QUALITATIVE SCREENING OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN WATER AND FARM GREEN MUSSELS AT STRAITS OF JOHOR

MUHAMMAD ARIF HAIKAL BIN MOHAMAD HANAFI

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School of Civil Engineering
Faculty of Engineering
Universiti Teknologi Malaysia

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ABSTRACT

Pharmaceuticals and personal care products (PPCPs) are ubiquitously found in surface water and aquatic organisms. They include antibiotic, pain killer, hypertension drug, anti-inflammatory drug and cosmetics compounds. Green Mussels (*Perna viridis*) are known as filter feeder, which can potentially accumulate PPCPs. Although this type of studies have been conducted in many parts of the world, information on PPCPs pertaining to mussels in South East Asian countries, specifically in Malaysia, is still limited. Therefore, the aim of this study was to qualitatively screen the PPCPs occurred in mussels and the respective surface water surrounding a commercially cultured mussel farm. The effects of tidal and depth on the occurrences of PPCPs in mussel and surface water were reticulated. Mussels and water samples were collected during high tide and low tide at different depth in the mussel farm located at the estuary of Sungai Melayu, Johor, Malaysia. The collected samples were extracted using Solid-Phase Extraction (SPE) method prior to the analysis by Liquid Chromatography tandem with Quadrapole Time-Of-Flight Mass Spectrometry (LC QTOF-MS/MS). The detected compounds were further screened using database by PubChem, WHO Drug Index and Human Metabolome Database for their type and category. The findings revealed that 10 PPCPs compounds were found in water samples and 73 compounds were found in mussel samples. Nigericin, nicotinyl, ammodendrine and 3,4-DMMA were among compounds that occurred in both mussel and surface water. It was also noted that compounds were detected higher during low tide in mussels compare to that of high tides. No significant difference for number of compounds was observed in mussel between both 0 m and 3 m. This study has demonstrated that mussels possess high affinity to accumulate PPCPs from their surrounding water owing to their filter feeding character.

ABSTRAK

Produk penjagaan diri dan farmasi (PPCPs) sangat mudah ditemui di permukaan air dan dalam organisma akuatik. Ianya merangkumi antibiotik, ubat tahan sakit, ubat darah tinggi, ubat anti keradangan dan sebatian kosmetik. Kupang Hijau (*Perna viridis*) dikenali sebagai organisma yang menapis makanan, dimana berpotensi mengumpul PPCPs. Walaupun kajian seperti ini telah dijalankan di kebanyakkan tempat di dunia, maklumat mengenai PPCPs dalam kupang di Asia Tenggara, khususnya di Malaysia, masih terhad. Oleh itu, kajian ini bertujuan untuk mengesan PPCPs yang terkandung di dalam kupang dan permukaan air sekitar kawasan penternakan kupang secara kualitatif. Kesan pasang surut dan kedalaman air terhadap kehadiran sebatian PPCPs di dalam kupang dan permukaan air. Sampel kupang dan air telah diambil ketika air pasang dan surut pada kedalaman yang berbeza di kawasan ternakan kupang yang terletak di muara Sungai Melayu, Johor, Malaysia. Sampel yang diperoleh diekstrak menggunakan cara pengekstrakan fasa pepejal (*solid phase extraction*) diikuti dengan penganalisaan sampel yang telah diekstrak menggunakan '*Liquid Chromatography*' gabungan bersama '*Quadrapole Time-Of-Flight Mass Spectrometry'* (LC QTOF-MS/MS). Sebatian kimia yang telah dikesan, ditapis lebih lanjut mengikut jenis dan kategori menggunakan pengkalan data dari PubChem, Indeks Ubat WHO dan Pengkalan Data Metaboloma Manusia. Menurut hasil kajian, 10 sebatian PPCPs dijumpai dalam sampel air dan 73 sebatian dijumpai di dalam kupang. Nigericin, nicotinyl, ammodendrine dan 3,4-DMMA merupakan antara sebatian yang dikesan di dalam kedua-dua kupang dan permukaan air. Selain itu, bilangan sebatian di dalam kupang juga didapati lebih tinggi semasa air surut berbanding air pasang. Tiada perbezaan ketara yang diperhatikan untuk bilangan sebatian pada kupang bagi ukuran bilangan sebatian PPCPs berdasarkan kedalaman (0 m dan 3 m). Kajian ini menunjukkan bahawa kupang mempunyai kebolehan yang tinggi untuk mengumpul PPCPs dari persekitarannya melalui cara pemakanan kupang.

