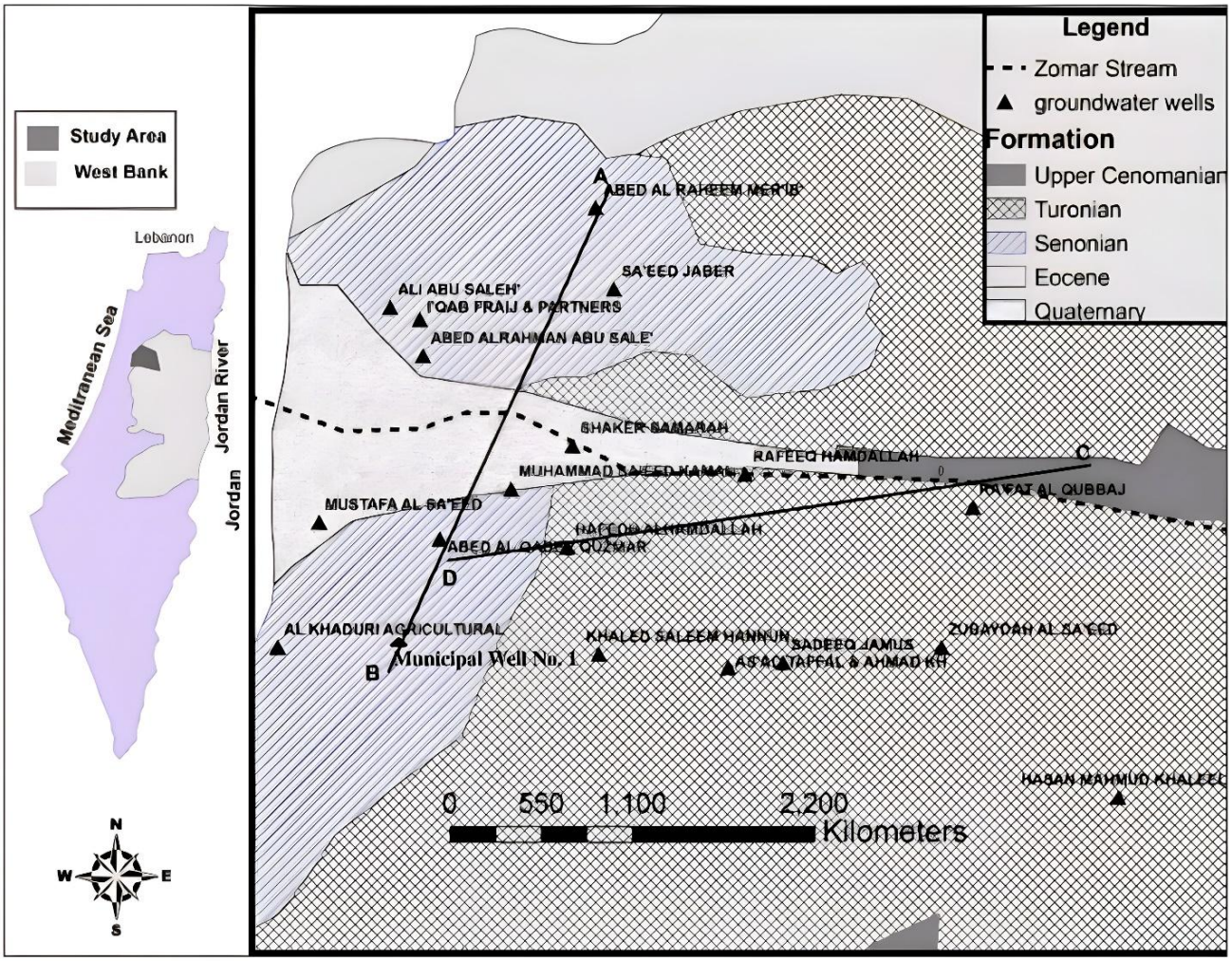

Figure (2) Vulnerability map of the studied area. The geological structure around and underneath Wadi Zomar. It has diverse geological structures that permit the seepage of different pollutants to layers below the earth's surface, where wells are dug normally. Vulnerability map adopted from *Khayat S, Marei A, Natsheh B, Abu-Khalaf N. Mechanisms of groundwater pollutants transport in Tulkarm area / Palestine. Resour Environ. 2012;2(6):281–90. doi:10.5923/j.re.20120206.06*

Hydrophilic-Lipophilic Balanced (HLB) sorbent membranes were used (Waters Corporation, Milford, MA). The POCISs were deployed in early April/2022 for 28 days. Two sets were used to avoid any misleading information regarding temporal variations of measured PhCs in groundwater samples, and the measurements from both sets were averaged. The POCIS were constantly submerged in Anabta's municipal groundwater

-reservoir after water was pumped from the groundwater wells. On the 28th day, the POCIS were removed from the groundwater tank, wrapped in aluminum foil, kept in an airtight, clean plastic bag, and preserved at 4°C during transportation and shipping to the analyzing laboratory (Royal Scientific Society, Amman, Jordan).

