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# PRIORITISATION OF ANTILIPIDEMIC IN SURFACE WATER OF MALAYSIA USING A RISK-BASED APPROACH

KAMSIA BUDIN[1,2]*, NUR ZAIDA ZAHARI[1,2], SURIANI HASSAN[3] AND ALYA AFIQAH SHAKAR[2]

*[1]Water Unit Research, Faculty of Natural Science and Resources, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia. [2]Environmental Science, Faculty of Natural Science and Resources, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia. [3]Mathematics with Economics, Faculty of Natural Science and Resources, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia.*

**Corresponding author: bkamsia@ums.edu.my*
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**Abstract**: Pharmaceutical is essential for modern human society, however when they are released into the environment, they may harm non-target organisms. This study investigates the potential of antilipidemic to exert biological effects on aquatic organisms by determining the risk of antilipidemic to algae, fish, and invertebrates. Predicted Environmental Concentrations (PECs) were determined from fractional excretion and emission from wastewater treatment of antilipidemic which was obtained from numerous trusted sources. The Risk Quotient (RQ) was defined from PEC/ PNEC (Predicted No Effect Concentration). The study shows that gemfibrozil has the highest PEC, followed by simvastatin, rosuvastatin, lovastatin, atorvastatin, pravastatin, fenofibrate, cholestyramine and ciprofibrate. However, based on the risk assessment, all the antilipidemic drugs obtained a value of RQ < 0.01 which indicates the antilipidemic has a significantly low risk towards aquatic organisms in Malaysia.

Keywords: Pharmaceutical, antilipidemic, Predicted Environmental Concentration (PEC), risk assessment, Risk Quotient (RQ).

## Introduction

According to a study in Malaysia by Wan Ahmad *et al*. (2011), cardiovascular disease is the leading cause of death in both men and women. The National Cardiovascular Database (NCVD) Registration of Acute Coronary Syndrome (ACS) shows that Malaysians with ACS at a younger age (58 years) than the population in Thailand (65 years), mainland China (63 years), and Western countries (GRACE Registry - 66 years, Canada - 68 years) (Wan Ahmad *et al*., 2011). At least 96% of 3,422 patients had at least one risk factor for cardiovascular diseases such as hypertension (72.6%), dyslipidaemia (55.9%) and diabetes (55.0%) (Wan Ahmad *et al*., 2011). The Malaysian National Health and Morbidity Survey 2006 shows dyslipidaemia is 28% in those aged 40 years and above (Wan Ahmad *et al*., 2011). The high prevalence of cardiovascular risk factors indicates the need for a primary prevention program.

In preventing cardiovascular disease, efforts must be aimed at reducing risk globally. Systematic reviews and large-scale randomised clinical trials have found that lowering cholesterol levels in someone at high risk for cardiovascular events can reduce the overall risk of death (Fauziah *et al.,* 2014). Antilipidemic agents remain a priority in the management of dyslipidaemia and cardiovascular event. These antilipidemic drugs are often classified into two groups of medicines. Among them are the statin and fibrate groups.

In general, statins work to inhibit reductase inhibitors, and at the same time, they also help in the process of cholesterol biosynthesis in the body (Isidori *et al.,* 2007). This drug is also the most effective method of reducing high plasma cholesterol levels. The fibrates work by stimulating the β-oxidation of fatty acids, mainly in peroxisomes and partly in mitochondria, lowering the levels of fatty acids and triacylglycerol in plasma (Pahan, 2007).

Currently, seven types of statin groups in the pharmaceutical industry are mainly used in Malaysia (MSOM, 2020). Among them are, lovastatin, simvastatin, pravastatin fluvastatin, atorvastatin, rosuvastatin and pravastatin. The discovery of several other fibrous drugs, such as ciprofibrate, bezafibrate, fenofibrate, and gemfibrozil, has revolutionised fat reduction research (Pahan, 2007). Yet, evidence shows that the antilipidemic has caused peroxisome proliferation, leading to hepatomegaly and tumour formation in the liver of rats (Vaziri & Liang, 2004; Sidharth & Naga, 2007). It has become a concern about the potential widespread of these drugs in the aquatic environment and their effect on aquatic organisms.

