Chemical Ecology of the Benthic Dinoflagellate Genus *Ostreopsis*: Review of Progress and Future Directions

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The genus *Ostreopsis* includes some species that produce high biomass blooms and/or synthesize toxic compounds that can be transferred through the marine food webs or aerosolized causing ecological, human health and socio-economic impacts. *Ostreopsis* species are increasing their biogeographic distribution from tropical to more temperate waters and causing recurrent blooms in certain coastal areas, thus constituting an emerging concern worldwide. The proliferation capacity of *Ostreopsis* is due to a complex and poorly understood combination of multiple factors, and may be a paradigm of chemical ecology reviewed here. A first section summarizes the basic knowledge on the different *Ostreopsis* species, the toxins they produce and the described foodborne and airborne effects of *Ostreopsis* toxins on humans. Secondly, direct and indirect interactions between *Ostreopsis* species and their environment are reviewed. Mucopolysaccharide substances produced by the cells to attach to different substrates appear to be a key element on the chemical ecology and requires further study. However, this research is challenged by technical limitations to conduct ecologically realistic and harmonized studies where organisms can be in direct contact with *Ostreopsis* cells, their mucus and/or the released extracellular toxic compounds. Understanding the transfer mechanisms of these substances within the food web, potentially affecting humans is critical and requires further study with new analytical tools. Still, the progress in knowledge achieved in the last years, combined with experimental and field studies using cutting edge methods will facilitate to address the open questions on the chemical ecology of *Ostreopsis* and understand its bloom dynamics now, and under future climate and anthropogenic change scenarios.

Keywords: marine chemical ecology, *Ostreopsis* spp., HABs, ovatoxins, dinoflagellates

INTRODUCTION

Marine Chemical Ecology (MCE)

Marine Chemical Ecology (MCE) is a cross-disciplinary and emergent research field which gives insights into chemical compounds that shape interactions among organisms and their environment and thus influence the structure, functioning and ecology of marine communities (Hay, 1996; McClintock and Baker, 2001; Pohnert et al., 2007). Chemical signals and cues are omnipresent in marine systems and play critical roles at different scales, by e.g., affecting cells communication, mating choices and behavior, feeding and habitats selection, food web dynamics, etc.,
with subsequent effects on other ecosystem-level processes (Bakus et al., 1986; Pawlik, 1992; Hay, 1996, 2009; Sieg et al., 2011; Schwartz et al., 2016). In general, chemical cues and signals occur at low concentrations in water and in air and are rapidly degraded likely to prevent miscommunication. This feature makes their sampling, isolation and structural elucidation very difficult and has limited their research. Fortunately, recent improvements in chemical technologies with the rise of high-throughput approaches have led to major advances in the understanding of the role of these compounds, notably in benthic systems (Prince and Pohnert, 2010; Kuhlisch and Pohnert, 2015). The terms “chemical signals” and “chemical cues” refer to compounds released intentionally and not intentionally, respectively. In the following, “chemical signals” comprise both concepts for simplicity.

**MCE of Harmful Algal Blooms (HABs)**

Chemical communication is particularly important in the life history and evolutionary strategies of eukaryotic microalgae, which live at low Reynolds numbers scale, while larger marine macro-organisms are functionally dependent on optical, acoustical and tactile sensing (Cembella, 2003; Ianora et al., 2011; Sieg et al., 2011). Chemical signals synthesized at the small cell level are dispersed by molecular diffusion assisted by small-scale turbulence and thus can operate at relatively larger scales influencing trophic interactions and life history. By fostering intra- and interspecific cooperation, or as defense mechanisms against predators, parasites or competitors (Prince et al., 2008; Poulsen et al., 2009; Schwartz et al., 2016) chemical signals can play a role in the blooms of certain species. However, the information of chemical signals in the domain of HABs is very limited mainly due (as noticed above) to technical limitations. It has been suggested that allelopathy, i.e., the chemical inhibition of one organism by another due to the release into the environment of substances acting as growth inhibitors (Rizvi and Rizvi, 1992), could be an effective mechanism reinforcing high cell density blooms (Granéli and Hansen, 2006) although not the main or direct cause of HABs (Jonsson et al., 2009). Benthic marine ecosystems could be a source of great diversity of chemical signals since the competition for space and substrate is higher than in pelagic systems (Hay, 2009). Moreover, compared to the three-dimensional space experienced by planktonic cells, benthic systems are bi-dimensional, which imposes unique constraints with distinct advantages for the effectiveness of chemical ecological interactions. The importance of chemical signals is been progressively recognized as a key factor to understand the dynamics of the benthic HAB dynamics and requires complex and sophisticated experimentation and field sampling.

