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Assessment of the Presence of Pharmaceutical Compounds in Wastewaters and in Aquatic Environment

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Abstract

In this work, we have analyzed the presence of pharmaceutical compounds in the wastewater of a regional hospital in Vlora, Albania, during June 2020 and June 2021. For this analysis, we measured the concentration of 19 preselected pharmaceutical molecules in discharging water by direct sampling in the waters, and we investigated the presence of pharmaceuticals in the algae *Ulva Lactuca*. Chemical analysis has been conducted via liquid chromatography in tandem with mass spectrometry at a limit of quantization of 0.1 ng/L. It resulted that, from the ensemble of 19 pharmaceutical molecules consisting of antibiotics, analgesics, psychiatric drugs, and beta-blockers, the antibiotics were found at the highest concentration. The quantity of medical chemicals' presence varies from 0.2 to 0.24 mg/L. Traces of pharmaceuticals are obtained from *Ulva Lactuca* algae in effluent water next to the city treatment plant. The concentration for each of the 19 molecules considered in this work remains below 0.1 ng/L. Finally, the values of physicochemical parameters were found within the range reported by several studies for hospital influent waters, collected in different countries and for many years.

Keywords: Pharmaceutical Residues; Tandem Mass Spectrometry; Water Pollution.

1. Introduction

The release of pharmaceutical residues into the environment is a growing concern due to the significant risks they pose to humans, animals, and microbial communities [1–3]. Pharmaceutical molecules get into the water supply via human excretion, by flushing the drugs into the water channels directly, by cleaning and washing hospital stuff, etc. Particularly, hospital wastewaters are a common source of water contamination with medical remnants and pharmaceutical molecules. The release of unconsumed medications or their metabolites into hospitals' discharge waters is practically unavoidable; therefore, wastewater treatment installations have been routinely applied to prevent pollution of the waters by hospital discharges. Also, continuous monitoring for the presence of pharmaceutical contaminants (PC) in groundwater, surface water, or living aquatic plants is quite common in environmental safeguarding and scientific activities. Recently, the problem of pharmaceuticals in hospitals' wastewaters has been a key concern for authorities and scientific communities in Albania, too. Despite inherited problems in this issue, significant progress on the treatment of medical remnants has been achieved recently in the country [4–6]. Also,

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improvements have been seen in environmental caretaking and in adopting adequate regulation about water quality, and several monitoring projects, mostly co-funded or fully supported by the EU, have been developed in some regions of the country. In this framework, we participated recently in an EU project for monitoring the presence of pharmaceutical compounds in the wastewater of the regional hospital of Vlora, Albania [4, 5, 7], which has been co-organized with the University of Ioannina, the University of Vlora, and the Hospital of Vlora. It enabled us to carry on with environmental studies following our recent studies [8–10], aside from similar studies and research or monitoring initiatives across the country [11, 12]. Notice that due to their costs, water monitoring activities were usually carried out by state agencies and were financed by EU programs or regional cooperation [13, 14, 5], which has limited the volume of independent studies. Regarding Vlora County, which is a very important touristic region of the country, recent observatory reports argue that some pollution problems might exist, but at a non-severe level.

Tahiri et al. [8] reported that concentrations of the Cu, Fe, Cd, and Mn ions, mostly of technological origin, were found within the range of their average values reported for other Adriatic places. Next, in Denaj et al. [9], the migration of Hg compounds from the landfill plant aimed at wasting dangerous chemicals inherited from the old industrial settlements has been classified as non-problematic. Regarding water quality and wastewater treatment efficiency, there are some reports from the state agencies, but within our knowledge, there were no scientific studies for our system. To fill this gap, in this work we have considered the assessment of pharmaceuticals' concentration in the wastewater of the regional hospital of Vlora and the occurrences of their presence in aquatic plants. Note that the data gathered herein were at a reduced volume because of the limitations of the source project [5], but they provide a solid initial assessment of the water contamination with pharmaceuticals in the city waters. For the first objective, we have planned the measurement of the concentration of 19 persistent pharmaceuticals directly in the water flows. This measurement is realized in the main collector of hospital wastewater. The measurement of the presence of pharmaceuticals in algae is conducted next to the city Wastewater Treatment Plant (WWTP) to estimate the final effect of the presence of those chemicals in water. The city's WWTP operates using a biological-based purification technology [5], which is not intended to eliminate or remove pharmaceutical molecules from the waters. Notice that even conventional technologies of the sewage treatment plant (STP) dedicated to chemical cleaning do not have elevated separation efficiency [15, 16], and small quantities of pollutants could escape the filtering stage. Those molecules reach surface waters, follow the water chains, and would be deposited in aquatic inhabitants. All those arguments suggested completing our investigation by measuring the presence of pharmaceuticals in aquatic plants. It is considered very important for a realistic pattern of pharmaceuticals in wastewater and can be used for recommending alternative improvements to hospital water cleaning by a pre-treatment station.

2. Pharmaceuticals in Water and Some Features of Vlora Regional Hospital Discharges

The Regional Hospital of Vlora is in Vlora city, at the beach of the Ionian Sea. It has a capacity of 300 beds, and nearly 10,000 people are treated annually in its departments. This number is projected to attain 40,000 in a few years, which highlights the relevance of monitoring the chemicals discharged in its wastewater. The hospital draining waters are assembled in a common wastewater collector that circulates the hospital area and connects hospital effluent water with the municipal wastewater network by a single junction. There is no pre-treatment station in this sub-network. The main WWTP of city waste waters is located close to the beach (Figure 1). Regarding the presence of some pharmaceuticals in water, in Malollari et al. [17], it has been stated that specific chemicals have been detected in the effluent waters. But this observation was made in 2022, after we performed our measurement in the framework of the co-project with Ioannina University scientists mentioned above [5, 7].

