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PHARMACEUTICALLY ACTIVE COMPOUNDS (PhACs) IN WATER OF ASIAN COUNTRIES: REVIEW ON THE OCCURRENCE, DISTRIBUTION AND ENVIRONMENTAL RISK

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Abstract: Pharmaceutically active compounds (PhACs) have received a lot of attention due to their enormous consumption proportions, significant bioactivity, and prospective ecotoxicity that tend to impact the health of marine ecosystems and humans. In this study, five commonly used pharmaceuticals were studied in water bodies of Asian countries. The main objective of this study was to review the occurrence and distribution of selected PhACs such as diclofenac, fluoxetine, caffeine, propranolol, and triclosan in the water bodies of Asian countries. This review was found that the range of concentration of pharmaceuticals was 0.055 to 11.4 x10^3 ng/L. Five distribution maps were plotted using the Geographical Information System (GIS) software. China has been identified as the country that discovered most of the selected PhACs occurrence and distribution compared to other nations. Data obtained from the present review was analyzed for risk assessment analysis using the Risk Quotient (RQ) technique, which is typically applied to assess PhACs with potential ecological concerns in water ecosystems. The findings of the study showed that 31 RQ was found to be non-significant. Fluoxetine compound was classified as having the highest RQ value calculated for phytoplankton, with an RQ value of 136.08. Hence, PhACs surveillance in the water ecosystems must be strengthened, and research on PhACs occurrence and potential risks should be highlighted in global environmental research.

Keywords: Asian countries, distribution, occurrence, risk assessment, water, Pharmaceutically Active Compounds (PhACs).

Introduction

Pharmaceutically Active Compounds (PhACs) are a class of Contaminants of Emerging Concern (CECs) that have received a lot of coverage in recent years due to their widespread occurrence and their potential to affect human health and aquatic ecosystems. Omar *et al*. (2021) stated that PhACs, Endocrine Disrupter Compounds (EDCs), and other classifications of Emerging Organic Contaminants (EOCs) have all been found in those matrices, which has resulted in substantial research on their toxicological effects and environmental fate. PhACs, along with several groups of micro-pollutants such as Personal Care Products (PPCPs), pesticides, estrogenic hormones, polyaromatic hydrocarbons, dioxins, and polychlorinated compounds, were among the chemical pollutants studied (Omar *et al*., 2018a). PhACs are usually discharged in wastewater through bathrooms, basins, or restrooms and transferred into Wastewater Treatment Plants (WWTPs) after use (Abdel-Shafy & Mohamed-Mansour, 2013).

The leftovers are deposited into waterbodies because traditional WWTPs can only remove these compounds to a limited extent. Sewage disposal, septic tank leakage, sewerage system leakage, livestock breeding, and fertilizer are several examples of direct pathways for PhACs into the aquatic environment. Due to the obvious possibility for humans and the environmental impact, the occurrence of PhACs throughout the environmental media has become a significant source of concern in recent decades. PhACs contaminants have been associated with a variety of human diseases, including cervical and breast cancer, diminished or enhanced thyroid activity, alterations in men's and women's reproduction processes, suprarenal gland, diabetes, and abnormalities in neuroendocrinology (Omar *et al*., 2018b; Lauretta *et al*., 2019; Kumar *et al*., 2020).

Due to improved human health regulations, the environmental discharge of PhACs such as antibiotics (e.g., amoxicillin, penicillin), anti-inflammatory drugs (e.g., ibuprofen, naproxen), pain relievers (e.g., acetaminophen, aspirin), and lipid regulators (e.g., simvastatin, trilipix), comparison information in the environment has increased dramatically in recent years and has grown as one of the most notable concerns for the environment in modern years (Molinari *et al*., 2006; Zhang *et al*., 2008; Jayasiri *et al*., 2013). As a result of the administration of significant quantities of medications in conventional medical attention, greater amounts of insistent PhACs leftover are being transported to Wastewater Treatment Plants (WWTPs) throughout domestic wastewater collection infrastructures. Most of these substances have been effectively eliminated, while some are just incomplete or never eliminated. The ineffective removal of several PhACs in traditional WWTPs seems to be problematic resultant various factors as well as low volatility, varying hydrophobicity, complicated compositions, enormously low concentration, impacting the microbes and relation with the other soluble compounds, and the extraction platform such as membrane and, soil (Heberer *et al*., 2002; Tran *et al*., 2010).