**Objectives of the Review**

Overall, 30% of the studies on *Ostreopsis* species focus on species identification and biogeography, 25% on toxins, 20% on the life cycle and physiology, and only 14% on ecological aspects including food web impacts, allelopathy, competition and links with the substrate. In other words, a small part of the research focuses directly on the chemical ecology of *Ostreopsis* species.

This work aims to review the present knowledge on the MCE concerning the biology and dynamics of blooms of the benthic dinoflagellate genus *Ostreopsis*. This genus has attracted scientific and social interest due to their negative impacts on certain benthic marine fauna, the production of toxins chemically close to the potent palytoxin (PLTX) associated to seldom but dramatic seafood borne poisonings in tropical areas, and the link of its blooms to mild respiratory and cutaneous irritations in beach users in temperate latitudes. The diversity, distribution and toxins produced by the *Ostreopsis* species are presented first, followed by a summary of the knowledge on the health impacts associated to aerosolized toxins. Next, a review of the potential chemical interactions between *Ostreopsis* species and their environment, from virus and bacteria to large herbivorous and carnivorous macroorganisms is presented. Overall, these aspects reveal the diverse and relevant aspects of the chemical ecology of *Ostreopsis*, which can constitute a model organism in this research field. The diverse produced toxins are considered until now, the main substance with a chemical ecology significance. However, very recent studies suggest that other compounds could be also at play. In the last section, some key scientific aspects and future steps to improve knowledge on MCE of *Ostreopsis* are suggested.

**THE GENUS *Ostreopsis***

**Species and Biogeographic Distribution**

The genus *Ostreopsis* and the type species *Ostreopsis siamensis* were first described a century ago from the Gulf of Siam (Thailand) by Schmidt (1901). Since then, 10 other species of *Ostreopsis* and 7 ribotypes have been identified (Tester et al., 2020): *O. ovata* (Fukuyo, 1981) *O. lenticularis* (Fukuyo, 1981) *O. heptagona* (Norris et al., 1985) *O. labens* (Faust and Morton, 1995) *O. mascarenensis* (Quod, 1994) *O. belizeanus*, *O. caribbeanus* and *O. marinus* (Faust, 1999) and more recently, *O. fattorussoi* (Accoroni et al., 2016a) and *O. rhodesae* (Verma et al., 2016). Traditionally, the description of *Ostreopsis* species was based on morphological approaches combining size, shape and thecal plates pattern (as illustrated for instance in Hoppenrath et al., 2014). Nevertheless, a big part of the taxonomy of the genus remains unclear and controversial due to the high morphological and cell size variability within the different species and the fact that original descriptions lacked genetic analysis. Application of molecular approaches based on the nuclear rDNA internal transcribed spacer region (ITS1 and ITS 2), partial nuclear LSU (D1/D2, D8-D10 domains) and ITS-5.8S rDNA gene (Penna et al., 2005, 2010; Tawong et al., 2014; Chomérat et al., 2019, 2020) are nowadays key in the identification and determination of phylogeny links. These methods allowed, for example, the description of *Ostreopsis* sp. by Tartaglione et al. (2016) as the new species *O. fattorussoi*, and clarified uncertainties about former descriptions of *O. lenticularis* and *O. mascarenensis* (Chomérat et al., 2019, 2020). In particular, there is still debate regarding the taxonomy of the most widespread species, *O. ovata* and *O. siamensis* since their first description was based on morphological features only. For this reason, these two taxa are often referred to as *O. cf. ovata* and *O. cf. siamensis*. In the following, including all the tables, the species are cited as written in the corresponding published document.
With the most recent progresses in chemical analysis, toxin profile could also become a taxonomic criterion. 