However, regarding the period of observation, there were no indicators or monitoring reports that confirmed the presence of the pharmaceutical in influent or effluent water related to the treatment installation. The period of monitoring coincided with the abnormal loads of medical use due to the COVID pandemic. This is also an opportune circumstance for enabling the detection of substances that are not abundantly present during normal activity in the hospital and for compensating for the moderately accurate deduction capacity of the instruments and methods used in the study. Based on the daily records of medical loads during the period (2020–2021), the amounts of pharmaceuticals used in its departments vary from 0.06 to 620 g/day, which consists of a relevant potential pollutant source for the discharged water. Obviously, those quantities would be mirrored in the concentration of the pharmaceuticals in the hospital's wastewater. In the best scenario, the analysis of the one-by-one relationship between the loads and concentration in wastewater would be very important for in-depth knowledge of the chemical pathway and lifecycle in the discharged waters. However, considering the small volume of the scheduled measurements, we are aware that this analysis is likely to be impossible. It limits our conclusions to a simple report and a descriptive analysis of the facts observed. A more interesting discussion was expected about the concentration of pharmaceuticals in aquatic plants. Those findings can provide valuable information about the effects of the chemicals in water and their lifecycle. Finally, let's note some details of the measurement process for this research. As mentioned above, the measurements and monitoring focus of the project has been oriented by the relevance of the risk factor of chemical substances in water and their toxicity and does not cover the tracing of all medical molecules in wastewater.

As a result, we have analyzed the presence in wastewater of only 19 pharmaceuticals that were selected as potentially more toxic by general agreements and common beliefs. The toxicity of pharmaceuticals into aquatic ecosystems is assessed by the risk quotient parameter (RQ), which is calculated as the ratio of predicted environmental concentration or measured environmental concentration to the predicted-no-effect concentration [13, 14, 18]. Non-steroidal anti-inflammatory drugs, antibiotics, and beta-blockers are considered to have a high toxic risk in water bodies [18, 19–21]. Therefore, we have considered those categories for our measurement, identifying them as Pharmaceutical Contaminants (PC). Regarding the final selection of the substances for the analysis, we have considered some general characteristics based on the common classification of pharmaceutical molecules according to their inherent possibility to affect the environment, their persistence, bioaccumulation, and toxicity properties referring to environmental contamination (EC), according to the definitions described in [13, 18–20]. As a result, we have considered as of particular interest the in-water presence of the following molecules*: Amikacin, Ampicillin, Cefazoline, Ceftazidime, Cefuroxime, Ceftriaxone, Ciprofloxacin, Imipenem+Cystatin Metronidazole, Azithromycin, Vancomycin, Diclofenac, Ketoprofen, Acid Salicylic, Ibuprofen, Dexamethasone, Carbamazepine, Metoprolol,* and *Nifedipine*.

3. Data and Method

In the first stage of planification of the measurement, also considering the costs of measurement and budgeting limits, we were concerned about the frequency of sampling and the details of the expected analysis. From the hospital's database, we observed that the use of medical supplies is characterized by high variability in their supply per patient, per day, and among departments. Regarding this last element, from the planimetry of the Regional Hospital of Vlora, which is a multifunctional entity [5, 7], we observe that the sewer system was not adapted to collect waters from each department separately [21], so we can only get data from the mixed waters. Also, the variations of the PC dispersal rate along the days and their quantities obstruct their linkage to consumption patterns. Regarding the time details and sampling, we expected that the variability of the consumption of the medications, the chemical pathway of each PC, etc. would inflict additional variability on the PC concentrations, which would impose extra uncertainty on the data. As a result, we expect high variability in the short time intervals; therefore, a strategy of both hourly and daily sampling is used. A qualitative time dynamic can be estimated by the occurrence of the event where the presence of a molecule was identified. Those heterogeneities and the reduced volume of measurement have implicated a limited and informative analysis based on the averaged values. On the other side, the sampling point is directly related to the WWPT location, which we will describe shortly below.

3.1. Location of the Sampling Stations

For measuring and analyzing the concentration of pre-selected chemicals, we scheduled direct measurement of the presence of the molecules in the discharged hospital waters. The selection of the location for the sampling stage was conditioned by the water network structure and WWTP locations. Initially, we considered four different sample stations, coinciding with collectors from hospital networks and junctions with the Municipal Wastewater Treatment Plant (Figure 1). Those sampling points also corresponded to wastewater from the main departments of the hospital. The first set of measuring points was focused on influent wastewater since there was no pre-treatment plant prior to joining with municipal wastewater. In Figure 1, those points are indicated by red marks.

Figure 1. Regional hospital of Vlora and wastewater system: With green line around hospital area, are represented waste waters systems and arrows show the flow direction of waste waters. Red lines represent the system of municipality waste waters. Also, here we can see the joint point of hospital wastewaters with municipal wastewater.

Through a preliminary investigation of a few initial measurements carried out in those stations during April 2020, we have observed that the concentration of medications in the water has changed significantly by hours and day to day. One reason for this inhomogeneity was related to the secondary water collector junctions, which mirrored the fact that those installations were connected to one or a few departments' discharges only. Since we were interested in reducing the side effects and other troubling factors for averaged estimation, we decided to disqualify all initial points or stations whose concentration of a few antibiotics considered in this stage showed high variability. Finally, the measurement station was selected at the point where one collects the inflows from all departments' discharges. At this point are connected all other sections of sewer hospital waste waters. The other station selected for the measurement has been positioned at the main collector, from which the wastewater is linked to the municipal waste water network. Those points are indicated by the yellow field and red dots in the right frame in Figure 1.

The second series of measurements was intended to examine the presence of chemical compounds in the aquatic species. For this purpose, we considered the algae *Ulva Lactuca* based on standard literature for those analyses. *Ulva Lactuca* is a widespread macroalgae growing along the Mediterranean coast that belongs to the phylum Chlorophyta, commonly known as "Sea lettuce" [10]. It is abundant in our waters, and regarding its biogeochemical cycle of nutrients, it represents an efficient plant for analyzing the deposition of the pollutant's chemicals [10, 22]. Details on the proper bio-chemical mechanism and other features that qualify this plant for measuring pharmaceuticals and other compounds in the wastewater can be found in Tahiri et al. [10], Nieto-Juárez et al. [24], etc. The point of this sampling activity is in the area near the main WWTP of Vlora Region, located on the coastline of the city's Bay. Notice that in this treatment plant, it is applied as a partial biological treatment. It consists of a general purification station for all municipal waste waters. The technology used in this WWTP is not aimed at removing pharmaceuticals. The second sampling station considers effluent WWTP wastewater next. We have chosen two monitoring points to check for evidence of differences between the concentration levels of pharmaceuticals in algae in the influent and effluent water of the treatment station.