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3,4-DMMA	-	3,4-dimethoxymethamphetamine
ARB	-	Antibiotic resistance bacteria
ATC	-	Anatomical Therapeutic Chemical
BAF	-	Bioaccumulation factor
DDD	-	Define Daily Dosage
JAS	-	Jabatan Alam Sekitar
MDMA	-	Methylenedioxymethamphetamine
MOH	-	Ministry of Health
PPCPs	-	Pharmaceuticals and Personal Care Products
US EPA	-	United State of America Environmental Protection Agent
US FDA	-	United State of America Food and Drugs Administration
WHO	-	World Health Organization
ETM	-	Estuarine turbidity maximum
WWTP	-	Wastewater treatment plant

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CHAPTER 1

INTRODUCTION

1.1 Background of Problem

Primarily, pharmaceuticals are used to prevent or treat human and animal disease, whereas personal care products are used to improve the quality of life including cosmetics (Boxall *et al*., 2012). Pharmaceuticals and personal care products (PPCPs) are contaminants of emerging concerns that present ubiquitously in aquatic environment ranging between 2.52 - 12400 ng/L (Castiglioni *et al*., 2011; Reddy *et al*., 2005; Bueno Martínez *et al*., 2007; Evgenidou *et al*., 2015; Weigel *et al*., 2004; Nguyen *et al*., 2018). When PPCPs used in our daily life, these compounds are channel by domestic waste drainage into wastewater treatment plant (WWTP). What happen next is that not all these PPCPs are successfully removed through WWTP process due to several known factor; transformation of compounds into metabolites, unsuitable treatment process for removing PPCPs compounds and inefficiency of available technologies in WWTP (Wang and Wang, 2016; Cizmas *et al*., 2015; Smith, 2011). Most popular adoption treatment in WWTP are conventional biological treatment by activated sludge system. The system use bacteria as decomposer during the process to decompose unwanted harmful compounds including nutrients such as nitrate, nitrite, phosphate and many more. However, PPCPs are not able completely being removed by such treatment system. Therefore, PPCPs compounds escaped from WWTP and discharge into aquatic ecosystem through effluent.

As introduced into aquatic ecosystem, these compounds are available in water bodies making any aquatic organism accumulate PPCPs via surrounding and their feeding behaviour. Mussel for example, able to accumulate any xenobiotic compounds by filter feeding surrounding water. When mussel filter feed water to gain food particle in water column, those xenobiotic compounds are also being filtered into mussel including PPCPs (Boxall *et al*., 2012). Overtime these compounds will be accumulated into mussel as the compounds keep on supplied to mussel surrounding water. Accumulation of pollutants in aquatic environment may driven by physical phenomenon such as tidal cycle occurred upon surface water (Artigas *et al*., 2017).

The accumulation of PPCPs, especially those that involve hormone drugs, has led to numerous effects toward aquatic organism. For example, the feminization and alteration of behaviour in male fish due to introduction of progesterone (Roast and Brighty, 2004). Some categorized as endocrine disruptors can inhibit spermatogenesis, reduce sperms count and lower egg production in fish (Mills and Chichester, 2005). These, however, did not include the "cocktail effects", in which the interaction between different PPCPs can trigger adverse combination effects since each compound produces specific biological response (Cizmas *et al*., 2015). According to recent news article (Hodgekiss, 2015), the existence of birth control hormones in the environment was associated with the declining human male sperm count in European countries via consumption of drinking water. Several studies have also showed that PPCPs in the environment can reach human through daily food consumption, especially those at the lower trophic food level (Zenker *et al*., 2014). These also could lead to insecurity and safety of our food security since the seafood supplied to consumer market are polluted and contaminated with PPCPs.