The present study was conducted (1) to identify the occurrence and distribution of selected Pharmaceutically Active Compounds such as diclofenac, fluoxetine, caffeine, propranolol, and triclosan in the water bodies of Asian countries and (2) to evaluate the environmental risk of diclofenac, fluoxetine, caffeine, propranolol, and triclosan in the water bodies of Asian countries. The aquatic compartment was highlighted in this study since it can be divided into several types, including surface water, groundwater, drinking water, seawater, and wastewater. As an outcome of studying the different types of water compartments, we were able to determine which type of water was the most affected and had significant concentrations of PhACs. The study discovered a significant association between PhACs metabolites and their presence in the water bodies of Asian countries, which constituted a risk. The findings additionally indicated that wastewater in aquatic environments had a high risk Quotient (RQ). These unique findings add to the body of knowledge on the consequences of environmental risk and offer fresh perspectives that may be used to guide practices and policies for enhancing global environmental monitoring.

Materials and Methods

Literature Retrieval

The Universiti Malaysia Terengganu student enrollment homepage was used to access the database. The research was conducted to analyze the number of studies on PhACs in drinking water and wastewater. Over 200 papers were examined, and 84 were chosen using the keywords "PhACs in Asian water", "Occurrence of PhACs", "Sources of PhACs", "Statistical analysis methodologies of PhACs", and "Risk assessments of PhACs". Papers published after 2000 were selected. All data was sorted and organized into tables.

The Reviewed Study Site

There are 51 countries in Asia, including three other territories: Hong Kong, Taiwan, and Macau. Asia is the largest of the world's continents, covering approximately 30% of the Earth's land (National Geographic Society, 2012). Asia is known as the world's most populous continent, encompassing the northern and eastern hemispheres. It is home to 60% of the world's current population, which covers an area of 44,579,000 square kilometres (17,212,000 sq mi). Asia not only has the world's second-lowest per capita water resources, but it also has the world's highest population (World Bank, 2020). Until 2021, the Asian population has already risen to 4,678,445,024 people, with China continuing to dominate with an overall population of 1.37 billion people. Meanwhile, the Maldives, with an estimated population of 345,000 people, is Asia's least populous country as recorded in 2021. Therefore, by 2050, Asian cities will be home to 52% of the world's metropolitan population (United Nations, 2014). The study area of Asian countries is depicted in Figure 1. Kondor *et al*. (2021) assessed that numerous studies have linked the presence of PhACs in untreated or treated tap water with significant adverse health effects, including genotoxicity and carcinogenicity, considering that PhACs toxicity could additionally have a detrimental effect on the sustainability of water resources. Having said that, PhACs have been discovered in a variety of environments, including Asia, America, Australia, Europe, and Africa, at low concentrations (ranging from ng/l to g/l) in drinking water (Couto *et al*., 2019), surface water, ground water, and wastewater (Kondor *et al*., 2021).

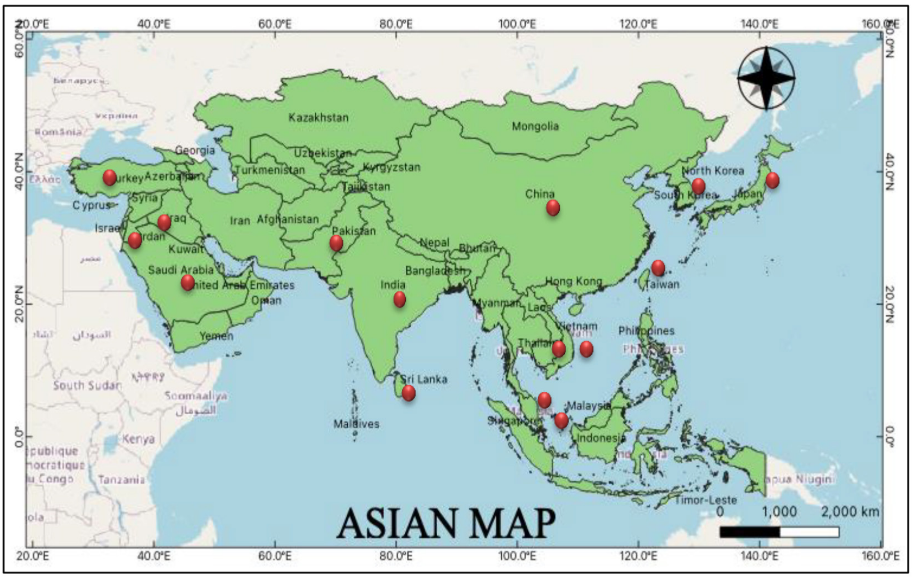

Figure 1: Map of Asian countries that are reviewed for this study. The red dots show the data occurrences that was retrieved

GIS Application

A Geographic Information System (GIS) is a computer programme that combines three main components which consist of information, system software, and system hardware to help enable the presentation, investigation, management, and capture of all types of geographically referenced information obtained from navigation systems such as Global Positioning System (GPS) (Ashkezari *et al*., 2018). GIS can display different types of information, such as maps, plants, streets, and water bodies (Burrough *et al*., 2015). It can generate digital cartographic resources, link road properties to spatial data, process large amounts of data, and display spatiotemporal extracted features (Zhang *et al*., 2021). In this paper, the GIS software was used to illustrate or plot the concentration data that was accumulated from the articles related to five maps distribution. The map distribution is used to identify which selected PhACs compound is distributed more in the Asian water.