Water Sample Preparation and Extraction

Chemicals

All chemicals, including all reference materials and labeled standards for antimicrobials and PhCs, are obtained from Sigma–Aldrich (St. Louis, MO, USA). Solvents used in sample preparation (acetone, methanol, ammonium formate, acetonitrile, formic acid) were of high-grade purity (>99.5%, >99.9%, >99.0%, >99.9%, and 99.0+%, respectively) (Optima, Fisher Scientific, Fair Lawn, NJ, USA).

Sample preparation and extraction

The extraction process was implemented as reported in the literature [48,49] and described as follows.

Grab samples were initially decanted to remove all suspended particles and then filtered through the vacuum filtration unit using a 0.45 µm glass fiber filter. Then the filtered sample is passed through the cartridges of polymeric Hydrophilic-Lipophilic Balanced (HLB) Oasis 6CC (200 mg) (Waters Corporation, Milford, MA) using a vacuum manifold system. The cartridges were first connected to a solid-phase extraction (SPE) manifold and vacuum pump and preconditioned by passing 6 mL of acetone (purity >99.5%) and then 6 mL of methanol (purity >99.9%), respectively, followed by passing 6 mL of distilled deionized water (ddIH_2O). The flow rate of samples through the SPE cartridge was set at 10 mL/min or less. The cartridges were then rinsed with ddIH_2O once the extraction process was completed. Drying was done using room air with continued suctioning for no less than 5 minutes. All cartridges are then removed, labeled, and stored in a clean bag at (-20°C) [49].

POCIS were disassembled once they arrived at the analyzing lab, and the sorbent was transferred into glass gravity-flow chromatography columns. Chemical residues were recovered from the sorbent by organic solvent elution. Methanol

was used to recover analytes from the pharmaceutical POCIS. The extracts were reduced in volume by rotary evaporation and under a gentle stream of nitrogen, then filtered through a glass-fiber filter. Solvent exchange was used as necessary and sealed in amber ampoules under nitrogen until further analysis [48].

Analytical methods

The cartridges were eluted using 10 mL of high-purity methanol into a disposable glass culture tube. The volume of the eluent was then reduced to 4 mL under nitrogen at 40°C. Subsequently, it was transferred to auto-sampler vials, where the inserts were silane-treated [48,49].

The separation of compounds was done using the AB-Sciex 5500 Qtrap (LC-MS-MS) equipped with Luna Omega polar C18 embedded column (100 mm × 3.0 mm, particle size of 3 µm) (Phenomenex) with a limit of detection (LOD) of 0.005 µg/L for all targeted PhCs. The limit of quantification (LOQ) is detailed for each targeted PhC in supplementary material 1. Gradient elution mode was considered in the following order: eluent A is 5 mM ammonium formate (purity >99%) and 0.1% formic acid, and eluent B is acetonitrile (purity >99.9%) and 0.1% formic acid (purity 99.0+%). The initial mobile phase conditions started with 98:2 A/B for 1 min, then a linear gradient pattern was used to reach a ratio of 70:30 A/B at 2 min, then the ratios were changed to reach 50:50 A/B at 6 min. Before returning to the initial conditions, the last ratio was maintained for 10 minutes. The flow rate was set at 0.6 mL/min and the injection volume at 5 µL [48,49].

Multiple reaction monitoring (MRM) was conducted with an AB-Sciex 5500 Qtrap equipped with an electrospray ionization interface, using the positive-ion mode (Santa Clara, CA, USA). Instrument control, data acquisition, and quantitation were run using analyst software. Setting the drying gas temperature at 350°C, the capillary voltage at 4.0 kV, the drying gas flow of 12 L/m, and the nebulizer pressure at 40 psi [48,49].