The procedure of extraction and performing preliminary operations with raw samples for MS analysis has been based on standard methods of liquid chromatography in tandem with mass spectrometry (LC-MS-MS), provided in standard textbooks or in applicative research [23–26], etc. The sampling procedure was performed daily and monthly for a one-year period, June 2020–June 2021. Daily measurements have been used to estimate the monthly average because we initially observed many occurrences of 'non-detected' events, so we intended to avoid empty data by elaborating on more measurements.

3.2. A Summary of the Analytic Techniques Used for Identification of the Pharmaceuticals in Water

For assessment of the presence and concentration of the 19 target molecules listed above, we used liquid chromatography in tandem with mass spectrometry, which is known as a powerful analytical technique that combines the separating power of liquid chromatography with the highly sensitive and selective mass analysis capability [27]. For general guidelines, the reader might find sufficient information in online manuals, as in Pitt et al. [28] or Munjanja [29]. Just for explaining some steps of sample elaboration in very few words, the method follows those steps: the sample is pumped through a stationary phase by a mobile phase flowing through at high pressure, and after some specific chemical interaction between the components of the sample, it finalizes with a separation of components, which are identified straightforwardly. For the sampling procedure, we have adjusted the wastewater triggering to fill a 20-liter bottle in one day to use for analyzing daily averaged quantities, and for hourly analysis, the water inflow is adjusted to fill a bottle of 1 liter. Next, the 24-hour sample is partitioned into roughly 200 sub-samples of 100 mL volume. Following standard practices of LC-MS-MS, for preventing samples from contamination and adsorption, we have used glass eprouvettes for all sub-samples, whereas the containers of 20 L are made of poly tetra fluor-ethylene (PTFE or Teflon).

Malollari et al. [17] provided that in those conditions, the containment of the sample would not be affected. Next, the sub-samples were homogenized by utilizing a small peristaltic pump. In-between 24 hours after gathering the samples, we proceeded with extracting the solid phase, and then the elaborated samples were frozen and stored for final LC-MS-MS. The physicochemical parameters of influent waste waters were determined by the standard methods shown in Table 1. This procedure has been accomplished at the NOVAL Lab, which is accredited for these analytical capabilities [17]. Notice that the experts in this laboratory have assisted in all stages of data elaboration and measurements. In this laboratory, one uses the multi-residues method for the dissolved fraction, the particulate fraction, and metabolites techniques, according to standard chromatography guides and application literature [30–32]. We refer the reader to general guides [6] or literature [33] regarding the dissolved and particulate fractions. Such techniques are proven to be effective in detecting small amounts of molecules in aquatic solutions [32], which was consistent with our general exception for the presence of chemicals in the wastewater. For the dissolved fraction, the limit of detection (LoQ) was at 0.1 ng/L, which is considered a good resolution for such measurement referring to the terms used in [32, 34] and the laboratories' accreditation standards (here it is the ISO/IEC 17025 protocol).

Table 1. List of the protocols used in the measuring process

Met (8): EPA METHOD 160.1	Met (8): EPA METHOD 160.1	Met (8): EPA METHOD 160.1
Met (11) APAT CNR IRSA 2100	Met (11) APAT CNR IRSA 2100	Met (11) APAT CNR IRSA 2100
Met (12) APAT CNR IRSA 2110	Met (12) APAT CNR IRSA 2110	Met (12) APAT CNR IRSA 2110
Met (15) UNI EN ISO 15705:2002	Met (15) UNI EN ISO 15705:2002	Met (15) UNI EN ISO 15705:2002

The second part of the analysis was focused on investigating the longer-term migration of some molecules and their presence in aquatic plants. Again, after gathering samples from algae, solid-phase extraction (SPE) was applied, and next, the measurement was conducted using the ultra-high-performance (UHP) LC-MS/MS method. It guarantees resolution, sensitivity, and efficiency with a quicker outcome and a smaller amount of solvent expenditure [35], consistent with our general interest and the fact that the presence of chemicals in algae could be at a low level of concentration.

3.3. Evidence of the Presence of Pharmaceuticals in Water

During the period under investigation, we noticed extensive use of the medicaments. It is atypical but normal to remember that this period coincides with the COVID-19 pandemic. From the records of drugs used in the hospital during the period, various quantities and magnitudes of the pharmaceuticals consumed are observed. In Figure 2, we have displayed the histograms of the quantity of drugs used monthly during the period of monitoring. Quantities of anti-inflammatory medicaments and some antibiotics are significantly higher than those of psychiatric drugs and beta blockers, which are also parts of the 19 molecules analyzed in this research. Also, their quantity varies by month. The quantities of used medications vary from 0.06 to 620 g/day. In Figure 2, we have used a logarithmic scale and mg units to visualize those quantities. Regarding our focus of the analysis, we expect that this level of used drugs will be mirrored in the wastewater.

Since the quantity of drugs used varies remarkably through the year, in this stage we have considered the yearly averaged values of pharmaceuticals in the water. Due to high input loads during the monitoring period (2020–2021), as indicated by the figures of used quantities of drugs represented by histograms in Figure 2, we expected that all molecules would be identified in measurable quantities at this stage.