*Ostreopsis* was initially considered a tropical genus, but it has been increasing its biogeographic distribution to temperate latitudes (Rhodes, 2011; Selina and Levchenko, 2011; Parsons et al., 2012; Tester et al., 2020 see Figure 5 in that paper-). In recent years, some reports have noticed the expansion of *Ostreopsis cf. ovata* in coastal waters of Australia, Brazil, China, Cook Islands, Caribbean Sea, French Polynesia, Hawaii, Indian Ocean, Japan, Malaysia, New Caledonia, New Zealand, Russia, Venezuela, Vietnam and specially in the Mediterranean Sea (Table 1). Other *Ostreopsis* species that appeared to have more confined distributions are also found in new areas. For instance, *Ostreopsis fattorussoi* isolated from the Eastern Mediterranean could be also growing in the Atlantic coast of the Iberia Peninsula (Portugal) although it has not been demonstrated yet (Accoroni et al., 2016a) and it was found in the Canary Islands (Fernández-Zabala et al., 2019). The wide expansion of the genus *Ostreopsis* is considered a potential problem for human health and wellbeing (economy, tourism, beach quality) issues due to the production of PLTX analogs which mode of action in humans is still not clear.

**Toxins Synthesized by *Ostreopsis* Species: The Main Chemical Substances Involved in the MCE of the Genus**

Several species in the *Ostreopsis* genus are considered potentially harmful to humans and other marine organisms due to the
production of palytoxin (PLTX) analogs (Table 1). PLTX is the most potent non-bacterial toxin of biological origin, initially isolated in 1971 from the tropical soft coral genus *Palythoa*, and now recognized as 42-OH-PLTX (see revision by Ciminiello et al., 2011 and references in Poli et al., 2018).

Progresses in chemical analysis technology, in particular on HR LC-MS/MS and Nuclear Magnetic Resonance (NMR) have revealed the high diversity of PLTX analogs (Table 1 and Figure 1) and eight *Ostreopsis* species have been described as toxic. Ostreocin D (Figure 2) was the first analog isolated from *O. siamensis* by Usami et al. (1995) and other PLTX analogs, namely, ovatoxins, ostreocins or mascarenotoxin have been characterized for *O. fattorussoi*, *O. mascarensis*, *O. cf. ovata* and *O. siamensis* (Mercado et al., 1994; Deeds and Schwartz, 2010; Parsons et al., 2012). However, the toxicity of *O. lenticularis* remains uncertain. Mercado et al. (1994) reported the production of Ostreotoxins 1 and 3 by cultures of *O. lenticularis* isolated from the Caribbean. This study was suggested to be taken with caution in the review by Parsons et al. (2012) since subsequent research indicated that bacteria could be involved in the toxicity of *O. lenticularis* strains from the Caribbean (Mercado et al., 1994, 1995; Meunier et al., 1997; Pérez-Guzmán et al., 2008). Recently, Chomérat et al. (2019) have reported no toxicity of *O. lenticularis* strains using CBA-N2a and LC-UV-MS/MS analysis. Toxicity of *O. heptagona*, *O. labens* and *O. rhodesae* has only been described using biological assays and toxins involved in these effects have not been identified yet (Table 1). In the case of *O. cf. ovata*, up to 12 ovatoxins (OVTX), from a to l (including j1 and j2) and the isobaric PLTX (isoPLTX, García-Altares et al., 2015 corresponding to the putative PLTX in other studies) have been identified among different isolated strains, and the toxinology profile is contributing to the taxonomic
characterization (Accoroni et al., 2016a). In most species and strains, OVTX-a and OVTX-b are the most common toxin forms, and isoPLTX is often absent or only accounting for no more than 1% of the total toxins (Tartaglione et al., 2017; Gémin et al., 2019). A main limitation to ascertain the health impacts risks associated to *Ostreopsis* blooms (and establishing legal toxin thresholds in seafood) is the lack of standards for the variety of toxins, all them complex and with high molecular weight (molecular formulas varying between $C_{129}H_{223}N_3O_{55}$ and $C_{131}H_{227}N_3O_{52}$, Table 1). As for species identification, information in Table 1 may change in the near future to rapid progresses in toxin analytical methods.