Antibiotics Dispensary Data Collection

Antibiotic consumption data from West Nablus hospitals were collected between January 1, 2021, and February 28, 2022. The collected dispensary data are comparative only. The West Nablus WWTP receives all hospital and domestic sewage without treatment, including PhCs residues. Environmentally stable PhCs (in supplementary material 1) were selected from the literature for this study [27,50–52].

$$RQ_{RD} = MEC/PNEC_{RD} \quad (1)$$

Where MEC is the measured environmental concentration in effluent wastewater and treated surface wastewater. $PNEC_{RD}$ is the predicted no-effect concentration in terms of AMR development for clinical bacteria. $PNEC_{RD}$ values are as published by *Bengtsson-Palme et al.* for clinically significant bacteria [31].

Their study is the most comprehensive study done regarding antibiotic threshold values promoting resistance development. The calculated values are based on the $MIC_{1\%}$ values for clinical bacteria according to the European Committee on Antibiotic Susceptibility Testing (EUCAST), where $MIC_{1\%}$ is the minimal inhibitory concentration required to inhibit the growth of 1% of bacterium inoculum [53]. Taking into account that resistance selection can occur at concentrations well below the MIC traditionally reported in the EUCAST and the interspecies diversity with MIC values, $MIC_{1\%}$ was chosen with an uncertainty factor of 10 as the $PNEC_{RD}$ [31]

Statistical Analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS version 22) to test for the significance of spatial differences between each point of sample collection with respect to seasonal differences as well. Descriptive statistics were reported in tables and figures. Due to the small sample size and data not normally distributed, the non-parametric Wilcoxon Signed rank test, was used to test the spatial differences between samples of the same campaign. The significance level (p-value) was set at 0.05. *Note*: The single detection of a compound among all collected samples in both campaigns is disregarded and excluded from data analysis, where further validation is required.

Results and Discussion

West Nablus WWTP performance

The plant was designed to receive an estimated flow of raw sewage of about 14,000 m^3/day. In 2022, it received an average of 12,591 m^3/day. BOD_5 and TSS average values in the inlet WW were 535 mg/L and 440 mg/L, respectively, in the same year. WWTP performance capacity for the removal of BOD and TSS was 98% -for both parameters [41]. Table 1 details wastewater quality parameters of wastewater samples during sample collection.

Table (1) COD, BOD & TSS parameters for inlet, outlet of West Nablus WWTP, and Anabta-Zomar surface wastewater during sampling.

Test	Unit	First sampling campaign 11th April/2022			Second sampling campaign 19th September/2022		
		WWTP Inlet	WWTP Outlet	Anabta surface WW	WWTP Inlet	WWTP Outlet	Anabta surface WW
COD	mg/L	687	38	78.4	1094	60	157
pH	*	7.76	7.69	NA[1]	7.8	7.59	8.11
Conductivity	µS/cm	1438	1360	NA	1730	1717	1724
TSS	mg/L	118	0	16	504	24	50
BOD_5	mg/L	543	12	11.4	461	12	22

1: not available. WWTP: Waste-Water Treatment Plant, WW: Waste-Water, COD: Chemical Oxygen Demand, pH: Potential of Hydrogen, TSS: Total Suspended Solids, BOD_5: Biochemical Oxygen Demand (five-day test), mg/L: milligram per 1 Liter, µS/cm: microSiemens per centimeter.

Antibiotics dispensary patterns

Dispensary patterns from hospitals (Table 2) indicated that piperacillin-tazobactam and amoxicillin-clavulanate are the most frequently dispensed antibiotics in hospitals in the studied period. The quantities dispensed were in the range of a few grams (for moxifloxacin) to 158 kilograms (for piperacillin-tazobactam). Despite their high prescription and dispensing rates, the targeted β-lactams—ampicillin and cefazolin—were consistently below the detection limit in all water samples analyzed. This class of antibiotics contains a beta-lactam ring that is unstable under ambient conditions (temperature, pH-especially alkaline) and can undergo fast degradation when present in the environment [54]

Table (2) Antibiotic classes used in hospitals from 1/1/2021 to 28/2/2022.