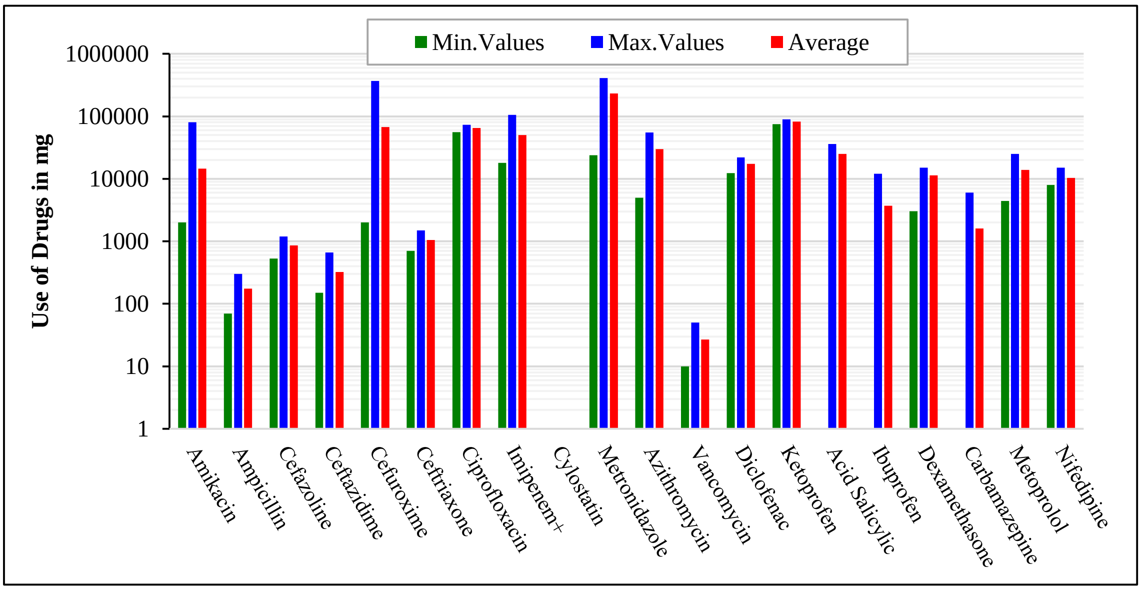

Figure 2. Quantity of used drugs at Vlora Hospital during 2020-2021 (Units are in mg, for visuality one used logarithmic scale)

To provide a summarized pattern of the pharmaceuticals found in water, we have shown in Table 2 external values of the quantity detected in mg/L for monthly averages of concentrations, the mean, and the frequency of detection over a 12-month reference period. The measurement of the monthly average has been realized according to a daily-based sampling, e.g., a bottle of 20L is scheduled to be filled during the whole day. Based on those samples, a monthly average quantity is calculated and reported herein as 'monthly average concentration'. Regarding detection by samples, we observed that usually there was an inhomogeneity issue. In a preliminary exploration of the results, we observed that concentrations of molecules were variable regarding the time of the measurement and the molecule entity. It varied from the lowest level of ng/L in some compounds like diclofenac or azithromycin to the mg/L level for antibiotics and analgesics classes. We observe that for several molecules that are qualified as typically present, the rate of detection among samples varies from 0.5 to 0.75. On the other side, chemicals that are considered undetected because their concentration was obtained lower the LoQ; the frequency of detection has been in the range of 0.17–0.5. It indicates high heterogeneity in the composition of the compounds in the influent waters.

Table 2. Summarized data for the presence of pharmaceuticals in water (Units are in mg/L)

Therapeutic c groups		Minimum (mg/L)	Maximum (mg/L)	Average (mg/L)	Detection Occurrence
	Amikacin	0.01	0.018	0.01367	0.67
	Ampicillin	0.001	0.0058	0.00308	0.67
	Cefazoline	0.0001	0.0002	0.00013	0.25
	Ceftazidime	<LoQ	<LoQ	<LoQ	0.17
	Cefuroxime	0.0001	0.0001	0.0001	0.5
	Ceftriaxone	0.0001	0.00035	0.00025	0.25
Antibiotics	Ciprofloxacin	0.021	0.03	0.025	0.58
	Imipenem Cystatin	0.0002	0.0006	0.0004	0.42
	Metronidazole	0.0004	0.003	0.0018	0.42
	Azithromycin	0.02	0.24	0.135	0.75
	Vancomycin	0.0015	0.002	0.0018	0.42
	Diclofenac	<LoQ	0.02	<LoQ	0.75
	Ketoprofen	<LoQ	0.0005	<LoQ	0.33
Analgesics/ anti-inflammatory	Acid Salicylic	0.0005	0.001	0.00073	0.25
	Ibuprofen	0.0006	0.0006	0.0006	0.42
	Dexamethasone	<LoQ	<LoQ	<LoQ	0.25
Psychiatric drugs	Carbamazepine	0.0002	0.0002	0.0002	0.17
Beta blockers	Metoprolol	<LoQ	<LoQ	<LoQ	0.42
	Nifedipine	<LoQ	<LoQ	<LoQ	0.33

Regarding the global view of the presence of pollutants in the water, we observed that monthly averages vary for all molecules, and in some cases, the concentration was below the limit of quantization LoQ or not detected at all. In Figure 3, we have displayed the average quantities of mostly used drugs for the period June 2020–June 2021. Notice that the quantity of use of drugs has been in the range of a few mg/days, which is mirrored in the very low level. Therefore, a very low level of pharmaceuticals in the wastewater is considered a raw fact conditioned by the low loads, not necessarily indicating an absolute or characteristic low level of presence.