Generally, PPCPs, which been frequently reported to bioaccumulate in aquatic organisms and mussels, are one of the best examples because of their filter feeding behaviour using water column (Zenker *et al*., 2014; Pechenik, 2010). Mussels or bivalves tend to accumulate higher concentration of PPCPs as compared to fish due to feeding behaviour between these organisms (Zenker *et al*., 2014; Du *et*

al., 2014). Mussel filter water into their body to gain organic substance for food consumption, hence any unintended foreign compounds will accumulate during feeding process. Since mussels are an important component in an aquatic food web as well as a local delicacy that is highly sought after, PPCPs could be easily transferred to human. It is important to note that small concentrations of PPCPs in mussels will be amplified five to ten-fold in human depending on the types of aquatic organism ingested (Castro and Huber, 2008; Zanker *et al.*, 2014). Although the bioaccumulation of mussels has been widely studied in different parts of the world, the data collected in Malaysian is still lacking.

Malaysia is also no exception to PPCPs detection in sewage and surface water but none for aquatic organism. Most study regarding toxicology and pollutants detection in Malaysia were focus on other contaminants such as heavy metals (cadmium, mercury, iron etc) and organic compounds (polycyclic aromatic hydrocarbons, polychlorinated biphenyls and others) were widely studied by previous literatures (Shahbazi *et al.*, 2010; Nicholson *et al.*, 2005; Yunus *et al*., 2011; Yap *et al*., 2006; Abdullah *et al*., 2014). To date, 18 PPCPs as low as 7 ng/L and 5 ng/L were observed in Malaysian sewage effluent and surface water, respectively (Tan *et al*., 2015; Yacob *et al.*, 2017; Al-Odaini *et al*., 2012). Their presence showed that they can escape, either as parent compounds or metabolites, from the current operating conventional biological treatment systems into Malaysian waterways. Furthermore, the treatment systems were not designed to remove such compounds (Cizmas *et al*., 2015).

1.2 Problem Statement

There is no study to be found about occurrence of PPCPs in Malaysia waters focused on mussel. Occurrence of PPCP study in mussels can be considered essential for assessment of potential risk due to consumption of contaminated seafood with

PPCPs. This study is focused on bioaccumulation of pharmaceutical compounds in organisms because some pharmaceutical compounds have properties to accumulate in the organism and it can be magnified through upper trophic level in the food chain. Although some of the compounds have short half-life and some aquatic organisms are able to disintegrate and metabolize the compounds, concentration of the compound increases when predators eat the prey. This problem needs to be of concern because the last consumer of most aquatic organism is human. As it passed to human, the toxicity of the compound also transferred and human may experience acute health problems as result of consuming aquatic organisms. Pollutants such as heavy metals and persistent organic pollutants were widely study for bioaccumulation in aquatic organism, specifically in mussels. PPCPs information are still less discovered and scarce in Malaysia. Most of the studies regarding bioaccumulation of pharmaceutical compound are focused on wastewater effluents, surface water and sediments. Study of bioaccumulation toward mussels are less studied because it cannot be conducted on site. The gap in the study for Malaysia regarding occurrence toward mussel need to be filled as cumulative information and a better understanding of toxicology study.

As observed from common method for mussel farming practices, it is noted that mussels were attached on a rope and placed vertically in water column. PPCPs were known to have settlement and detection on near-sediment depth. This raises a question; what are PPCPs can be found on the surface and at bottom depth? Can depth influence occurrence of compounds in surface water and mussel?

Next, due to less study on bioaccumulation of pharmaceutical compound toward fish or invertebrate, the study in Malaysia and toxicology can act as preliminary study of toxicology bioaccumulation in organism. The new understanding of bioaccumulation in mussels on targeted species help to answer questions regarding bioaccumulation in mussels, for example, what are pharmaceutical compound can be accumulated in studied mussels? What is the distribution of the compound in the studied site? How can a compound be considered bioaccumulated in mussels?