Antilipidemic drugs were found in natural waters due to high human consumption (Hernando *et al.,* 2007) and their persistence towards biological treatment plants (Fabbri & Franzelitti, 2016). The active ingredients or metabolites of the statin and fibrate medications are ingested and eliminated through the urine and faeces. Up to 70% of expelled chemicals are found in urine, whereas only 30% are found in faeces (Isidori *et al*., 2007). In addition to human excrement, additional resources include discarded drugs and related wastes from the manufacturing process (Boxall *et al*., 2012). Large quantities of pharmaceutical drugs that enter the wastewater of the treatment system are not eliminated during the treatment process (Kolpin *et al*., 2002; Isidori *et al*., 2007; Boxall *et al*., 2012; Fabbri & Franzelitti, 2016). They act as persistent pollutants despite some having high degradation rates because, unlike many other pollutants, they directly affect the biological activity of bacteria and, in most cases, continue to be released into the environment. (Costanza *et al.*, 2005). Once released into the environment, more questions arise about its effect on non-target organisms, especially in the aquatic environment. Toxicity tests of antilipidemic on several fish species showed reproduction declining, growth inhibition, decreased testosterone, morphology abnormalities and induced peroxisome germination (Mimeault *et al*., 2005; Fent *et al*., 2005; Santos *et al*., 2016).

In general, research related to antilipidemic compounds in the aquatic system of Malaysia is very limited. The concerns of these substances must be investigated as new antilipidemic medication classes are introduced. A systematic approach must be taken to monitor the presence of these substances in the water. In addition, wastewater treatment plants in Malaysia were not designed to eliminate emerging contaminants. It would be costly and impractical to investigate them all. Thus, a practical, relevant, cost-effective, and less time-consuming alternative approach is needed. This study is essential in providing the base knowledge on the most concern of antilipidemic compounds in the surface water of Malaysia.

There are two (2) objectives in this research: To identify the Predicted Environmental Concentration (PEC) of antilipidemic compounds on the surface water of Malaysia and to rank the most concerned antilipidemic from the lowest to the highest risk on aquatic organisms in surface water of Malaysia.

## Materials and Method

The study location is in Malaysia, a developing country in Southeast Asia, consisting of West Malaysia in the Peninsula and East Malaysia on Borneo Island. Due to difficulties obtaining data from recent years, 2015 and 2016 were chosen as the reference points. The annual consumption of antilipidemic was calculated based on Al-Qaim *et al*. (2018). Data for excretion fraction unchanged ($F_{excreta}$) for each antilipidemic compound were obtained from peer-reviewed literature and online databases. As there are no data on the efficiency of wastewater treatment (WWTP) systems in Malaysia for each antilipidemic, published studies from other nations were chosen as the references for the effectiveness of the standard WWTP system.

The PEC values for the antilipidemic in surface water estimated in this study were calculated using Equation 1 (Besse *et al*., 2008; Guo *et al*., 2015).

$$\text{PEC (mg L}^{-1}) = \frac{\text{Consumption (mg)} \times F_{excreta} \times F_{stp}}{\text{Winhab (l/inh/day)} \times \text{hab} \times \text{dilution} \times 365} \quad (1)$$

where,

Consumption = The annual usage data of antilipidemic compounds (mg)

$F_{excreta}$ = The excretion fraction unchanged of the compound

$F_{stp}$ = Calculated as 1-WWTP removal efficiency

Winhab = The volume of wastewater per person per day (litre/inh/day)

hab = The number population

dilution = The dilution factor from WWTP effluent to surface waters

(default value set to 10) (Besse, 2008)

A Risk Quotient (RQ) was used to rank the antilipidemic compounds. The risk quotient is the ratio PEC/PNEC used to evaluate the risk towards aquatic organisms, which has been explained in (Sanchez-Bayo *et al*., 2002; Hernando *et al*., 2006). PNEC is the predicted no-effect concentration obtained from peer-reviewed literature and online databases. Table 1 shows the details of the risk quotient. A risk quotient larger than one (RQ ≥ 1) indicates that environmental risk characterisation and the management of pharmaceuticals are required.