Descriptive statistics

The occasional and yearly fluctuations of the pharmaceuticals was evaluated using descriptive statistics which are mean, median, and standard deviation. The PAST4 software was used to analyze statistically significant differences between pharmaceuticals and sampling sites, timeframe, and inflow because most of the data is not regularly distributed.

Risk Quotient (RQ)

Several studies have utilised the Risk Quotient (RQ) approach to characterise environmental and ecological risk in aquatic ecosystems (Lee *et al*., 2008; Stasinakis *et al*., 2011; Pereira *et al*., 2015; Thomaidi *et al*., 2016). Omar *et al*. (2018a) characterised the risk of pharmaceuticals in the marine ecosystem as non-significant risk (< 0.01), minimal risk (0.01 - 0.1), moderate risk (0.1 - 1.0), and significant risk (> 1). The ratio of Measured Environmental Concentration (MEC) against Predicted No - Effect Concentration (PNEC) was used to calculate RQ.

$$RQ = \frac{MEC}{PNEC} \quad (1)$$

where,

MEC: The highest concentration of pharmaceutical chemicals discovered in the tested water samples.

PNEC: Assuming the lowest NOEC, LOEC or E(L)C50 values among the most vulnerable species and dividing them.

$$PNEC = \frac{EC50 \text{ or } LC50}{1000} \quad (2)$$

The RQ method was utilised to determine the environmental risk caused by the presence of PhACs in all categories of water elevations. According to relevant EU legislation, a RQ technique has typically been conducted to assess compounds with potential ecological concerns in rivers and streams depending on concentration data for specific contaminants (Zhou *et al*., 2019). The concentrations of pharmaceuticals in the environment, as well as toxicological assessments, are significant for assessing their environmental and human health consequences. Hence, phytoplankton, zooplankton, and fish were included as aquatic matrices to assess whether the measured estimated concentration is adequate for the marine food chain or otherwise.

Results and Discussion

The distribution map of each selected PhACs in different types of water compartments are shown in Figures 2, 3, 4, 5, and 6 (drinking water, groundwater, seawater, surface water, wastewater). Approximately 182 samples from different types of water bodies (drinking water, groundwater, seawater, surface water, wastewater) throughout Asian countries were reviewed. From Figure 2, caffeine in wastewater samples was widely distributed, particularly in China, based on a study by Sui (2011), Sun (2016a), Ashfaq (2017), Ben (2018) and Li (2018). Meanwhile, from Figure 3, diclofenac was dominant in the eastern part of Asia and there is one occurrence of diclofenac in drinking water detected.

However, in Figure 4, due to limited studies of fluoxetine distribution in water bodies throughout Asian countries, their distribution can only be seen in China, Sri Lanka, and Pakistan, as collected from studies by Sun (2016b), Ashfaq (2019), Guruge (2019), Patel (2019) with occurrence in wastewater as the highest value (10.75 ng L^{-1}). Then, the distribution of propranolol in Figure 4 were mostly conducted in Peninsular India. Other than that, the distribution of Triclosan based on Figure 5 was also dominant in India, especially in Peninsular India, with occurrence in seawater and wastewater. Figure 6 depicts the whole distribution of the five selected PhACs according to the compound types.

Caffeine is abundant in China's wastewater, as shown in Figure 1. However, there is only one caffeine concentration occurred in groundwater located in Taipei with a value concentration of 930.7 ng L^{-1} (Patel *et al*., 2019). Diclofenac was ubiquitously found in all different types of water at concentrations between 0.31 and 10,200 ng L^{-1} (Ali *et al*., 2017; Patel *et al*., 2019). Simazaki *et al*. (2015) revealed that drinking water concentration was found in Japan IWPPs with a concentration of 16 ng L^{-1}. These drinking water sources were significantly impacted by the