Phycotoxins in general and the PLTX group as well, are considered as secondary metabolites and their physiological role in the cells is unknown. Environmental factors such as temperature, salinity, light or nutrients, depth or macroalgal substrate, but also strain characteristics (isolation site, time kept in culture, growth phase of the culture) may influence toxin production (Granéli et al., 2011; Ciminiello et al., 2012; Pezzolesi et al., 2012, 2014; Scalco et al., 2012; Vanucci et al., 2012b; Gémin et al., 2019). However, it has been suggested that other microorganisms co-occurring along the *Ostreopsis* blooms could be involved in the toxin production as well. Tosteson et al. (1989) and Ashton et al. (2003) found that bacteria associated with the surfaces or the extracellular matrices of *O. lenticularis* were correlated with the high dinoflagellate toxicity during the stationary phase of the cultures. Biological assays and analytical chemistry analysis are both used for toxin presence detection and/or quantification. Mouse Bioassay (prohibited in Europe since 2005 for ethical reasons), Haemolysis Neutralization Assay (HNA) or *Artemia* bioassay have been long recognized for toxicity detection (Delaney, 1984; Bignami, 1993; Botana, 2014). Advantages provided by analytical chemistry, i.e., LC-MS/MS, are the absence of restrictions in terms of reproducibility, specificity, precision and consistency. Unfortunately, this methodology relies on very expensive technical equipment, it requires high-qualified personnel skills and it produces significant chemical waste. The variety of toxins produced by the different *Ostreopsis* species are considered the main substances involved in the chemical ecology of these dinoflagellates, and with this perspective are considered in this revision. However, recent studies indicate that other non-identified compounds could also be involved in the chemical ecology of *Ostreopsis* (sections 3.3.1. and 5.2).

**Ostreopsis Marine Chemical Ecology Affecting Human Health**

Health impacts in humans due to exposure to PLTX analogs synthesized by *Ostreopsis* constitute an indication of its related chemical ecology. Health impacts can occur: i) after...
TABLE 1 | Representative information about the range of toxin content on *Ostreopsis* species from different locations reported in the literature.

| Species | Toxins/Formula | Quantification | Distribution | References |
|---------|----------------|----------------|--------------|------------|
| *O. belizeanus* (Faust, 1999) | Unknown |  |  | Faust, 1999 |
| *O. caribbeanus* (Faust, 1999) | Unknown |  |  | Faust, 1999 |
| *O. fattorussoi* (Accoroni et al., 2016a) | isoPLTX | LC–HRMS 0.06 to 2.8 pg eq. PLTX/cell (2) | Canary Islands, Crete, Cyprus Island, Lebanon, Puerto Rico, Atlantic coast of Iberia Peninsula | Accoroni et al., 2016a; Tartaglione et al., 2016; Fernández-Zabal et al., 2019 |
| *O. heptagona* (Norris et al., 1985) | Unknown but extracts described as toxic to mice (In Accoroni et al., 2016b) |  |  | Norris et al., 1985; Rhodes, 2011 |
| *O. labens* (Faust and Morton, 1995) | Unknown but described as toxic in Rhode (2002) | Artemia assay Death of 24h old larvae of Artemia in standard assay | Beize, Caribbean Sea, Malaysia, Japan | Faust and Morton, 1995; Rhodes, 2011 |
| *O. lenticularis* (Fukuyo, 1981). Includes the cryptic species *Ostreopsis* sp. 5 in Chomérat et al., 2019 | No toxic (1) | N2a analysis: EC50 (PLTX) = 1191 ± 175 pg.mL⁻¹ (O⁻ condition) (1) | Australia, Cape Verde, Caribbean Sea, French Polynesia, Indian Ocean, Malaysia, Mexican Pacific, New Caledonia, New Zealand, Philippines, Venezuela, Vietnam | Tindall and Miller, 1988; Tosteson et al., 1989; Mercado et al., 1995; Meunier et al., 1997; Ashton et al., 2003; Sato et al., 2011; Carnicer et al., 2015b; Chomérat et al., 2019; Fernández-Zabal et al., 2019 |
| *O. marinus* (Faust, 1999) | Unknown | No pPLTX activity by HA using sheep erythrocytes | Caribbean, Indian Ocean, Vietnam | Faust, 1999; Carnicer et al., 2015a |
| *O. mascarenensis* (Quod, 1994) | Mascarenotoxin–A | HPLC–ESI–MS/MS: 0.04 pg eq.PLTX/cell | Rodrigues and Reunion Islands, Indian Ocean | Lenoir et al., 2004; Ramos and Vasconcelos, 2010; Chomérat et al., 2020 |
| *O. ovata* (Fukuyo, 1981) | pPLTX C₁₂₃H₂₂₂N₄O₆₄ (2) | LC–HRMS pPLTX: 0.02 to 3.6 pg eq. PLTX/cell | Australia, Belize, Brazil, China, Cook Islands, Caribbean, French Polynesia, Hawaii, Indian Ocean, Japan, Malaysia, Mediterranean, New Caledonia, New Zealand, Puerto Rico, Reunion, Rodrigues Island | Penna et al., 2005; Ciminiello et al., 2008, 2006, 2011, 2012; Guerini et al., 2010; Granèl et al., 2011; Rhodes, 2011 |
|  | Ovatoxin-a |  |  |  |
|  | Ovatoxin-b |  |  |  |
|  | Ovatoxin-c |  |  |  |
|  | Ovatoxin-d |  |  |  |
|  | Ovatoxin-e |  |  |  |
|  | Ovatoxin-f |  |  |  |
|  | C₁₃₁H₁₂₇N₃O₆₃ (1) | Hemolytic test PlTX/cell |  |  |