## Results and Discussion

According to the statistical data on antilipidemic drugs from the Ministry of Health Malaysia (MSOM, 2016), ten antilipidemic drugs have been listed as essential for cardiovascular disease treatment. The annual consumption of these ten antilipidemic drugs in Malaysia in 2015 and 2016 is shown in Table 2.

As shown in Table 2, simvastatin, lovastatin, pravastatin, fluvastatin, gemfibrozil, and fenofibrate usage in 2016 slightly decreased compared to 2015. On the other

Table 1: Risk Quotient (RQ)

| Risk Quotient (RQ) | Risk |
|---|---|
| RQ ≥ 1 | High risk |
| 0.1 ≤ RQ < 1 | Medium risk |
| 0.01 ≤ RQ < 0.1 | Low risk |
| RQ < 0.01 | Insignificant risk |

Table 2: Total annual consumption of antilipidemic drugs in Malaysia in 2015 and 2016

| Antilipidemic | Annual Usage (kg) | |
|---|---|---|
| | 2015 | 2016 |
| Simvastatin | 8147.772 | 7738.339 |
| Gemfibrozil | 5113.668 | 4061.246 |
| Fenofibrate | 1610.926 | 1609.457 |
| Atorvastatin | 1581.224 | 2243.057 |
| Rosuvastatin | 216.008 | 243.154 |
| Lovastatin | 113.766 | 98.329 |
| Pravastatin | 39.630 | 34.191 |
| Ciprofibrate | 17.424 | 18.860 |
| Cholestyramine | 15.493 | 32.397 |
| Fluvastatin | 10.392 | 7.845 |

hand, atorvastatin, rosuvastatin, ciprofibrate, and cholestyramine have increased in a year. Although rosuvastatin and lovastatin have the highest $F_{excreta}$ among the antilipidemic, gemfibrozil still calculated with the highest PEC in 2015 and 2016, as shown in Table 3.

Figure 1 illustrates that the PEC values of all antilipidemic drugs decreased from 2015 to 2016, except for rosuvastatin and atorvastatin. The PEC value of gemfibrozil was the highest (2.215 $ngL^{-1}$ for 2015 and 2.171 $ngL^{-1}$ for 2016, followed by simvastatin, rosuvastatin, lovastatin, pravastatin, fenofibrate, fluvastatin, cholestyramine and ciprofibrate. All the PEC values were very low, predicted at a nanogram per litre level.

The antilipidemic concentration in rivers from other countries (Table 4) shows that the

Table 3: The $F_{excreta}$, $F_{stp}$, PEC 2015 and PEC 2016 for the antilipidemic

| Antilipidemic | $F_{excreta}$ | $F_{stp}$ | PEC 2015 | PEC 2016 |
|---|---|---|---|---|
| | | | ($ngL^{-1}$) | ($ngL^{-1}$) |
| Simvastatin | 0.01 | 0.89 | 2.215 | 2.171 |
| Gemfibrozil | 0.7 | 0.42 | 45.920 | 36.469 |
| Fenofibrate | 0.01 | 0.11 | 0.054 | 0.054 |
| Atorvastatin | 0.01 | 0.76 | 0.367 | 0.521 |
| Rosuvastatin | 0.90 | 0.31 | 1.481 | 2.072 |
| Lovastatin | 0.93 | 0.53 | 1.713 | 1.480 |
| Pravastatin | 0.50 | 0.35 | 0.212 | 0.183 |
| Ciprofibrate | 0.70 | 0.00 | *nc | *nc |
| Cholestyramine | 0.01 | 0.50 | 0.002 | 0.006 |
| Fluvastatin | 0.05 | 0.52 | 0.001 | 0.050 |