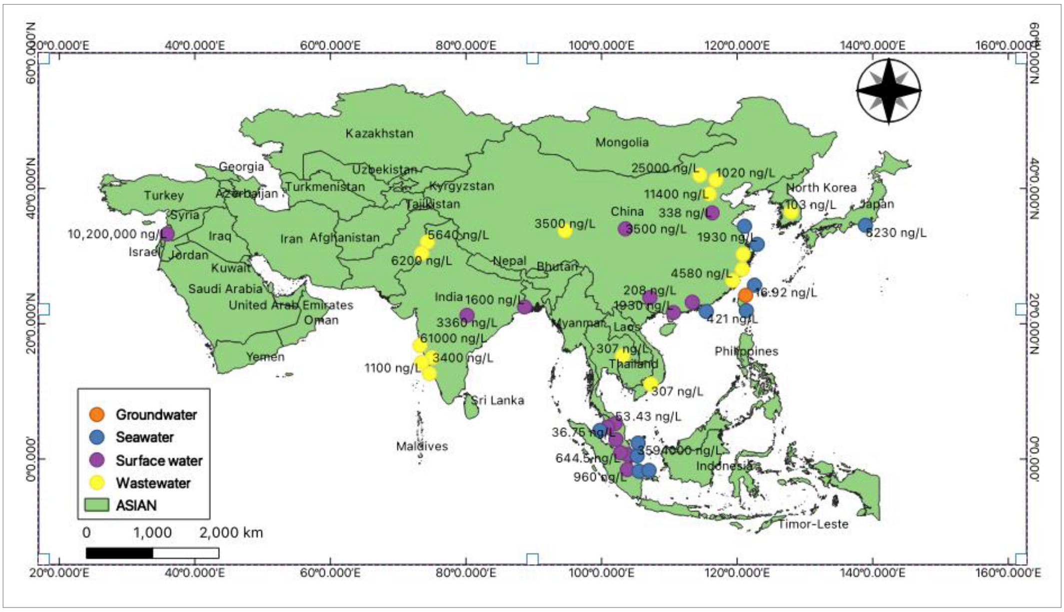

Figure 2: Occurrence and distribution of caffeine in waters of Asian countries

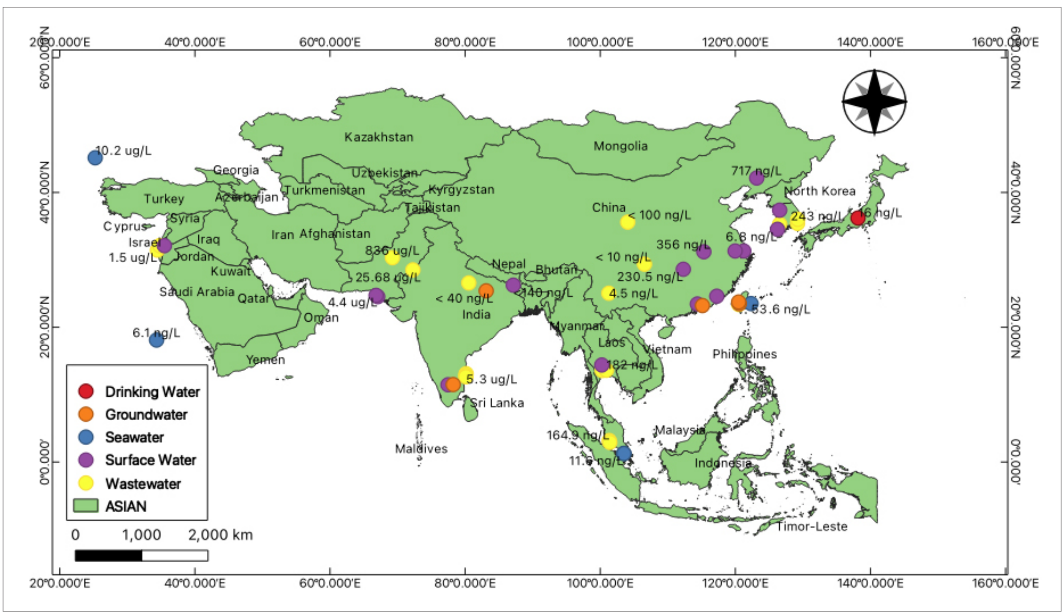

Figure 3: Occurrence and distribution of diclofenac in waters of Asian countries

