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Ecotoxicological impacts of pharmaceuticals on marine biota: A Systematic Review

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Abstract Pharmaceuticals are a wide class of chemicals used for human and veterinary purposes. As many other anthropogenic organic substances, they can be introduced into various aquatic ecosystems including marine and coastal waters via accidental incidents or spatial sources. Consequently, a variety of potential toxic effects on marine inhabitants that are inevitably exposed to those chemicals are provoked. The present study is a systematic review of the scientific literature that has been published up to 31/12/2022 regarding the scientific research which has been conducted and concerns the evaluation of potential toxic effects of pharmaceuticals on marine biota that belong to several different levels of the food chain. Based on the gathered information from the collected and classified articles, useful conclusions, and observations are reported about research trends. At the same time, knowledge gaps and weaknesses in the current research are identified and highlighted. Furthermore, suggestions for future research on this topic are also reported.

Keywords: Pharmaceuticals, Marine ecosystems, Environmental effects, Toxicity, Marine biota

1. Introduction

Among the multiple parameters that can act as stressors on marine ecosystems such as climate change, over-fishing and eutrophication phenomena, the release of pharmaceuticals into coastal ecosystem is also included. Pharmaceuticals, which are also known by the terms drugs or medicines, are chemical compounds that are used world widely for humans and animals to diagnose, cure, relieve symptoms, delay the outbreak or the progression of a disease, and prevent unwanted complications for patients.

Unfortunately, these compounds can be released in seawater and marine sediments in residual concentrations via effluent discharges, mainly due to their incomplete removal by wastewater treatment plants, where pharmaceutical compounds end up after use.

According to the related published scientific data pharmaceutical residues of various synthetic compounds that belong to different groups of drugs (such as antibiotics, antiepileptics, anti-inflammatories, antiseptics, anticonvulsants, steroids, anti-inflammatories, etc.) have been detected in coastal and offshore seawater samples world widely in the range of ng/L to μg/L level concentrations [Fabbri and Franzellitti 2016]. For instance, diclofenac is a pharmaceutical substance that has been detected in seawater samples up to a concentration level of 15 μg/L [Almeida et al., 2020 after Mezzelani et al., 2018]. The same steroid anti-inflammatory medicine, diclofenac, has been identified and measured in the Mediterranean region at concentration levels of 1500 ng/L [Mezzelani et al., 2018 after Togola & Budzinski, 2008] and in the Indian Ocean at concentrations varying into the range 4–38 ng/L [Mezzelani et al., 2018 after Wu et al., 2010]. Moreover, diclofenac has also been detected at higher levels along the North Atlantic coast and in the North Pacific Ocean, reaching 460 ng/L [Bonnefille et al., 2018 after McEneff et al., 2014] and 843 ng/L [Bonnefille et al., 2018 after Yang et al., 2011] respectively, as well as in points adjacent to wastewater discharges. The pharmaceutical compound ibuprofen has also been determined in seawater up to 2 μg/L [Almeida et al., 2020 after Mezzelani et al., 2018]. In addition, the non-steroidal anti-inflammatory drug ketoprofen has been detected in the Mediterranean area up to 6,000 ng/L as well as another drug belonging to the antidepressant class, amitriptyline, in concentrations ranging from 23 to 200,000 ng/L [Mezzelani et al., 2018 after Gros et al., 2012; Togola & Budzinski, 2008].

The induced consequences of pharmaceuticals inputs in coastal areas were recognized as an environmental pollution issue in recent years when an increase in the human population in coastal zones occurred that implied higher anthropogenic pressure and interference in these zones resulting in the influx of many synthetic pollutants from the coastal zone into the marine environment.

Consequently, marine organisms can be exposed to pharmaceuticals over widespread geographical areas [Gaw et al., 2014]. Regardless the dilution of pharmaceuticals into the seawater that is assumed as a safety factor, the occurrence of those chemicals in marine ecosystems can cause a variety of triggered biological impacts on marine biota exposed to those pollutants.

This paper reviews the scientific published data that has been published up to 31/12/2022 regarding the impacts of pharmaceuticals in marine and coastal environments. Based on the gathered information from the collected and classified articles, useful conclusions and observations are reported about research trends. At the same time, knowledge gaps and weaknesses in the current research are

identified and highlighted. Furthermore, suggestions for future research on this topic are also reported.