*nc – non-conclusive

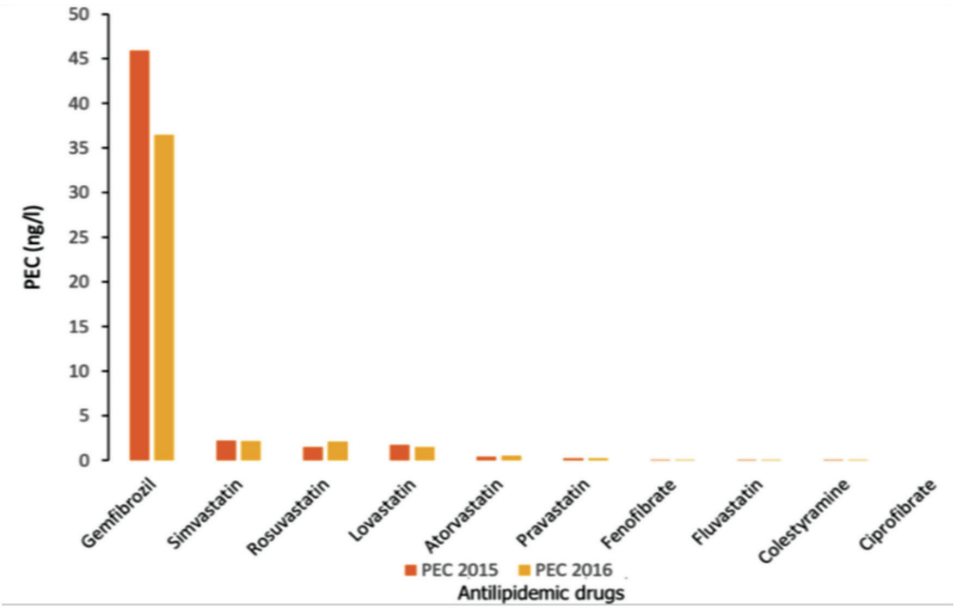



Figure 1: PEC values of the antilipidemic in the years 2015 and 2016

Table 4: Previous Studies on the concentration of antilipidemic in rivers

| Antilipidemic | Measurement Environmental Concentration ($ngL^{-1}$) | References |
|---|---|---|
| Simvastatin | 109 ± 5.25 | Tete *et al*. (2020) |
| Gemfibrozil | 1.53 | Ido *et al*. (2017) |
| | 96 ± 4.80 | Tete *et al*. (2020) |
| | 790 | Kolpin *et al*. (2002) Giebultowicz *et al*. (2016) |
| | 0.9 | |
| Fenofibrate | 106 ± 5.3 | Ido *et al*. (2017) |
| | 3.0 | Giebultowicz *et al*. (2016) |
| Atorvastatin | 102 ± 5.1 | Tete *et al*. (2020) |
| | 1 – 59.1 | Lee *et al*. (2009) |
| | 114 | Giebultowicz *et al*. (2016) |
| Rosuvastatin | 2.1 – 74.9 | Lee *et al*. (2009) |
| Lovastatin | 100 ± 5.00 | Tete *et al*. (2020) |
| Pravastatin | 101 ± 5.05 | Tete *et al*. (2020) |
| Ciprofibrate | 60 | Giebultowicz *et al*. (2016) |
| Cholestyramine | *nr | *nr |
| Fluvastatin | 90 ± 4.50 | Tete *et al*. (2020) |

*nc – non-conclusive

PEC values predicted in this study were not too different from the concentration measured in the field. This signifies that the PEC predicted in this study reflected the real concentration in an aquatic environment supported by Roos *et al*. (2012) and Burns *et al*. (2018). The PECs used in the risk prioritisation provided meaningful and better outcomes than those based on the usage data only. Data on the amount of drug consumption and sales only do not provide meaningful information regarding the environmental fate and the potential toxicity of the APIs to aquatic organisms. According to Roos *et al*. (2012), a holistic risk-based prioritisation scheme must involve the estimations of both exposure and effects on its assessment. The risk quotient (RQ) used in this study is a risk-based ranking method used to characterise the potential risk of antilipidemic drugs to the environment. It incorporated usage data, degradation, bioconcentration ability, sewage treatment removal efficiency and the API highest concentration where no effect was observed. The ratio between PEC and PNEC implies the possibility that the concentration absorbed in the organisms will affect the organism's well-being (Gros *et al*., 2010).