Antibiotic class	Antibiotic
Penicillins – β-lactam agents	Piperacillin-Tazobactam* Amoxicillin-Clavulanate*
Glycopeptide	Vancomycin *
Lincosamide	Clindamycin
B-Lacatams	Ceftriaxone*, Cefuroxime*, Cefazolin* Ceftazidime *, Cefotaxime, Cephalexin
Carbapenems	Meropenem*, Ertapenem
Penicillin	Ampicillin*, Amikacin, Amoxicillin
Fluoroquinolones	Ciprofloxacin*, Levofloxacin, Moxifloxacin
Polymyxin	Colistin *
5-nitroimidazole	Metronidazole*****
Tetracyclines	Doxycycline
Amphenicol	Chloramphenicol
Glycylcycline	Tigecycline
Folate pathway inhibitor	Trimethoprim-Sulfamethoxazole*
Macrolides	Azithromycin, Erythromycin
Aminoglycoside	Gentamicin

*: Top most frequently dispensed quantities of antibiotics (>5000 grams in the studied period).

Grab samples results and West Nablus WWTP PhCs removal performance

Grab Samples Results

In total, 14 PhCs were detected from different classes. Ciprofloxacin was measured as the highest detected PhC residue of 8 µg/L in the WWTP inlet of the spring campaign. Whereas the most frequently detected PhCs among all wastewater samples were carbamazepine (CBZ), sulfamethoxazole (SMX), ofloxacin (OFX), diclofenac (DIC), pyrimethamine (PYR), trimethoprim (TMP), and sulfapyridine (SP) (Table 3). The physicochemical properties of detected compounds; molecular weight (g/mol), acid dissociation constant (pKa), log of the octanol/water partition coefficient (Log K_{ow}), water solubility, Chemical Abstracts Services (CAS) number, and chemical formula) are displayed in **Error! Reference s ource not found.**

The observed variances in the presence and concentration of identified pharmaceutical compounds and antibiotics can mostly be attributed to several factors. Pre-analytically, it could relate to the initial decantation step before filtration, where it, accidentally, may have removed particle-bound pharmaceutical compounds, potentially affecting the reported concentrations. Given that we are screening for a number of pharmaceuticals and not targeting a single compound, the decantation and extraction approach may be different [55]. Additionally, variations can be attributed to the administration patterns observed in this research area [56]. Furthermore, the elimination of any PhCs varies depending on the species, dosage, and method of administration [57]. For instance, the excretion of CBZ as a parent compound is minimal [58], but with long-term use and inadequate breakdown, it can still be detected over a prolonged period of time. Conversely, a significant proportion of the original medication is eliminated without undergoing any changes for CIP, OFX, TMP, and DIC [59–61].

Furthermore, discrepancies were identified between the types and residues of PhCs, as well as inconsistencies between the antibiotics detected in this investigation and the reported antibiotic patterns by local hospitals. Some antibiotics, such as CIP, OFX, SMX, TMP, and PYR, can be used in both human and animal medicine. However, there are other antibiotics, such as lincomycin (LCM), flumequine (FLU), and sulfonamides (sulfaquinoxaline), that are specifically intended for veterinary usage and are not utilized in human medicine [62,63]. These findings indicate that hospital discharges are not the sole contributors to PhCs' contamination; domestic wastewater and industrial discharges also represent significant sources. This observation carries particular relevance for FLU, which is extensively used in veterinary practice to manage enteric infections in livestock and aquaculture [51], and which is known to exhibit mutagenic adverse effects [64]. Importantly, the effectiveness of regulatory oversight concerning veterinary antibiotic use within the Palestinian context remains limited [65], potentially exacerbating environmental exposure. While the detected residues likely arise from a confluence of sources, the present study was not designed to quantify the contribution of each source.

The concentrations of DIC, OFX, and CIP in the spring inlet samples were higher compared to their counterparts in the autumn inlet sample, with DIC being 2 times higher, OFX being 3 times higher, and CIP being 26 times higher. Reasoning for this finding could likely reflect local hydrology or wastewater inputs, local antibiotic consumption, or less degradation capacity in the cold temperatures, while regional studies from the Middle East more often report autumn or winter peaks, and global evidence for CIP points to wastewater source intensity as a major driver [66,67]. The authors are currently unaware of any seasonal fluctuations in local infections or medical disorders that necessitate the use of this particular antibiotic.