(Continued)
The review is not exhaustive and progresses in molecular and toxin analyses may result in rapid changes concerning both identity of species and their toxicity (Chomérat et al., 2019, 2020). More information on toxicity tests as well as on other Ostreopsis strains (that can become new species) is found in Tester et al. (2020). *Indicates that the isolate(s) were genetically identified, confirming described or cryptic (ribotype) species designations. eq.: Equivalents; HA: Hemolytic Assay - ability of cellular extract to induce erythrocyte cell lysis vs. a saponin control; HPLC: High-Performance Liquid Chromatography; LD₅₀: median lethal dose; LC₅₀: median lethal concentration; LC–HRMS: Liquid Chromatography – High Resolution Mass Spectrometry; MBA: Mouse BioAssay - toxicity determined by intraperitoneal injection of Ostreopsis cellular extracts; MU: Mouse Units, the 24 h LD₅₀ dose estimated using ~20 g mice; nd: Not Detectable, below detection limits; N2a: neuroblastoma cell line cytotoxicity assay; pPLTX: putative palytoxin; isoPLTX: isobaric palytoxin (García-Altares et al., 2015).}

**TABLE 1 | Continued**

| Species | Toxins/Formula | Quantification | Distribution | References |
|---------|----------------|----------------|--------------|------------|
| **O. cf. ovata** | pPLTX C₁₂₉H₂₂₉N₉O₅₄ | LC–HRMS: pPLTX: 0.1 to 24.8 pg eq. PLTX/cell; OVTX a: 0.065 to 171 pg eq. PLTX/cell; OVTX b: 2 to 205 pg eq. PLTX/cell; OVTX c: 0.7 to 37 pg eq. PLTX/cell; OVTX d-e: 2 to 80 pg eq. PLTX/cell; OVTX g: 0.35 to 24.8 pg eq. PLTX/cell | Australia, Brazil, China, Canada, Islands, Caribbeïan, Egypt, Portugal, Thailand, South West Mediterranean Sea, New Caledonia, New Zealand, Madeira, Mediterranean Sea, Thailand, South West, Indian Ocean, Vietnam | Rossi et al., 2010; David et al., 2013; Horneil et al., 2013; Nascimento et al., 2012a,b; Pezzolesi et al., 2012; Sechet et al., 2012; Hwang et al., 2013; Brissard et al., 2014, 2015; Dell’Aversano et al., 2014; Garcia-Altares et al., 2015; Giussani et al., 2015; Ben et al., 2017 |
| **O. rhodesae** (Verma et al., 2018) | Unknown but described as toxic in Verma et al. (2016) | LC–MS/MS: No PLTX analogs; Fish gill cell line assay for toxicity: ≥ 98.5% decrease of gill cell line RTgill-W1 viability | Heron Reef Lagoon, southern Great Barrier Reef, Coral Sea, Australia | Verma et al., 2016 |
| **O. siamensis** (Schmidt, 1901) | Ostreocin-A C₁₂₇H₂₁₈N₉O₅₄ | Haemolysis Neutralization Assay: 0.3 pg PLTX eq/cells (Rhodes, 2011) | Belize, Gulf of Siam, Irinome Island, Madagascar, Mayotte, Mexico, Puerto Rico, Reunion, Rodrigues Island | Ukena et al., 2001; Rhodes et al., 2000, 2002; Fernández-Zabala et al., 2019; Terajima et al., 2019 |
| **O. cf. siamensis** | Ostreocin-D C₁₂₇H₂₁₈N₉O₅₃ | LC–MS/MS: 0.17 pg. eq PLTX. cell⁻¹ (1) Mouse bioassay: LD₅₀ = 26.1 mg.kg⁻¹ (intraperitoneal injection) (2) | Atlantic, Australia, Belize, Canary Islands, Caribbeïan, Eastern Atlantic coast (Portugal, Cape Verde), Japan, Mediterranean Sea, Mexico, New Caledonia, New Zealand, Southwest Indian Ocean, Tasmania, Thailand, Vietnam | Cagide et al., 2009; Ciminiello et al., 2013; David et al., 2013; Verma et al., 2016 |