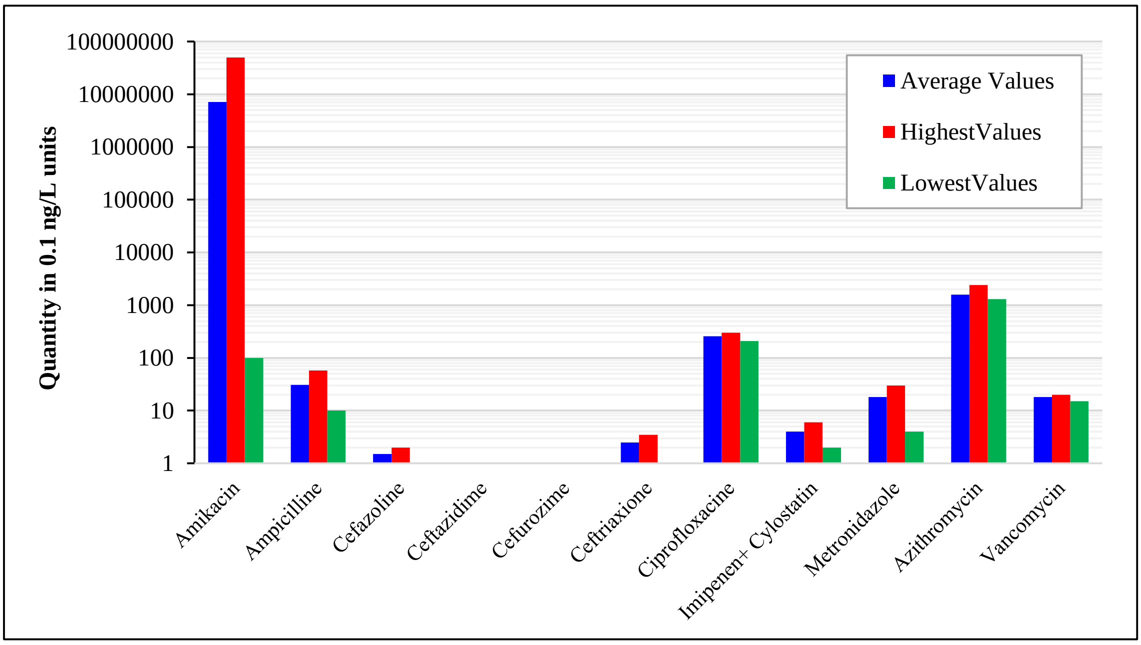

Figure 3. Highest, lowest, and average antibiotic concentration for June 2020-June 2021 (A Logarithmic scale is used for visuality. We chose the 0.1 ng/L unit to avoid negative values on the graph)

For some molecules, their fraction of presence in the water was below 0.1 ng/L, which is the limit of quantification as per our laboratory protocols; therefore, all deducted values of ng/L are considered LoQ, conditioned that they have been recorded and read by the instrument. Almost all cases represent a trend that culminates in the December–January period, which corresponds with a COVID wave. We observed a general tendency in the concentration of those chemicals in water, but most of the cases were at the limit of detection threshold. What is obvious and supported by the data gathered is that the quantities of drugs obtained in water are not homogenously proportional to their use in the hospital (Figure 4).

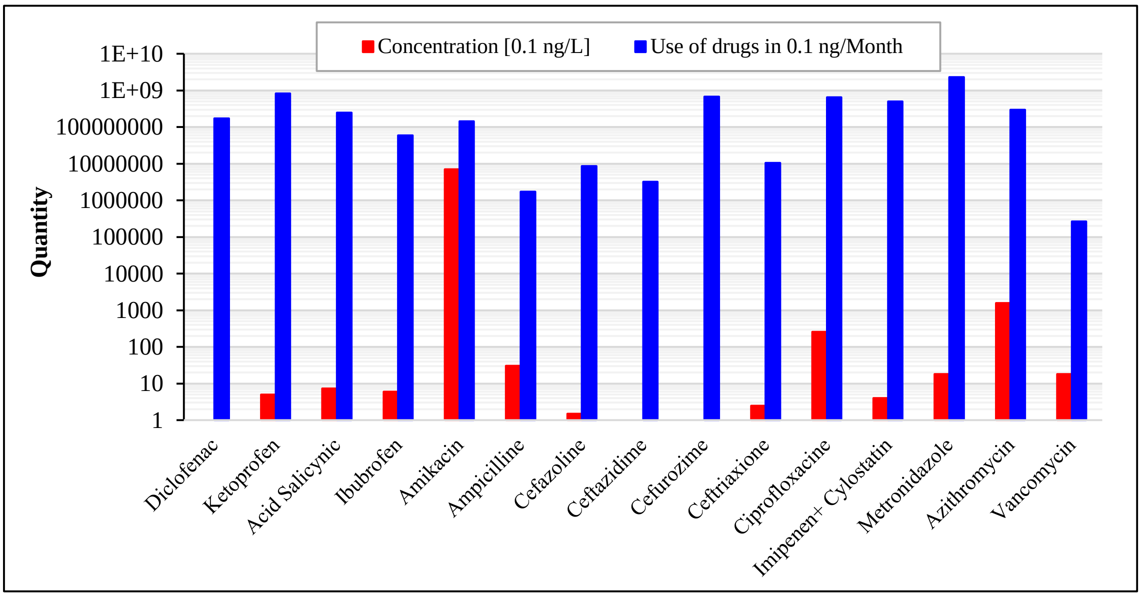

Figure 4. Monthly used drugs and corresponding quantities obtained in the water (Representation in logarithmic scale for visualization. Units are in 0.1 ng, to avoid negative values)

Notice that the measurement has been conducted instantaneously for all substances, but as mentioned above, those are just one day's measurements (spot values) and not statistical averages. It resulted in the highest average concentrations in the inflow of WWTP for four medicals (antibiotics), respectively: azithromycin (0.24 mg/L), ciprofloxacin (0.03 mg/L), diclofenac (0.02 mg/L), and amikacin (0.018 mg/L). On the other side, some chemicals do have a low concentration in the water, and for the antibiotic drugs Ceftazidime and Vancomycin, for the analgesics Dexamethasone and two beta blockers, their presence was identified but below the limit of quantization. Also, the frequency of detection (meaning traced but below the LoQ) has been low for those molecules in Table 2. It indicates a factual low presence of them in wastewater.

3.4. The Average Concentration of Pharmaceuticals on the Aquatic Algae

Next, we analyzed the presence of the antibiotics in algae at two different stations. Supposedly, it would mirror a longer-term behavior of chemicals in the groundwater and water drainage systems, and it represents an averaged effect of pharmaceuticals under investigation in the ecosystem. Undigested pharmaceuticals and their metabolites constitute a significant class of potentially hazardous aquatic pollutants and can threaten food chains [36]. However, within our best knowledge, there were no relevant domestic studies for the presence of pharmaceuticals in algae in the wastewaters of this hospital, which highlights the contribution of such analysis. Considering the quantities of pharmaceuticals used during the period of monitoring, we expect that those measures would represent a general view of the average presence of pollutants in the water for our system. The results of this analysis are displayed in Table 3.