Notably, the residual concentration of SMX surpasses that of TMP in all the samples that were analyzed. Additionally, the residual levels recorded in the spring WWTP influent sample are higher compared to the autumn WWTP influent sample. In the systematic review by *Frascaroli et al.,* seasonal fluctuations for SMX is also reported, with higher winter influent residues than in their spring counterparts [68]. In contrast, SMX reached a maximum summer residue more than winter, while TMP was

only detected in the winter season [69]. In the medical field, the prescribed ratio for administering this combination is 5 parts SMX to 1 part TMP, which is done to address the issue of antibiotic resistance [60]. However, the ratio found in wastewater samples is higher than the ratio reported earlier. The ratio of detection in the WWTP spring influent sample is 10:1, but in its equivalent autumn sample, the ratio is 14:1. The observed differences in the administration SMX/TMP between the spring and autumn seasons may be due to higher administration patterns of SMX/TMP in the spring [70]. Alternatively, TMP may degrade more quickly in raw wastewater before it reaches the wastewater treatment plant [69]. Another possibility is that the higher ratios of SMX detected suggest that SMX is being administered alone, rather than as part of combination therapy. Some researchers have suggested using the SMX: TMP ratio as a "pollution marker" to determine the source of wastewater [71]. On the other hand, N4-acetylsulfamethoxazole, a main human metabolite of SMX, is found to transform back into the active parent drug SMX in untreated wastewater during treatment, thus extrapolating to higher residual concentrations and the 'apparent' incomplete removal [72].

Sulfapyridine is a major human sulfasalazine metabolite, a drug widely prescribed for inflammatory bowel disease and rheumatoid arthritis. This metabolite undergoes a renal clearance giving a direct route into domestic wastewater [73].

A significant spatial difference was seen in the sum of PhCs between the WWTP effluent sample and the sum of PhCs in the treated surface wastewater sample at the Anabta sampling location of the spring campaign (Wilcoxon signed rank test, $p = 0.016$). The variation observed can be attributed to the dilutional effect caused by the rainy season in the spring. This effect resulted in artificially larger clearance percentages during the spring campaign at the two collection stations. The sorption capacity that some PhCs exhibit leads to substantial removal of PhCs mitigating their seepage into groundwater [74,75]. In contrast, there was no significant variation in the spatial distribution of the sum of PhC concentrations between the WWTP outlet sample and the treated surface wastewater in Wadi Zomar at the Anabta sampling location during the autumn campaign (Wilcoxon signed rank test, $p = 0.646$).

Table (3) Summary of Grab Sampling Campaigns results and PhC removal efficiency by West Nablus WWTP.

	Inlet Spring	Outlet Spring	Anabta Spring	Inlet Autumn	Outlet Autumn	Anabta Autumn	Removal %
Carbamazepine	0.806	0.554	0.529	1.044	0.433	0.4	44.9
Ciprofloxacin	8.043	ND	ND	0.312	0.019	0.054	97
Diclofenac	0.936	0.961	0.872	0.498	1.021	0.436	-53.8
Erythromycin	ND	ND	0.022	ND	ND	ND	NA
Flumequine	ND	ND	ND	0.029	ND	0.019	100
Lincomycin	0.058	0.037	0.015	ND	0.01	ND	36.2
Ofloxacin	2.67	1.002	0.584	0.824	0.276	0.121	64.5
Pyrimethamine	0.232	0.219	0.045	0.422	0.102	0.09	40.7
Sulfaguanidine	ND	0.007	ND	ND	ND	ND	NA
Sulfamethoxazole	0.95	0.266	0.143	0.818	0.183	0.257	74.8
Sulfapyridine	0.266	0.133	0.037	0.365	0.094	0.078	62.1
Sulfaquinoxaline	ND	0.013	0.011	0.031	ND	ND	NA
Testosterone	ND	ND	ND	0.09	ND	ND	NA
Trimethoprim	0.092	0.019	0.021	0.055	ND	0.014	89.7

[a] WWTP: Wastewater Treatment Plant, [b] WW: wastewater, [c] ND: Not detected (below the detection limit of 0.005 µg/L), [d] NA: Not applicable. Cell shading indicates relative magnitude and is a visual aid only; all values are reported numerically. The six concentration columns share a single three-color scale applied across all measurements: gray = not detected (< LOD, 0.005 µg/L), yellow = the dataset median (0.041 µg/L), red = the maximum observed value (8.043 µg/L, ciprofloxacin, spring inlet). The Removal % column is shaded on a separate diverging scale: red = negative removal (effluent concentration exceeding influent), white = 0%, green = > 50%. Removal % is the mean removal of the two sampling campaigns. Negative values indicate effluent concentrations exceeding influent concentrations. Influent and effluent grab samples were collected at the same time point. A detailed evaluation is provided in Supplementary material 2.

Table (4) Physiochemical properties of detected pharmaceuticals.