Malaysia water experienced high and low tide cycle as natural phenomenon. PPCPs occurrence in surface water during these tidal differences surely give impact on PPCPs detection, as evidenced by some literature reporting low detection during high tides due to current and mixing processes causing dilution between freshwater with estuary that contains PPCPs and other contaminants. However, there still uncertainty of relationship PPCPs occurrence in mussel as affected by tidal difference. Difference in tidal may or may not give impact toward PPCPs detection in surface water and mussel, hence this issue should be focused and address the study.

1.3 Objectives of the Study

There are three objectives of the study need to answer the problem statement, which are:

1- To qualitatively analyse PPCPs found in mussel and water surrounding mussel farm.

2- To examine tidal effect towards PPCPs occurrence in mussel and surface water.

3- To evaluate the effect of depth on the presence of PPCPs in mussel and surface water

1.4 Scope of the Study

The scope of the study has been selected to ensure the objectives are able to be obtained. The chosen sample collection site is estuarine where commercial aquaculture activities are conducted. This sampling sites also received effluent discharge from six wastewater treatment plants.

This study focused on Green mussel (*Perna viridis*) as an aquatic organism for determining PPCPs occurrence. Filter feeding behaviour by Green mussel causing PPCPs compounds bioaccumulated into mussel. *P. viridis* were highly commercialised seafood consumed locally in Malaysia and exported globally, giving the organism plus point for sample selection. Surface water surrounding mussel farm were also collected to determine the PPCPs presence because whatever compounds detected in surface water, there will be possibilities the compounds would be detected in mussel too. Samples collection was collected during low and high tides at various depth for study regarding occurrence between tidal and depth difference.

Extraction of PPCPs from samples was conducted using solid phase extraction because the method offered the best approach to extract pollutant from environment besides it costly effective and practical. This extraction method was adopted from Method 1694: Pharmaceuticals and Personal Care Products in Water, Soil, Sediment and Biosolids by United State of America Environmental Protection Agency. The method that used in the study use chromatography and mass spectrum (MS) signal which help for analysis and identification of compounds.

However, the study faced number of limitations such compounds extraction methods. PPCPs has multiples functional and active groups attached on the molecules which cause molecules only reacted and spiked for either acid or base fraction. Second, avoiding thermolysis in PPCPs compounds are quite challenging especially during compounds data analysis specifically using liquid chromatography.

Although different compounds have different mass value, it is difficult to determine for which compounds has which mass in mass spectrum signal because mass-to-charge value sometimes overlaps in MS signal. This create uncertainty for determining and identifying individual compound. As tidal and depth difference included as parameter in the study, samples collection needed to be done on exact time where the lowest low tide and highest high tide occurred. Regarding depth through water column, mussel occurrence on the rope not exactly attached on the same rope for next sampling conducted. For example, during first sampling, there mussel collected on the rope, while on the next sampling, no mussel attached on the same rope. Mussel on the adjacent rope were collected for the study. Lastly, one of biggest limitation in the study was this is the first ever study regarding detection of PPCPs on aquatic organism in Malaysia. There were little amount of literatures reporting experimental study but none Malaysian literatures could be referred to consider parameters that may influence the findings such as the estuary where the mussel collected, tidal cycle and depth difference.

1.5 Significance of Study

The study will make a significant contribution toward PPCPs occurrence in Malaysian aquatic environment. This is due to lack of information on PPCPs contamination in the environment. Latest information regarding what type of PPCPs found in mussels will help to add better understanding of compounds detection especially regarding depth difference and tidal phenomenon.

Furthermore, the result obtained from the study may help responsible authority in law and regulation enforcement of PPCPs manufacture. This also give better insight and suggestion for which time and depth suit the best practice for mussel farming activity. By following which tidal and at which depth yields less

PPCPs detection during harvest can act as precautionary measures toward exposure to contaminants.

The study conducted also might help to increase food safety. Contaminated aquatic organism by pollutant represent unsafe and unhealthy seafood for consumption. Although the main focus here are human as the last consumer, along the way the contamination may spread to other organisms in trophic level because contamination occurred in ecosystem mostly via prey-predation relationship and absorption from surrounding environment.

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