Table 3. The yearly averaged presence of the antibiotics in algae

Therapeutic c groups	Pharmaceutical name	Minimum	Maximum	Detection occurrence
	Amikacin	<LoQ	<LoQ	0.67
	Ampicillin	<LoQ	<LoQ	0.67
	Cefazoline	<LoD	<LoQ	0.25
	Ceftazidime	<LoD	<LoQ	0.17
Antibiotics	Cefuroxime	<LoD	<LoQ	0.5
	Ceftriaxone	<LoD	<LoQ	0.25
	Ciprofloxacin	<LoD	<LoQ	0.58
	Imipenem + Cystatin	<LoD	<LoQ	0.42
	Azithromycin	<LoQ	<LoQ	0.75

We observe that the presence of the antibiotics in the algae has usually been below the limit of detection, and in some cases, they were even undetectable in absolute figures. Also, there were no distinguishing levels of concentration for the two stations considered, which confirms that the results obtained herein represent a realistic pattern of the presence of antibiotics in the aquatic plants. For clarifying the issue, we have considered the cases where the data were classified as lower than the limit of deduction, but some traces were observed, which were classified as detection occurrences for frequency. It was shown in the last column of Table 3. We observe that despite the small value and the level of incertitude of the measurement as per our laboratory standard, traces of medical products under scrutiny herein have been detected. Interestingly, we observed herein the same rate of detection as found for the presence of all antibiotics in the waters above. We will reconsider this finding in another re-examination, but it looks that qualitatively, the presence of the antibiotics in waters after being treated in the WWTP has been nearly constant at average, which is mirrored in the level of presence in the metabolized structures of the algae.

3.5. Observation for Monthly Concentrations of the Pharmaceuticals

Herein, we have considered a comparative view of the concentrations of pharmaceuticals found in wastewater and their quantity used in the hospital based on the observations of the monthly averages. We might discover more details by pairing used values with quantities found in wastewater. As mentioned above, it is difficult to model direct interdependency due to the complexity of the processes involving drug consumption, digestion, chemical reactions in drainage systems, etc. However, we can discuss our findings within the framework of a basic descriptive analysis. In fact, by using a naïve linear model for the relationship between the quantity of medicaments used and their quantity found in the water, we obtained very high changes between pseudolinear parameters, which indicates that the underlying relationship is not linear. We next observed that the expected monotony between the used quantity and the in-water presence was not observed for some molecules.

It is an immediate consequence of the values under the detection limit, but it also indicates a more complex behavior that cannot be modeled using our sparse data. On the other side, these findings signal the unexpected or unpredictable behavior of the presence of some chemicals in the wastewater regarding their initial discharges or quantity used in the hospital. To clarify this issue, more measurements are needed, and especially, higher accuracy and improved methodology should be conducted in another study for those systems. In Figures 5 and 6, we have shown the concentrations of the pharmaceuticals that were found in wastewater for at least one month in a measurable quantity. As mentioned above, for visualization purposes, we have used logarithmic scales, and to avoid the appearance of negative logarithmic values, we have used the limit of quantity as units (0.1 ng). In Figure 7, the quantity of antibiotics in water (in ng/L units) is displayed, whose monthly values were found to be above the limit of detection.

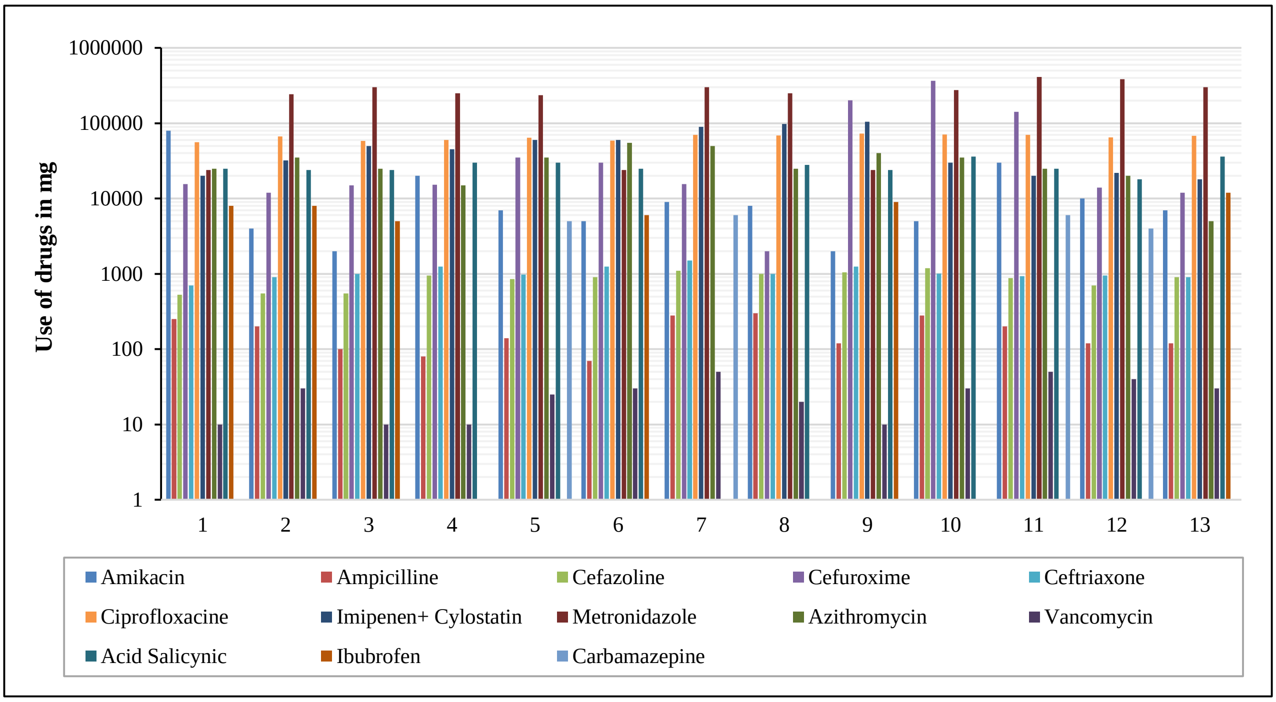

Figure 5. Monthly average use of the medicals in wastewaters (mg); Y axis is in logarithmic scale for visualization