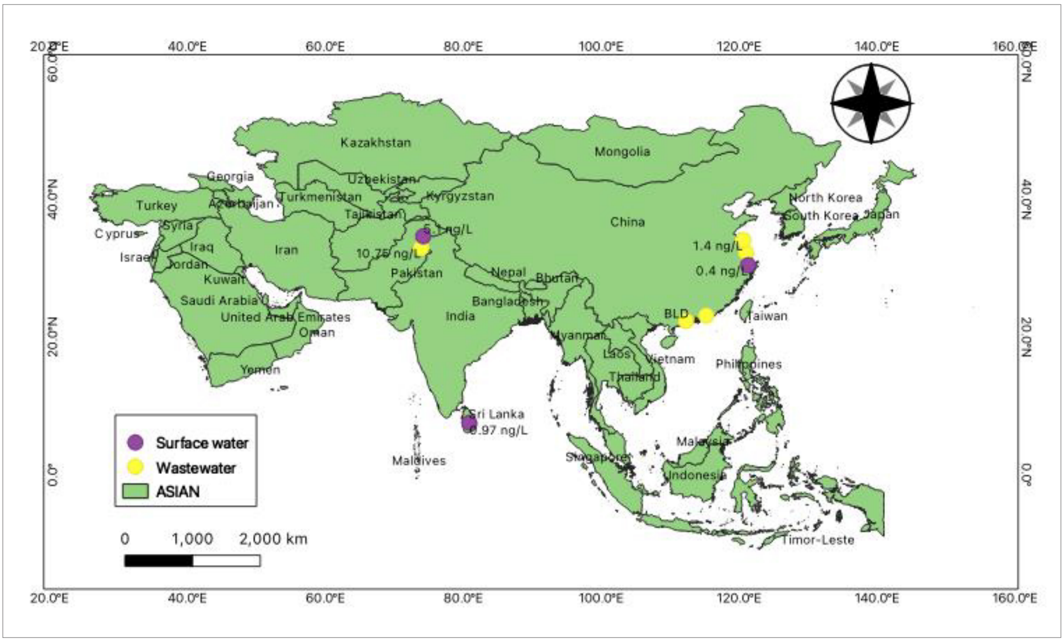

Figure 4: Occurrence and distribution of fluoxetine in waters of Asian countries

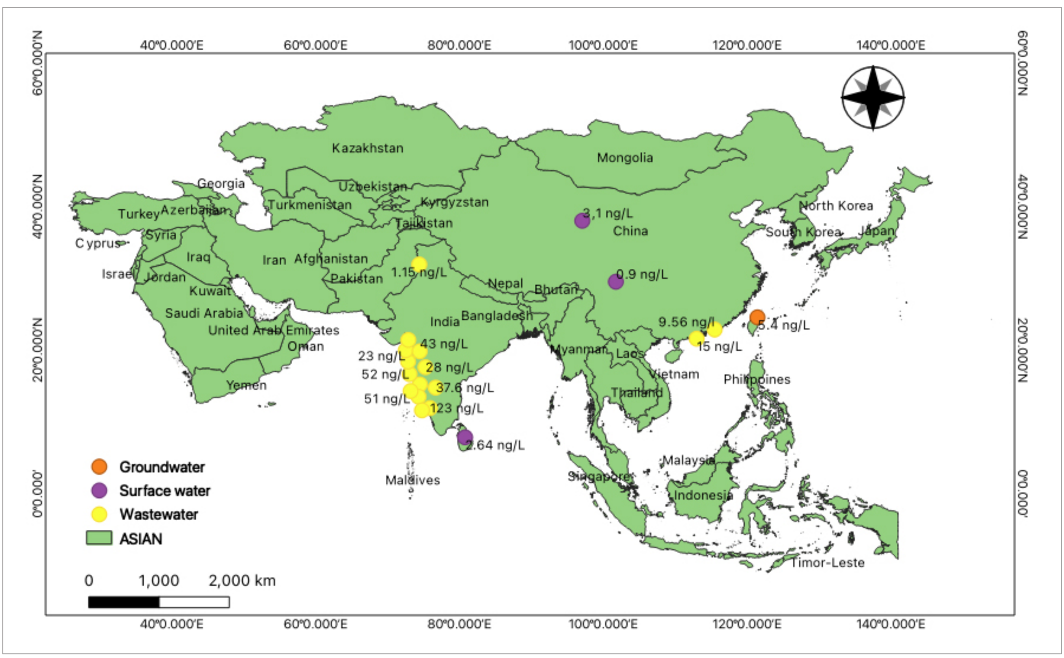

Figure 5: Occurrence and distribution of propranolol in waters of Asian countries