2. Methods and materials

The present systemic approach was conducted after the identification of the relevant published scientific articles by using Scopus Search (abstract and citation database). The current search was focused only on peer-reviewed journal articles that were published up to 31 December 2022. The selection of studies was made by using the combination of terms/keywords summarized in **Table 1**.

Table 1. Combination of terms and keywords used for the collection of relevant data in Scopus Database

Combination of terms/keywords	Number of found documents
"Pharmaceuticals" AND "Marine" AND "Toxicity"	478
"Pharmaceuticals" AND "Marine" AND "Ecotoxicity"	90
"Pharmaceuticals" AND "Marine" AND "Impacts"	367
"Pharmaceuticals" AND "Marine" AND "Effects"	1228
"Pharmaceuticals" AND "Marine" AND "Stress"	258
"Pharmaceuticals" AND "Marine" AND "Response"	403
TOTAL	**2,824**

As illustrated in **Table 1**, the search provided a total of 2,824 published articles. Only original research documents which were available in English were included in this analysis, whereas reviews and critical analysis studies were rejected. After the elimination of duplicates, and triplicates (to have unique entries/articles) and the rejection of irrelevant documents 175 unique entries remained in the final database of current systemic review.

Further study of 175 finally approved bibliographic documents was conducted to specify the reported research data regarging the following information: (i) pharamaceutical substances involved in the conducted bioassays, (ii) concentration levels tested of target analytes, (iii) marine organisms exposed, (iv) type of toxicity control test conducted, (v) observed effects (endpoints), and (vi) values of characteristic toxicity parameter (LC50, LD50, EC50, IC50, NOEC, LOEC, etc.).

3. Results and conclusions

Overall, 175 selected scientific articles that met the criteria of the current bibliographic research were included in the present systemic review and provided relevant information for assessing the potential toxic impacts of pharmaceuticals on exposed marine organisms. Based on the number of gathered information it becomes obvious that there has been a significant scientific interest and therefore relevant progress in research to investigate exposures and evaluate potential hazards of pharmaceuticals in marine and coastal ecosystems.

According to the findings of the current review (**Figure 1**) the first scientific document concerning the evaluation of the toxic impacts of pharmaceuticals in the marine environment was published in 1983 by Lee et al. who studied the chronic toxicity of ocean-dumped pharmaceutical wastes to the marine amphipod *Amphithoe valida*. Nevertheless, the next scientific publication appeared after 22 years (more specifically, in year 2005). It is also evident that during the period from 2005 to 2022 there have been various fluctuations in the number of published scientific publications. As depicted in **Figure 1**, most published articles were observed from 2015 onwards, with most publications occurring in the years 2016 and 2018 (23 published papers in each year). The peak of published articles dates to the last reporting year of this paper, in 2022 when the annual number of bibliographic documents reached 25 reports.

According to the obtained scientific data that have been published up to 31/12/2022 a total of 76 pharmaceutical substances (either individually or in mixtures) have been tested on 92 species of marine organisms (excluding periphyton) were collected and reviewed. The results obtained after the classification of all the bibliographic findings according to the following criteria are presented: (1) date of publication of the bibliographic finding, (2) taxonomic classification of the marine organism exposed to the medicinal substance, (3) pharmaceutical substance, and finally (4) type of observed toxic effect.

Based on the collected data shown in **Figure 2** it becomes evident that the majority of publications gathered and reviewed from the relevant scientific literature concerned toxicity studies that have been conducted on organisms that belong to the marine phylum Mollusca (~45% of 175 articles). More specific, several different species of the taxonomic classes Bivalvia, Gastropoda and Cephalopoda (representing ~87%, ~11% and ~2% of reviewed data gathered for Mollusca, correspondingly), have been exposed to a variety of pharmaceuticals, whereas the mussel *Mytilus galloprovincialis* is the species that has been investigated to the greatest extent of all. For example, published results regarding the toxicity of cetirizine (antihistamine) [Teixeira et al., 2017], paracetamol, acetaminophen (analgesics and antipyretics), diclofenac, ibuprofen, ketoprofen and nimesulide (non-steroidal anti-inflammatory drugs) [Mezzelani et al., 2016a, 2016b] among numerous others were reviewed. Mollusca phylum is followed by the phylum of Chordata (~13% of 175 articles), Annelida (~10% of 175 articles), and Arthropoda (~9% of 175 articles). It was also observed that among the various species of marine algae that have been used for bioassays, Ochrophyta is the phylum that has been studied the most of all (~ 7% of 175 articles), while Echinoderma phylum appears with a slightly smaller percentage of 6%. Next, Chlorophyta (~4.5% of 175 articles) were studied, followed by Proteobacteria (~2.5% of 175 articles).