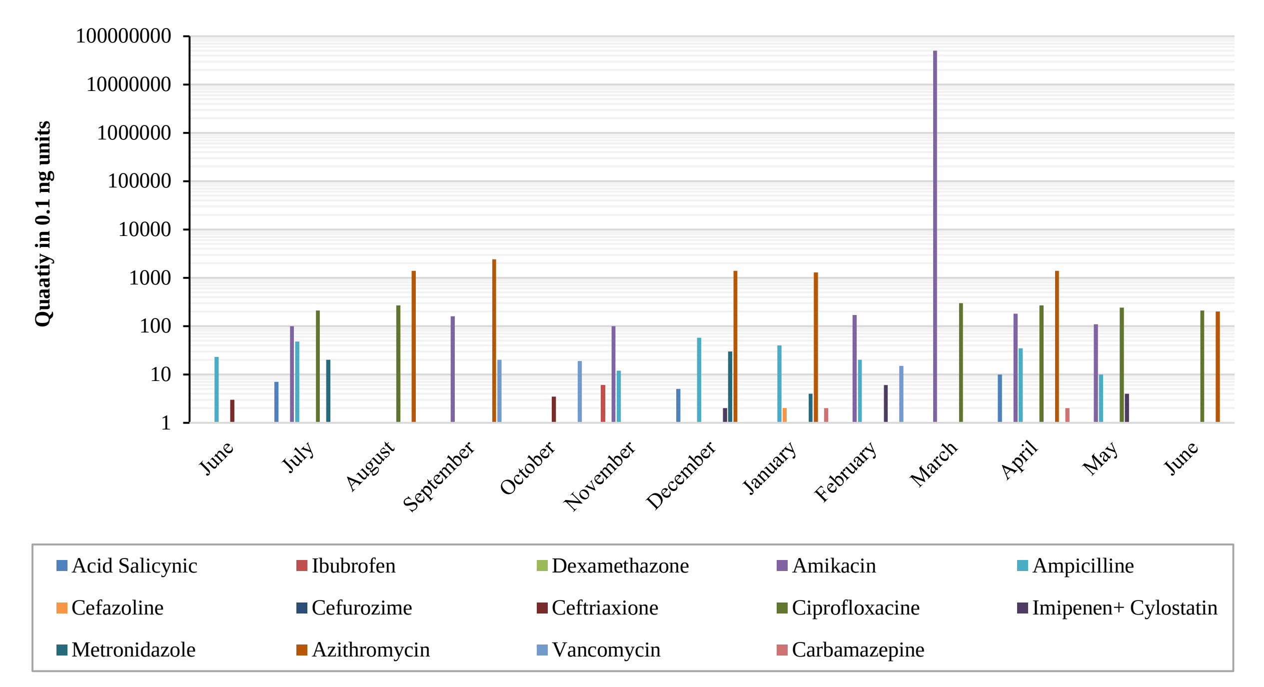

Figure 6. The quantity of Pharmaceuticals in water (Used units of 0.1. ng/L to facilitate logarithmic visualization for all items)

We observed the proportion of the pharmaceuticals found in the waters varied not proportionally to the use of the drugs. In this case, by using monthly data we were able to observe the variation by time, and by chemicals used. To enhance the measurements for more chemicals we should also consider a dynamic view, rather than the static one employed herein. Pharmaceuticals, in the sense of contaminants, are produced in batch processes leading to the presence of a variety of products and wide level quantities in wastewater [37]. Also, their quantity depends on the fraction of unchanged molecules extracted after consumption by humans. Next, they can be transformed or can degrade under the effect of solar exposition, absorption by plants. Such transformations occur at distinguishable different rates, depending also on the persistency feature of each item. Therefore, variation on the PC concentration in wastewater is a complex output and does not necessarily mirror the time variation of their discharges, at least, not obviously. This final remark suggests reconsidering a detailed monitoring and measurement activity based on modelling perspective, in addition to higher accuracy measurement mentioned above, which remain an objective for our incoming works.

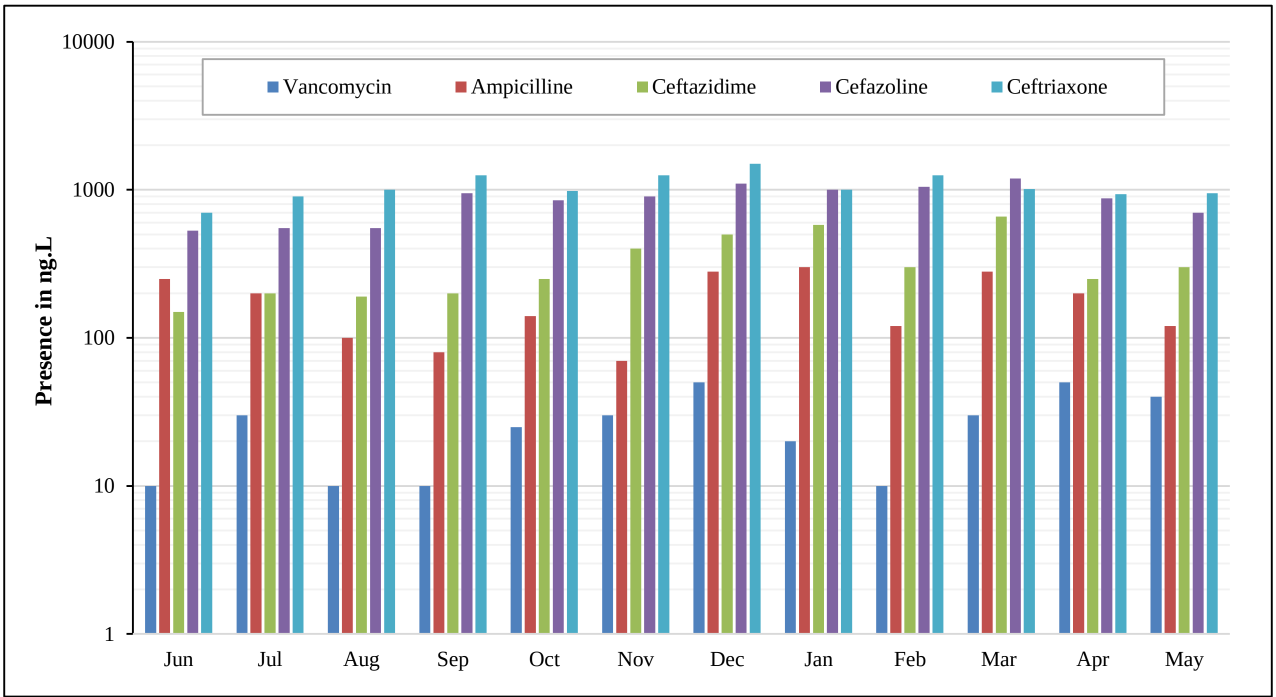

Figure 7. Concentration of the antibiotics in the water (Figures are on ng/L, in logarithmic scale)