The PNEC value of the antilipidemic for aquatic organisms in the three trophic levels, algae, invertebrates and fish were recorded at the level of $mgL^{-1}$ (Table 5) which is more than 100,000 times higher than the PEC values (ng $L^{-1}$) predicted in this study. The PEC value for 2015 and 2016 was estimated at ng $L^{-1}$ and all PNEC values were at the mg $L^{-1}$. As a result, for both years, the RQ value for all examined antilipidemic cases was less than 0.01. The estimated value at ng $L^{-1}$ is very low compared to the highest level of concentration value (mg $L^{-1}$) which does not have any effect on the aquatic organisms (Hernando *et al*., 2007; Roos *et al*., 2012). This indicates that fish, algae, and macroinvertebrates were not significantly in danger from antilipidemic in Malaysian surface water.

Table 5: PNEC value for the antilipidemic

| Antilipidemic | Algae | | Invertebrate | | |
|---|---|---|---|---|---|
| | PNEC (mg $L^{-1}$) | References | PNEC (mg $L^{-1}$) | References | PNEC (mg $L^{-1}$) |
| Gemfibrozil | 195 | Santos *et al*. (2010) | 57.1 | Santos *et al*. (2010) | 77.3 |
| Simvastatin | 22.8 | Santos *et al*. (2010) | 1.18 | Santos *et al*. (2010) | 0.81 |
| Rosuvastatin | 330 | Astrazeneca (2017) | 0.0018 | Astrazeneca (2017) | nr |
| Lovastatin | 0.064 | Khetan and Collins (2007) | *nr | - | 0.13 |
| Atorvastatin | 0.036 | Khetan and Collins (2007) | *nr | - | 0.086 |
| Pravastatin | *nr | - | 0.10 | Isidori *et al*. (2007) | *nr |
| Fenofibrate | 1.34 | Santos *et al*. (2010) | 64.97 | Santos *et al*. (2010) | 3.25 |
| Fluvastatin | 1.35 | Tete *et al*. (2020) | 5.27 | Hernando *et al*. (2007) | 0.0014 |
| Cholestyramine | *nr | - | *nr | - | *nr |
| Ciprofibrate | *nr | - | 100 | Isidori *et al*. (2007) | *nr |

*nr – no record

## Conclusion

This study presents a preliminary scenario on the possibilities of antilipidemic effects on the environment. By computing the fractional excretion, fractional emission, and consumption data, the data given in this research study were described as the ubiquitous PEC of antilipidemic compounds in the surface water of Malaysia. Although the gemfibrozil PEC was the highest, it was still lower than the concentration detected in surface water worldwide. Based on the RQ value, the concentration predicted in this study for all antilipidemics probably does not affect the non-target organisms. Therefore, a conclusion achieved is that the antilipidemic was not of the utmost concern in terms of its effect on the aquatic environment of Malaysia. There are still several medications whose possible impact on creatures other than the target population needs to be considered. Additional data needed to be included, such as the efficiency of Malaysia WWTP and over-the-counter drugs. Most recent data would also be more useful as it is comparable to the current situation.

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## References

Al-Qaim, F. F., Mussa, Z. H., Yuzir, A., Abu Tahrim, N., Hashim N., & Azman, S. (2018). Transportation of different therapeutic classes of pharmaceuticals to the surface water, sewage treatment plant, and hospital samples, Malaysia. *Water*, *10* (7), 916.

Alves, N., Neuparth, T., Barros, S., & Santos, M. M. (2021). The anti-lipidemic drug simvastatin modifies epigenetic biomarkers in the amphipod Gammarus locusta. *Ecotoxicology and Environmental Safety*, *209*, 111849.