Both bioconcentration and oxidative stress of the edible clam *Ruditapes philippinarum* after contamination by pharmaceutical drugs (antiepileptic carbamazepine and antihistamine cetirizine, individually and combined) under ocean acidification scenario were evaluated and revealed that regardless the pH value, drug combination had fewer

impacts than drugs acting alone [Almeida et al., 2022]. Finally, behavioral effects have been also observed in marine animals after exposure to pharmaceuticals. For example, Chabenat et al. (2021, 2017) apart from effects of selected antidepressants (fluoxetine and venlafaxine) on color change and locomotor behavior in juvenile shore crabs, *Carcinus maenas*, they reported effects on sand-digging behavior in juvenile shore crabs (*Carcinus maenas)* reported alterations of burying behavior in shore crabs *Carcinus maenas* and cuttlefish *Sepia officinalis* by antidepressant exposure as well (**Table 2**).

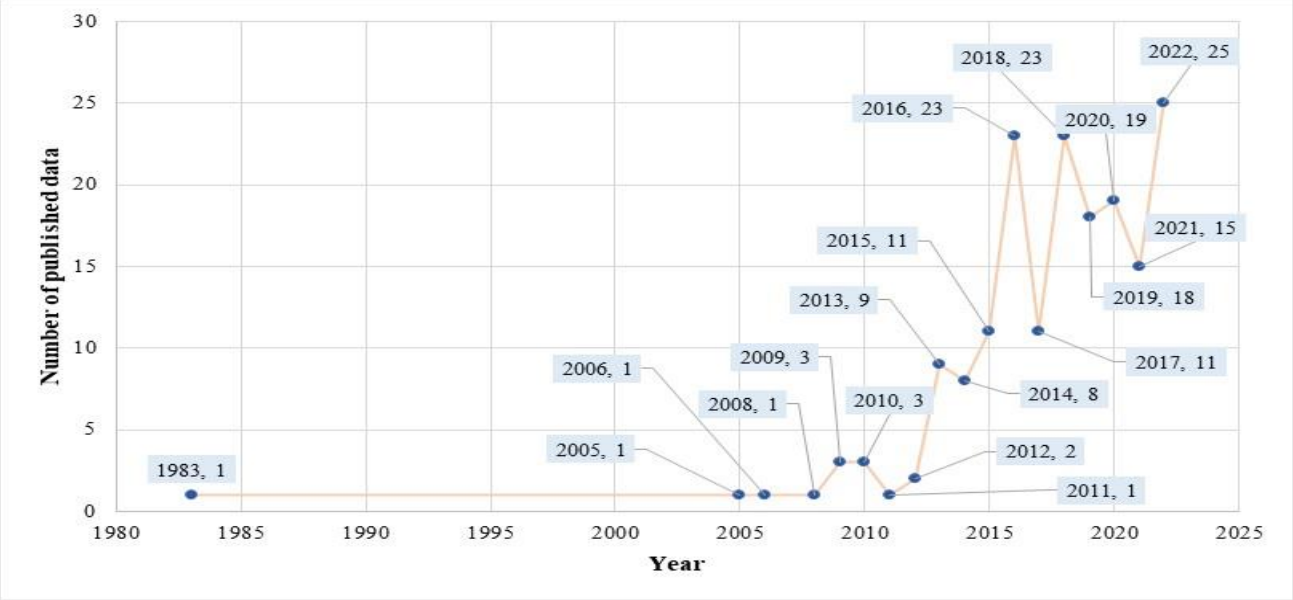

Figure 1. Number of published data vs year of publication

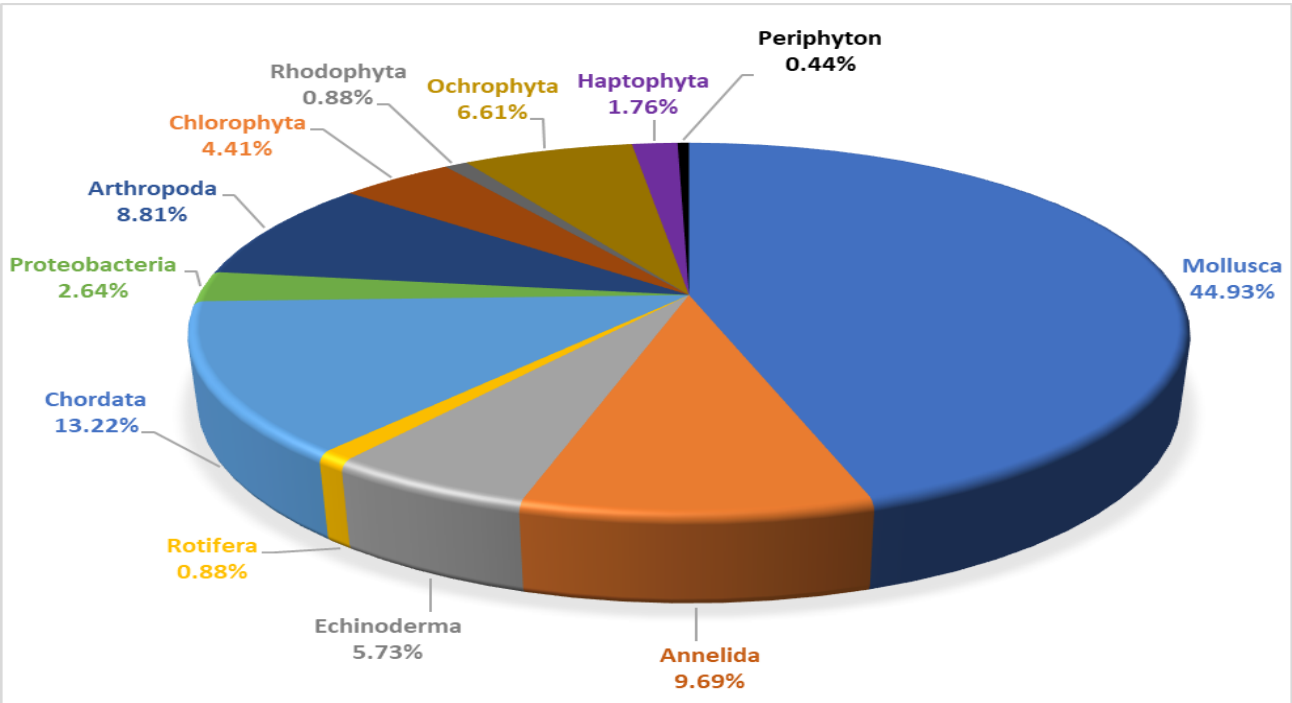

Figure 2. % Relative frequency of bioassays conducted for each individual taxonomic phylum of marine biota.

Table 2. Selected bibliographic data collected and reviewed regarding species of marine biota tested for ecotoxicological impacts of pharmaceuticals (Review of Scopus database up to 31/12/2022).