3.6. Physicochemical Properties of Waste Waters Treatment Plant of Vlora Hospital

Finally, we have considered some complementary measurements regarding the physicochemical features of influent wastewater. Based on standard literature considering such analysis [23, 38, 39], etc., we have considered the measurement of the total dissolved solids (TDS), Conductivity, Turbidity, the pH, Chemical and Biological Oxygen Demand (COD, BOD), nitrite, and phosphorus containment. The temperature and pH are measured immediately after sampling, whereas other physicochemical parameters are analyzed at the laboratory. The results of those measurements are shown in Table 4.

Table 4. Physical-chemical parameters of hospital waste waters for one year period of sampling

	Minimum	Maximum	Mean	Std. Deviation
TDS (mg/L)	259	7800	3491,23	316.37
Conductivity (µS/cm)	400	3450	1581.85	795.262
Temperature (ºC)	4.9	35.1	18.431	9.3987
Turbidity (NTU)	16.9	26.3	21.2	3.3116
Ph	6.9	7.81	7.2723	0.30595
COD (mg/L)	100	264	163.92	46.241
NO3 – (mg/L)	0.85	20.15	3.38915	5.258532
Salinity (0/00)	0.13	0.93	0.5546	0.29271
P2O5 (mg/L)	1.02	4.89	2.7015	1.34702
BOD5 (mg/L)	18	74	44.92	16.337

4. Results and Discussion

This work involves the analysis of the presence of pharmaceuticals in the wastewater of the Vlora hospital, in the waters of WWTP, and in the algae *Ulva Luctaca*, covering the period 2020–2021. The results indicate that the concentration of 19 pharmaceutical molecules, initially chosen based on toxicity arguments, fluctuates between 0.1 ng/L and a few mg/L. In some cases, the presence of molecules has been detected, but their fraction in the water was found below the LoQ, at 0.1 ng/L. In general, the quantity of pharmaceutical chemicals in water changes significantly during the day, resulting in a remarkable heterogeneity of detection occurrences among the samples. The frequency of detection varies from 0.5 to 0.75 for most molecules that were classified as present in water and from 0.17 to 0.5 for some molecules whose concentration was found below the LoQ. Dexamethasone, Metoprolol, Nifedipine, and Ceftazidime were detected as traces, whereas Diclofenac, Azithromycin, Amikacin, Ampicillin, and Ciprofloxacin are classified as present in wastewater, and their concentrations are measurable. The azithromycin had the highest concentration in water at 0.24 mg/L, which corresponds to the highest concentration of all other antibiotics.

The lowest concentration for this molecule was obtained at 0.02 mg/L. The lowest antibiotic’s concentration belongs to ceftriaxone at 100 ng/L. For the analgesics/anti-inflammatory group, the highest average concentration was observed for diclofenac at 0.02 mg/L in November 2020, while the lowest concentration for this group was observed for dexamethasone, which resulted below the LoQ. Low concentrations are obtained for psychiatric therapeutic pharmaceuticals. For this category, carbamazepine has a concentration of 0.2 ng/L. For beta blockers analyzed in this study, concentration has been found at the traces level corresponding below the LoQ. Regarding the therapeutic drugs, the concentration levels for metoprolol and nifedipine were found to be between non-detected and the LoQ limit, but the frequency of detection was relatively high, around 42%. Regarding physicochemical parameter values, we observed that they are within those reported for hospital influences collected in different countries over a 20-year span.

Considering that the quantities of pharmaceuticals in the influent wastewater were not negligible and that WWTPs were not aimed at removing pharmaceutical compounds, this work can urge the use of a pre-treatment station for hospital wastewater. This suggestion becomes more realistic if we consider the projected enlargement of the hospital and the fact that, in this monitoring, the discharges from pediatric departments, which are in another area, were not considered. Also, it goes in line with the country’s advancing standards and attitudes toward environmental issues. Remember also that we have investigated only 19 molecules, providing only an indicatory examination of the overall presence of pollutants in the water. By nature, pharmaceutical residues cannot be substantially removed by conventional sewage treatment plants (STPs) used in filtering installations on the WWTP of the city, so advanced technologies, including nano-membranes [40, 41], purification by specific chemical reactions [42], ion floatation and reverse osmosis, and microbiological techniques [15, 43, 44], etc., could be recommended for an efficient long-term solution.

5. Conclusion

The study analyzing pharmaceuticals in the wastewater of the Vlora hospital, the waters of WWTP, and the algae *Ulva Luctaca* from 2020 to 2021 revealed varying concentrations of 19 pharmaceutical molecules, with some below the LoQ. The research also highlighted significant daily changes in the quantity of these chemicals in water, indicating considerable variability in detection instances among the samples. The study underscored the need for a pre-treatment station for hospital wastewater, considering the potential expansion of the hospital and the exclusion of discharges from pediatric departments. It concluded by suggesting the use of advanced technologies, such as nano-membranes, specific chemical reactions, ion floatation and reverse osmosis, and microbiological techniques, for a long-term solution. However, the study only examined 19 molecules, providing only an indicative examination of the overall presence of pollutants in the water, highlighting the need for further research to fully understand and mitigate the impact of pharmaceuticals on the environment.

6. Declarations

6.1. Author Contributions

Conceptualization, A.D. and V.T.; methodology, V.T.; formal analysis, D.P.; investigation, V.T.; resources, V.T.; data curation, V.T.; writing—original draft preparation, V.T. and A.D. All authors have read and agreed to the published version of the manuscript.

6.2. Data Availability Statement

Data sharing is not applicable to this article.

6.3. Funding

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6.4. Institutional Review Board Statement

Not applicable.

6.5. Informed Consent Statement

Not applicable.

6.6. Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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