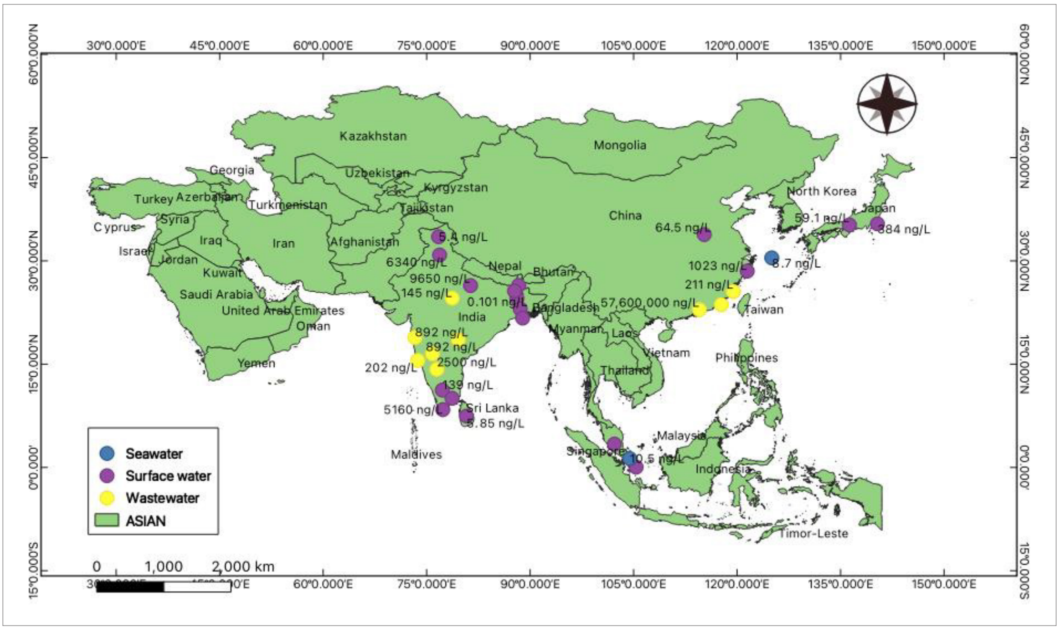

Figure 6: Occurrence and distribution of triclosan in waters of Asian countries

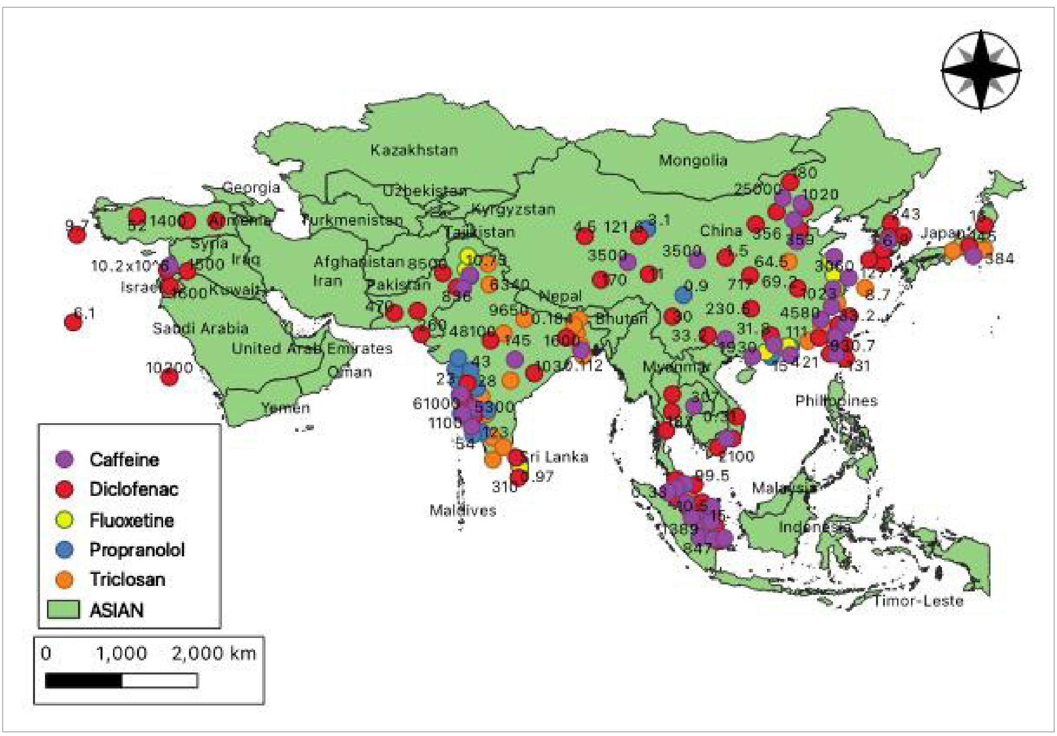

Figure 7: Occurrence and distribution of selected PhACs in waters of Asian countries

discharge of sewage treatment plants during industrial usage, including washing and cooling water (Simazaki *et al*., 2015).