Pharmaceutical	Molecular Weight (g/mol)	pKa[a]	Log Kow[b]	Water solubility (mg/L)	CAS[c] Registry Number	Chemical Formula
Carbamazepine [d]	236.3	13.9	2.45	115.0	298-46-4	$C_{15}H_{12}N_2O$
Diclofenac[d]	296.1	4.15	4.51	2.37	15307-86-5	$C_{14}H_{11}Cl_2NO_2$
Sulfamethoxazole[d]	253.3	pKa_1: 1.6 pKa_2: 5.7	0.9	610	723-46-6	$C_{10}H_{11}N_3O_3S$
Ciprofloxacin[d]	331.34	acidic 6.09 basic 8.74	0.28	$3 * 10^5$	85721-33-1	$C_{17}H_{18}FN_3O_3$
Erythromycin[d]	733.9	8.9	3.06	F4.2	114-07-8	$C_{37}H_{67}NO_{13}$
Lincomycin[d]	406.5	7.6	0.2	927	154-21-2	$C_{18}H_{34}N_2O_6S$
Ofloxacin[d]	361.4	pKa_1: 5.97 pKa_2: 9.28	-0.39	$1.08 * 10^4$	82419-36-1	$C_{18}H_{20}FN_3O_4$
Pyrimethamine[d]	248.71	7.34	2.69	10	58-14-0	$C_{12}H_{13}ClN_4$
Sulfaguanidine[d]	214.25	pKa_1 [e]: 2.21 pKa_2:[e] 11.97	-0.99	$2.6 * 10^5$	57-67-0	$C_7H_{10}N_4O_2S$
Sulfapyridine[d]	249.3	pKa_1: 4.5 pKa_2: 10.6	0.1-2.5	268	144-83-2	$C_{11}H_{11}N_3O_2S$
Sulfaquinoxaline[d]	300.34	5.1	1.68	7.5	59-40-5	$C_{14}H_{12}N_4O_2S$
Trimethoprim[d]	290.3	7.12	0.91	400	738-70-5	$C_{14}H_{18}N_4O_3$
Flumequine[d]	261.3	6.5	1.6	2190	42835-25-6	$C_{14}H_{12}FNO_3$
Testosterone[d]	288.4	19.09	3.32	23.4	58-22-0	$C_{19}H_{28}O_2$

[a] pKa: acid dissociation constant, [b] Log Kow: Log of the octanol/water partition coefficient, [c]CAS Chemical Abstracts Services,
[d] Parameters are adopted from PubChem, and ChemSpider, [e] as reported [76].

Diclofenac was the only compound to show negative apparent removal in both campaigns (−2.7% in spring and −105.0% in autumn; mean −53.8%). Two explanations are plausible and not mutually exclusive: the grab-sampling design, in which influent and effluent samples were collected at the same time point rather than following a defined volume of wastewater through the plant and therefore do not track the same wastewater; and in-plant processes that regenerate the parent compound or return it to the aqueous phase, principally deconjugation of metabolites and desorption from suspended solids. These are examined in supplementary material 2.

The discrepancy in values between the third autumn sample (Anabta treated surface wastewater) and the autumn effluent sample can be attributed to the ongoing introduction of untreated wastewater into Wadi Zomar. This is evident from the higher values of COD, BOD, and TSS parameters in the third autumn sample compared to the measured values in the autumn effluent sample (Table 1). Additionally, the concentrations of certain PhCs are also increased (Table 3). *K'oreje et al.* observed a rise in PhC concentrations in multiple effluent samples. This phenomenon was caused by the release of illicit and untreated residential wastewater into the same rivers where wastewater treatment plant effluents are also being released [7]. Or it could be attributed to sunlight and high-temperature drying effect that can make concentrations appear higher than they already are, as reported by *Wendott et. al.* in Kenya [77]. A detailed evaluation of the West Nablus WWTP removal performance is available in supplementary material 2.

POCIS results and the occurrence of PhCs in groundwater

Four PhCs are detected in the POCIS groundwater sample that are in agreement with the most frequently detected PhCs in raw and treated wastewater samples in our study here. Those are carbamazepine, diclofenac, ciprofloxacin, and sulfamethoxazole (188.3, 5.8, 6.7, and 7.2 ng/POCIS, respectively).