AstraZeneca. (2017). Environmental Risk Assessment Data Rosuvastatin. Retrieved from https:// www.astrazeneca.com/content/dam/az/our-company/Sustainability/2017/Rosuvastatin.pdf

Besse J-P., Kausch-Barreto, C., & Garric. J. (2008) Exposure assessment of pharmaceuticals and their metabolites in the aquatic environment: application to the french situation and preliminary prioritization. *Human Ecological Risk Assessment*, *14*, 665-695.

Boxall, A. B. A., Rudd, M. A., Brooks, B. W., Caldwell, D. J., Choi, K., Hickmann, S., Innes, E., Ostapyk, K., Staveley, J. P., Verslycke, T., Ankley, G. T., Beazley, K. F., Belanger, S. E., Berninger, J. P., Carriquiriborde, P., Coors, A., Deleo, P. C., Dyer, S. D., Ericson, J. F., Gagné, F., Giesy, J. P., Gouin, T., Hallstrom, L., Karlsson, M. V., Larsson, D. G. J., Lazorchak, J. M., Mastrocco, F., McLaughlin, A., McMaster, M. E., Meyerhoff, R. D., Moore, R., Parrott, J. L., Snape, J. R., Murray-Smith, R., Servos, M. R., Sibley, P. K., Straub, J. R., Szabo, N. D., Topp, E., Tetreault, G. T., Trudeau, V. L., & Kraak, G. V. D. (2012). Pharmaceuticals and personal care products in the environment: What are the big questions? *Environmental Health Perspectives*, *120*(9), 1221 - 1229.

Burns, E. E., Carter, L. J., Snape, J., Thomas-Oates, J., & Boxall, A. B. A. (2018). Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals. *Journal of Toxicology and Environmental Health - Part B: Critical Reviews*, *21*(3), 115-141.

Chiew Fong, M. C., & Azzy Iyzati, A. S. (2020). *Malaysian Statistics on Medicines (MSOM). 2015-2016*. Pharmaceutical Services Programme, Ministry of Health Malaysia. Retrieved https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/malaysian-statistics-medicines-2015-2016.pdf

Costanza, S. D., Murby, J., & Bates, J. (2005). Ecosystem response to antibiotics entering the aquatic environment. *Marine Pollution Bulletin*, *51*, 218-223.

Fabbri, E., & Franzellitti, S. (2016). Human pharmaceuticals in the marine environment: Focus on exposure and biological effects in animal species. *Environmental Toxicology and Chemistry*, *35*(4), 799-812.

Fauziah, A. S., Kamarudin, A., & Aklima, N. O. N. N. (2014). *Malaysian statistics on medicines 2009 & 2010. Ministry of Health Malaysia*. Pharmaceutical Services and Clinical Research Centre Ministry of Health, 1-206. https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/malaysian-statistics-medicines-2009-2010.pdf

Fent, K., Weston, A. A., & Caminada, D. (2005). Ecotoxicology of human pharmaceuticals. *Aquatic Toxicology*, *76*(2), 122-159.

Giebułtowicz, J., Stankiewicz, A., Wroczyński, P., & Nalecz-Jawecki, G. (2016). Occurrence of cardiovascular drugs in the sewage-impacted Vistula River and tap water in the Warsaw region (Poland). *Environmental Science and Pollution Research*, *23***,** 24337-24349.

Gros, M., Petrovic, M., Ginebreda A., & Barcelo, D. (2010) Removal of pharmaceuticals during wastewater treatment and environmental risk assessment using hazard indexes. *Environment International*, *36*(1), 15-26.

Guo, J., Boxall, A. B. A., & Selby, K. (2015). Do pharmaceuticals pose a threat to primary producers? *Critical Reviews in Environmental Science and Technology*, *45*(23), 2565-2610.

Hernando, M. D., Aqüera, A., & Fernandez-Alba, A. R. (2007). LC-MS analysis and environmental risk of lipid regulators. *Analytical and Bioanalytical Chemistry*, *387* (4), 1269 - 1285.