Eight concentrations of the fluoxetine compound were found in three Asian countries which are China, Pakistan, and Sri Lanka. Ashfaq *et al*. (2019) detected the highest fluoxetine concentration in Lahore WWTPs, Pakistan with a concentration value of 10.75 ng L^{-1}. Propranolol concentration is major distributed in the southern part of India or also known as Peninsular India, as shown in Figure 3. Generally, 20 over 25 propranolol concentrations have been found in wastewater (effluents and influents) ranging between 1.15 to 187 ng L^{-1}. The distribution map of triclosan consists of three different types of compartment water which are seawater, surface water, and wastewater. Patel *et al*. (2019) detected nine triclosan concentrations in three countries which are China, India, and Singapore. Two concentrations that are presence in Malaysia were not detected in surface water (Praveena *et al*., 2018).

Figure 7 depicts the whole distribution of selected PhACs concentration in one map distribution and diclofenac concentration has been found to be the most distributed especially in the China region. The five selected PhACs concentrations presence in China. Sui *et al*. (2011) revealed that the highest concentration was caffeine and its presence in China wastewater (influents) with a value of 11.4 x 10^3 ng L^{-1}. The lowest concentration is in India (triclosan), with a value of 0.055 ng L^{-1} (Das Sarkar *et al*., 2020). In this review, East Asia was found to have PhACs in countries such as in China, Japan, and South Korea. The least occurrence of the selected PhACs was found in Central Asia countries including Kazakhstan, Kyrgyz Republic, Tajikistan, Turkmenistan, and Uzbekistan.

Omar *et al*. (2018a) characterised the risk of pharmaceuticals in the marine ecosystem as non-significant risk (< 0.01), minimal risk (0.01 - 0.1), moderate risk (0.1 - 1.0), and significant risk (> 1). The findings of the environmental risk assessment for the selected PhACs found in aquatic ecosystems are shown in Figure 8. As shown in Figure 8, the Risk Quotients (RQs) of diclofenac in phytoplankton, zooplankton, and fish in Asian countries were generally less than 1, indicating that they were unlikely to cause health harm or had limited potential for doing so. The RQ results revealed that 21 of the 48 RQ values were found to be non-significant, nine values were found to be low risk, six moderate risks and 12 values were revealed to be high risk.

As mentioned previously, diclofenac and caffeine represented two of the PhACs that displayed elevated concentrations in Asian countries other than other pharmaceutical compounds. To make it much easier to comprehend, Figure 8 illustrates the ecological risk characterisation for selected PhACs utilising four colour descriptors (blue, green, yellow, and red) to make it much easier to comprehend. The RQ values obtained in these types of water could be a reliable indication of ecological risk. Table 3 shows that fluoxetine had the greatest RQ of all three standard test species examined, with an RQ of 136.07. All of the computed RQs for caffeine concentration were less than 0.01, demonstrating no caffeine risk in water from Asian countries.

RQ was analysed for different water matrices from diverse geographical backgrounds, and the results showed a high level of findings (Figure 8). Surface Water and Wastewater Treatment Plants (WWTPs) pose a higher risk to the aquatic environment. Ashfaq *et al*. (2019) reported a high RQ value for fluoxetine in WWTPs from Pakistan, while the lowest RQs were also observed for caffeine in surface water from the Selangor River in Malaysia (Praveena *et al*., 2018). This Risk Quotient indicates that the environmental risks connected with chemical compounds in the study area were minor, indicating that the current concentrations are still sustainable for the aquatic environment. On the other hand, precautions continue to be necessary to prevent catastrophic consequences.

The apparent presence of PhACs compounds in the Asian water ecosystem suggests that there is a likelihood of uncontrolled releases into the ecosystem. Hence, it is of the utmost importance to carry out periodic assessments of PhACs compounds in Asian countries' water ecosystems, with a particular emphasis on other different variables such as surface water, groundwater, drinking water, seawater, and wastewater. Regardless of these studies, the presented fundamental knowledge can be beneficial when comprehending possible aquatic environment pollution owing to the ongoing trend of PhACs contaminants.

According to Peng *et al*. (2020), PhACs contaminants originating from many different sources might eventually spread to the marine ecosystem by transmitting pathways such as riverside input, airborne settlement, mariculture, pollution from coastal areas release, and aquifer infiltration, which is becoming a significant form of newly discovered aquatic organic contaminant. PhACs may additionally build up in marine creatures via alimentary chains, becoming significant environmental threats to marine creatures and potentially jeopardising the whole marine ecosystem and perhaps even human well-being (Howard & Muir, 2011). Meanwhile, the mixing of PhACs metabolites in the water ecosystem will impact the food chain cycle of the marine environment through bioaccumulation.