The consumption of seafood potentially contaminated with PLTX analogs, or ii) after direct exposure to seawater and/or aerosol during *Ostreopsis* blooms. The characterization of human poisonings potentially due to exposure to PLTX analogs was reviewed by Tubaro et al. (2011) and it is briefly presented here. The effects of *Ostreopsis* species in different marine organisms have also been reported and are presented in section 3.
Severe illness and even lethal fatalities after consumption of seafood potentially contaminated with PLTX analogs have been rarely reported in tropical and subtropical latitudes since the 1970s (see Tables 1–3 in Tubaro et al., 2011). Among them, only a few cases were confirmed through direct PLTX analogs detection in seafood leftovers. In many other cases, screening tests on seafood samples collected or purchased after or before the poisoning episode combined or not with clinical observations and symptoms, concluded that consumption of PLTX contaminated seafood was the causative reason of the health disorders. PLTX poisoning symptoms include nausea, tiredness, diarrhea, vomiting, dizziness, numbness of the extremities, muscle cramps, paresthesia, restless-ness, respiratory distress and bradycardia. In dramatic cases, patients died after 15h to 4 days following seafood poisonings, even after hospitalization. Unusual metallic taste of the seafood is one of the common signs noted by potential PLTX intoxication.

In the Mediterranean coasts, the proliferation of O. cf. ovata and O. cf. siamensis since the end of the 21th century raised concern about the potential risk of seafood intoxication. Amzil et al. (2012), Biré et al. (2013), Biré et al. (2015), and Brissard et al. (2014) reported the presence of toxin content in macrofauna (mainly sea urchin, rock shell, crab and flathead mullet) sampled during O. cf. ovata blooms. OVTX-a was the most abundant toxin detected, and in some cases PLTX equivalents accounted on average for 223 to 392 µg·kg⁻¹ of whole flesh, exceeding the threshold of 30 µg·kg⁻¹ in shellfish recommended by the European Food Safety Authority (EFSA). The key questions are whether Ostreopsis was the ultimate organism synthesizing the PLTX-like compounds that contaminated the seafood and, how toxins can be transferred through the food webs. Fortunately, until now, seafood poisonings due to PLTX analogs have not been reported in the Mediterranean zone.

### Mild Respiratory and Cutaneous Symptoms After Direct Exposure to Seawater and/or Aerosol During Ostreopsis Blooms

In the last 15 years, in several Mediterranean and Brazilian beaches, Ostreopsis blooms have been associated to mild skin and respiratory symptoms and general malaise in beach users, workers and inhabitants of the first coastline, after direct contact with water and/or after inhalation of marine aerosols (Table 2).

| Year, Species | Location | Affected people (n) | References |
|--------------|---------|---------------------|------------|
| 1998, 2004, Ostreopsis sp. | NW Med (Spain) | 74 (estimated~200) | Vila et al., 2008 |
| 1998, 2000, Ostreopsis ovata | Tiranian (Italy) | ~100 | Sansoni et al., 2003 |
| 2001, 2003, Ostreopsis sp. | S Adriatic (Italy) | 28 | Gallitelli et al., 2005 |
| 2005, 2006, Ostreopsis ovata | Ligurian (Italy) | 228, 19 | Brescianini et al., 2006 |
| 2005, Ostreopsis ovata | Genoa (Italy) | 209 | Durando et al., 2007 |
| 2006, Ostreopsis ovata | NW Med (Spain) | 37 | Vila et al., 2016 |
| 2006-2009, Ostreopsis ovata & O. siamensis | France | 47 | Tichadou et al., 2010 |
| 2006, Ostreopsis sp. | SW Med (Spain) | 57 | Garcia et al., 2008 |
| 2009, Ostreopsis sp. | SW Med (Algeria) | 150-200 | Iloul et al., 2012 |
| 2010, Ostreopsis cf. ovata | Adriatic (Croatia) | 7 | Pfannkuchen et al., 2012 |
| 2013, Ostreopsis cf. ovata | NW Med (Spain) | 13 | Vila et al., 2016 |
| 2014, 2015, 2016, 2017, 2019, Ostreopsis sp. | NW Med (Spain) | N/A | Abós-Herrándiz et al., unpublished |