Hernando, M. D., Mezcua, M., Fernández-Alba A. R., & Barceló, D. (2006). Environmental risk assessment of pharmaceutical residues

in wastewater effluents, surface waters, and sediments *Talanta*, *69*(2), 334 - 342.

Ido, A., Hiromori, Y., Meng, L., Usuda, H., Nagase, H., Yang, M., Hu J., & Nakanishi, T. (2017). Occurrence of fibrates and their metabolites in the source and drinking water of Shanghai and Zhejiang, China. *Scientific Reports*, *7*(1), 45931. https://doi.org/10.1038/srep45931

Isidori, M., Nardelli, A., Pascarella, L., Rubino M., & Parrella, A. (2007). Toxic and genotoxic impact of fibrates and their photoproducts on non-target organisms. *Environment International*, *33*(5), 635 - 641.

Khetan, S. K., & Collins J. T. (2007). Human pharmaceuticals in the aquatic environment: A challenge to Green Chemistry. *Chemical Reviews*, *107*(6), 2319- 2364.

Kolpin, D., Furlong, E., Meyer, M., Thurman, E., Zaugg, S., Barber, L. B., & Buxton, H. T. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. *Environmental Science & Technology*. *36*, 1202-1211.

Lee, H. B., Peart, T. E., Svoboda M. L. & Backus, S. (2009). *Chemosphere*, *77*(10), 1285-1291.

Mimeault, C., Woodhouse, A. J., Miao, X. S., Metcalfe, C. D., Moon T. W., & Trudeau V. L. (2005). The human lipid regulator, gemfibrozil bio concentrates, and reduces testosterone in the goldfish*, Carassius auratus*. *Aquatic Toxicology*, *73*(1), 44-54.

Pahan, K. (2007). Lipid-lowering drugs. *Cell Molecule and Life Science*, *63*(10), 1165-1178.

Roos, V., Gunnarsson, L., Fick, J., Larsson, D. G. J. & Rudén, C. (2012). Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first tier selection. *Science of the Total Environment*, *421-422*, 102-110.

Sanchez-Bayo, F., Baskaran, S., & Kennedy, I. R. (2002). Ecological Relative Risk (EcoRR): another approach for risk assessment of pesticide in agriculture. *Agriculture, Ecosystem & Environment*, *91*(13), 37 - 57.

Santos, L. H. M. L. M., Araújo, A. N., Fachini, A., Pena, A., Delerue-Matos, C., & Montenegro, M. C. B. (2010). Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment. *Journal of Hazardous Materials*, *175*(1-3), 45-95.

Santos, M. M., Ruivo, R., Lopes-Marques, M., Carmen, T. B. T., Castro, L. F. C., & Neuparth, T. (2016). Statins: An undesirable class of aquatic contaminants? *Aquatic Toxicology*, 174, 1-9. https://doi.org/10.1016/j.aquatox.2016.02.001

Sidharth, S. B., & Naga, C. (2007). Lipid-lowering agents that cause drug-induced hepatotoxicity. *Clinics in Liver Disease*, *11*(3), 597 - 613.

Tete, V. S., Nyoni, H., Mamba, B. B., & Msagati, T. A. M.(2020). Occurrence and spatial distribution of statins, fibrates, and their metabolites in aquatic environments. *Arabian Journal of Chemistry*, *13*(2), 4358 - 4373.

Vaziri, N. D., & Liang, K. (2004). Effects of HMG-CoA reductase inhibition on hepatic expression of key cholesterol-regulatory enzymes and receptors in nephrotic syndrome. *American Journal of Nephrology*, *24*, 606 - 613.

Wan Ahmad, W. A., Zambahari, R., Ismail. O., Sinnadurai, J., Rosman, A., Piaw, C. S., Abidin I. Z., & S. Kui Hian. (2011). Malaysian National Cardiovascular Disease Database (NCVD) - Acute Coronary Syndrome (ACS) registry: How are we different? *Global Heart, 6*(3), 81-89.