Consequently, the marine organisms will become contaminated when they consume PhACs metabolites. Thus, this will be another step in how humans will be affected by the harmful PhACs metabolites via food consumption which is by consuming marine organisms that have been contaminated. PhACs can penetrate the aquatic environment through a multitude of methods, including human and animal excretion, landfill, manure, or biosolids applications, and inappropriate disposal (Jayasiri & Purushothaman, 2013). As a result, determining the occurrence and distribution of PhACs is necessary in order to study and understand the issue of PhACs to not cause significant environmental disruption by harming the marine environment or marine organisms or impacting humanity's environment by destroying habitats and organisms and negatively impacting individuals.

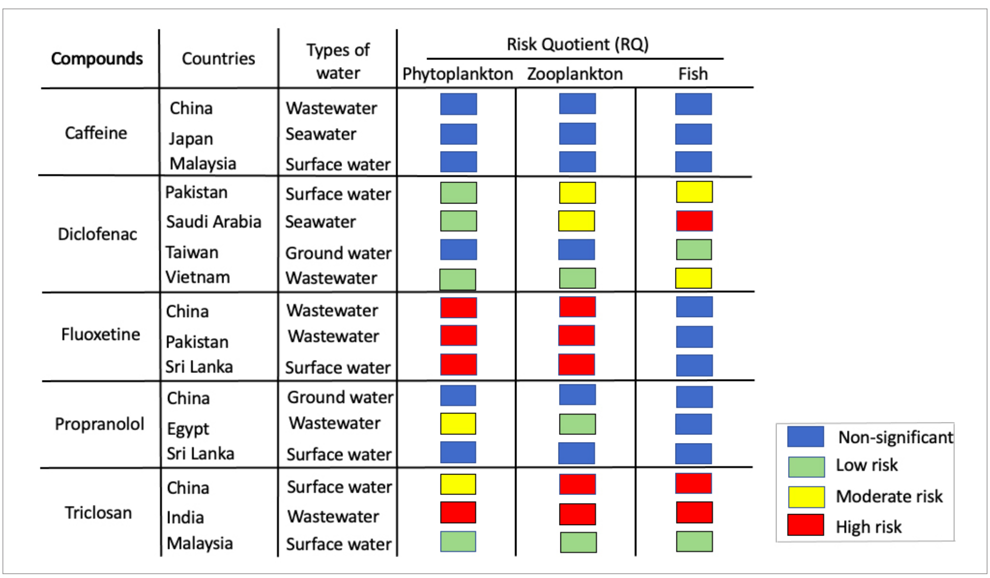

Figure 8: The ecological risk characterization of the selected PhACs concentration for three different test species (phytoplankton, zooplankton and fish) in aquatic ecosystems according to the colour labelling

Table 1: Statistical analyses of selected Pharmaceutically Active Compounds that focus on descriptive statistics (mean, median, standard deviation), *p*-value and significancy

Compounds	Mean	Median	Standard Deviation	*p*	Significancy
Caffeine	175.26	17.46	282.1354	0.00016885	Significantly different
Diclofenac	148.64	65.6	206.2194	3.0417E-08	Significantly different
Fluoxetine	2.6525	1.185	3.686023	0.081267	Not significantly different
Propranolol	33.8892	18.5	42.00999	0.00048416	Significantly different
Triclosan	412.2043	15	1172.383	0.051848	Not significantly different

p value < 0.05: statistically significant difference
p value > 0.05: not statistically significant difference

Descriptive statistics that show the significance of the selected PhACs occurrence in water from Asian water bodies is depicted in Table 1. The significance of the collected data computed to compare the compound type and determined using the PAST4 software. As for the selected PhACs, three compounds; caffeine, diclofenac, and propranolol, are found to be significantly difference, with a p-value less than 0.05. Fluoxetine and triclosan are found not to be significantly different as the *p*-value indicated more than 0.5.

Conclusion

Global environmental monitoring studies have proven that PhACs and their metabolites are ubiquitously present in almost all water and soil-related environmental compartments, as well as the biota (animals and plants). It was also observed that China has been recorded as the country that is commonly found of have these selected PhACs concentrations. Pharmaceutically Active Compounds are known to be a form of new pollution that is not apparent to the naked human eye, hence this research is essential. Humans who have not been exposed to Pharmaceutically Active Compounds may be unaware of the types of contaminants contained in their water supply. Finally, this review suggests that the above challenges will be addressed by shifting to comprehensive monitoring research, as well as improving the efficiency of WWTPs through advanced technologies without any secondary pollution in all countries inorder to save the water cycle and ecosystem. Hence, from the viewpoint of future expansion, using a synergistic technique to identify and implement an autonomous solution to eliminate and reduce environmentally related emergent contaminants of significant concern might be a prominent alternative.

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