On a global scale, groundwater and tap water harbor 16 different PhCs across countries. CBZ, DIC, SMX, ibuprofen, and naproxen are most frequently detected worldwide and in various aquatic and soil compartments [1]. In the MENA region, several emerging pollutants were reported in drinking water at levels exceeding thresholds set by the WHO and the European Commission (EC) [9]. Mahmood et al. reported CIP (1.312 µg/L) in the finished water of a drinking water treatment plant in Iraq [78]. In Algeria, researchers reported the occurrence of ibuprofen and ketoprofen in drinking water at concentrations of 142.1 and 110.9 ng/L, respectively [20]. Similar results were also observed in Saudi Arabia [22], Iran [79], and Egypt [18]. In Palestine, antibiotics were detected in pumped groundwater for irrigation, with concentrations ranging from 0.3 ng/L for azithromycin to 76 ng/L for triclocarban [24]. To our knowledge, this study is the first to report the occurrence of PhCs in drinking groundwater in Palestine.

The detection of different PhCs in groundwater might be indicative of the probable sorption of PhCs into the soil of Wadi Zomar and along its banks and into aquifers, as well as natural recharge. The sorption and degradation capacity that some PhCs exhibit in soil minimizes part of the load seeping toward groundwater, though the extent is strongly compound-dependent: OFX has strong sorption capacity, whereas SMX and LCM interact weakly with soil and remain mobile [74,75]. Other studies have established their presence in both soil and underground water [7,78]. Local studies have demonstrated, at lab-scale soil-columns, that PhCs were detected in water leachate in both varying concentrations and PhC compound [79,80]. However, the study here wasn't designed to screen the soil for PhCs' presence.

So far, there is a research gap in estimating the human health risk regarding exposure to trace residues in drinking water. Few studies point towards neglected acute health risks from trace residues of PhCs [81], or consider exposure to pharmaceutically contaminated drinking water as a minor source in comparison to pharmaceutically contaminated plant sources [12], and the major shift in ecotoxicological studies is towards environmental trophic organisms[82,83], and a clear research gap in chronic human health effects [4]. Some studies investigated human health risks for carbamazepine (CBZ) exposure through drinking water and fish consumption (high bioaccumulation factor). For carbamazepine (CBZ) to be considered a risk to human health, the PNEC in drinking water and fish consumption is calculated at 226,000 ng/L, and the carbamazepine (CBZ) detected residuals in drinking water are below this threshold[84]. So far, the main scientific emphasis is rather directed toward PhCs quantification in different water bodies with limited data on chronic ecotoxicological effects, rather than studying the possible human health impacts [25,85,86].

Up to this point and according to the results of this study, it can be argued that multiple factors have collaborated to permit PhCs' entry into groundwater, which can be summarized as follows. (a) The chronic persistence of PhCs in wastewater and resistance to degradation [75] as patterns of PhCs among sampled wastewater (b) The inefficient ability of WWTP to remove PhCs from wastewater before the effluent is discharged [86], (c) The natural hydrological structure surrounding the environmental body receiving treated surface wastewater [45,46], (d) The uncontrolled release of untreated domestic wastewater into aquatic surfaces, and (e) The location of natural aquifers where natural purification processes are absent.

The scientific evidence thus far necessitates the application of advanced wastewater treatment processes for higher removal efficiencies of different pharmaceutical residuals. This requires the incorporation of advanced infrastructure for WWTP operations, e.g., oxidation &/or ozonation coupled with UV application, membrane bioreactors, nanoconstructed activated biochar, multi-walled carbon nanotubes, or simply solar systems [87–93]. However, it is recommended to implement mitigating strategies specifically for PhCs observed in groundwater.

Screening risk assessment for antibiotic resistance development

The most significant negative public health impact on human health is caused by elevated levels of persisting antibiotics in the environment and the development of antimicrobial resistance. The Risk Quotient = (MEC/PNEC) for resistance development (RQ_{RD}) was estimated based on the antibiotic class, adopting threshold values developed by *Bengtsson-Palme and Larsson et al.* [31]. A number of antibiotics were lacking in an assigned PNEC, and as a result, they were not included in the estimate of RQ_{RD}.

The estimated resistance development risk, determined using the RQ_{RD}, was less than 1 for all detected antibiotics in effluent and treated wastewater samples, except for ofloxacin.

The analysis reveals that the residual content of OFX in the spring effluent sample from the WWTP presents a significant risk for the development of AMR in clinical bacteria, with an RQ_{RD} more than 1. These findings align with the conclusions of *Booth et al.*, which showed that OFX was frequently found in surface water at concentrations higher than the MIC, while CIP had the highest percentage of analyses exceeding the MIC on a global level [94].