Tested species	Pharmaceutical (Concentration)	Major findings	Reference
Sparus aurata	Amitriptyline (0.2 μg/L)	Increased bioaccumulation in different tissues (brain, gills and liver) on day 7. Decrease in the activity of the antioxidant enzyme superoxide dismutase in the liver. Decrease in the stability of the lysosomal membrane in the liver. Increase in the activity of the cyclooxygenase enzyme in gills (fish responses to stress).	Blanco-Rayón et al., 2021
Carcinus maenas	Fluoxetine &	Color change of young crabs exposed to 5 ng/L fluoxetine. Juvenile crabs exposed to the combination of the 2 antidepressants were less	Chabenat et al., 2021

	Venlafaxine (5 ng/L FLX & mixture 5 ng/L FLX + 5 ng/L VEN)	effective in adapting their coloration to their environment. Juvenile crabs exposed to combined antidepressants showed increased locomotor activity. The organisms moved for a longer time and traveled a greater distance at a higher speed compared to control organisms or those exposed to fluoxetine alone.	
Paracentrotus lividus	Fluoxetine, Sulfamethoxazole, Ibuprofen: (range: 1 mg/L - 8,8 g/L	Sulfamethoxazole: EC_{10} (early larval growth, 48h) = 6134 µg/L Fluoxetine: EC_{10} (early larval growth, 48h) = 14 µg/L Ibuprofen: LOEC (early larval growth, 48h) = 10000 µg/L	Beiras, 2021

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