Table (5) Comparison between PNEC-MIC values provided by *Bengtsson-Palme, et al.* [31] and concentrations of detected antibiotics in the WWTP effluents and treated surface wastewater of the present study with their respective RQ.

Antibiotic	PNEC-MIC (µg/L)	Outlet Spring (µg/L) Autumn (µg/L)	Treated Surface WW Spring (µg/L) Autumn (µg/L)	RQ_{RD}
CIP	0.064	0 0.019	0 0.054	<1
FLU	0.25	0 0	0 0.019	<1
LCM	2.0	0.037 0.01	0.015 0	<1
OFX	0.5	1.002 0.276	0.584 0.121	**>1**
SMX	16.0	0.266 0.183	0.143 0.257	<1
TMP	0.50	0.019 0	0.021 0.014	<1

PNEC-MIC: Predicted no-environmental concentration-minimum inhibitory concentration, µg/L: microgram per liter. CIP: Ciprofloxacin, FLU: Flumequine, LCM: Lincomycin, OFX: Ofloxacin, SMX: Sulfamethoxazole, TMP: Trimethoprim.

The wastewater medium is regarded as a habitat abundant in nutrients, which allows for the growth and multiplication of both vulnerable and resistant microorganisms. Horizontal gene transfer is quite likely, and mobile genetic components such as plasmids and transposons can be shared within the gene pool [95,96]. This is significant since Wadi Zomar naturally flows through densely populated and actively cultivated areas on both sides. The situation is a concerning issue due to the possible danger of effluents spreading resistance in the environment, which can have negative effects on human and animal health as well as agricultural life forms.

Nonetheless, it is not possible to definitively determine whether the identified antibiotic residues here contribute to the development of resistance or not. Theoretical values suggested to enhance selection pressure may occasionally deviate from their actual experimental values. According to *Le Page et al.*, the experimental PNEC for CIP is 0.01 µg/L, while *Bengtsson-Palme et al.* reported a slightly higher value of 0.064 µg/L, and *Gullberg et al.* reported a minimum selective concentration value of 0.1 µg/L [28,31,32]. This complicates the process of determining a value to officially endorse and consider as a universal standard.

Measuring environmental toxicity caused by PhCs is challenging due to the diverse range of doses that have been documented to impose ecotoxicological pressure on various ecological objectives, such as growth rate, reproduction, or death, as summarised by *P. Sathishkumar et al* [97]. Trace quantities of contaminants in surface water are enough to cause changes in biological processes and genetic mutations in brown mussels [98]. *Cleuvers et al, and Zind, et al.* have all concluded that toxic effects of mixtures containing various PhCs can be detected at concentrations significantly lower than the no observed effect concentration (NOEC) of individual compounds [27,99]. This finding is also supported by *Pereira et al*. [4].

This study presents an additional avenue for investigation into the connection between the identification of particularly alarming residues of antibiotics and the existence and magnitude of resistance genes/bacteria in wastewater and sediment. The ecological impact of all PhCs in this context varies, and much of the available data is derived from controlled laboratory experiments. This is also evident in the lack of a consistent threshold value at which hazardous consequences are anticipated [4,27,32,100,101].

Conclusions

In Palestine, both wastewater and groundwater have been found to be contaminated with carbamazepine, ciprofloxacin, diclofenac, and sulfamethoxazole. Therefore, it is highly recommended for stakeholders to consider integrating additional technologies at West Nablus WWTP to improve the removal of pharmaceutical compounds. Results from this study, together with other local studies reporting effective removal technologies [87,88], can guide the implementation of targeted mitigation protocols and strengthening strategies for the safe disposal of treated wastewater into the receiving environment. Furthermore, develop and implement antimicrobial stewardship programs to regulate and reduce the use of pharmaceuticals, thereby minimizing their environmental impact. Elevated residual concentrations of ofloxacin surpass the PNEC-MIC, potentially contributing to antimicrobial resistance. This requires conducting further studies to assess the extent of antimicrobial resistance linked to elevated concentrations of ofloxacin, and taking proactive measures to mitigate its impact.

Disclosure Statements

Ethics approval and consent to participate This study was reviewed and approved by the An-Najah National University (ANNU), Institutional Review Board (IRB) (Ref: Mas. April. 2022/12). Designated facilities were informed of the scope and intent of the research before the initiation of sample collection. Approvals from hospitals, the Nablus municipality, and the Anabta municipality were granted before the antibiotics dispensary data collection.

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