### Chemical Ecology of Ostreopsis spp.

### References

Pavaux et al. (2020)
| Species/Strain                      | Organisms                  | Stage                  | Effects                                              | References        |
|-----------------------------------|----------------------------|------------------------|------------------------------------------------------|-------------------|
| **Ostreopsis ovata**              | *Tigriopus fulvus* (Fisher, 1860) | I-II stage Nauplii     | Mortality                                           | Faimali et al., 2012 |
| isolated by A. Penna              |                            |                        |                                                     |                   |
| **Ostreopsis cf. ovata**          | *Tigriopus fulvus* (Fisher, 1860) |                        | Mortality                                           | Giussani et al., 2016 |
| **Ostreopsis ovata**              | *Amphibalanus amphitrite* (Darwin, 1854) | II-III stage Nauplii   | Mortality                                           | Faimali et al., 2012 |
| isolated by A. Penna              |                            |                        |                                                     |                   |
| **Ostreopsis cf. ovata**          | *Amphibalanus amphitrite* (Darwin, 1854) |                        | Mortality                                           | Giussani et al., 2016 |
| **Ostreopsis cf. ovata**          | *Dinophysylus gryociliatus* (Schmidt, 1857) | Juveniles              | Mortality                                           | Simonini et al., 2011 |
| Natural samples, Ligurian Sea      |                            |                        |                                                     |                   |
| (44°3’27”N; 9°56’43”E)           |                            |                        |                                                     |                   |
| **Ostreopsis ovata**              | *Paracentrotus lividus* (Lamarck, 1816) | Juveniles              | Mortality                                           | Privitera et al., 2012 |
| isolated by A. Penna              |                            |                        |                                                     |                   |
| **Ostreopsis cf. ovata**          | *Tigriopus fulvus* (Fisher, 1860) | Nauplii                | Mortality                                           | Prato et al., 2011 |
| Natural samples, Gulf of Taranto, Ionian Sea | *Corophium insidiosum* (Crawford, 1893) | 2-4 mm body length     | Mortality                                           | Rhodes et al., 2000 |
| **Ostreopsis siamensis**          | *Sarsamphiascus cf. propinquus* (Sars G.O., 1906) | Larvae                | Mortality                                           | Pavaux et al., 2019 |
| CAWD73/74/75/96                   |                            |                        |                                                     |                   |
| **Ostreopsis cf. ovata**          | *Sarsamphiascus cf. propinquus* (Sars G.O., 1906) | Adults               | Mortality                                           |                   |
| MCCV 054                          |                            |                        |                                                     |                   |
| **Ostreopsis ovata**              | *Phytal meiofauna*         | Community composition | 72 % decrease of nauplii                            | Guidi-Guivard et al., 2012 |
| Natural samples from French and Italian NW Med. Coasts | | | | |
| **Ostreopsis ovata**              | *Sarsamphiascus cf. propinquus* (Sars G.O., 1906) | Females               | Reproduction                                        | Pavaux et al., 2019 |
| MCCV 054                          |                            |                        |                                                     |                   |
| **Ostreopsis cf. ovata**          | *Paracentrotus lividus* (Lamarck, 1816) | Toxin quantification  | LC-MS/MS: 77 to 361 µg eq PLTX.g.kg⁻¹             | Amzi et al., 2012 |
| Natural samples (French Mediterranean coasts) | | | | |
| **Ostreopsis ovata**              | *Paracentrotus lividus* (Lamarck, 1816) | Toxin quantification  | LC-MS/MS: 103 to 423 µg.kg⁻¹                        | Brissard et al., 2014 |
| Field sample - Villederfranche-sur-Mer, Mediterranean Sea | *Sarpa salpa* (Linnaeus, 1758) | | Hemolytic test: 179 to 270 µg.kg⁻¹ | |
| **Ostreopsis ovata**              | *Sarpa salpa* (Linnaeus, 1758) | Toxin quantification  | LC-MS/MS: 33 to 152 µg.kg⁻¹                        | Miliardi et al., 2010 |
| Field samples (Tyrrhenian Sea)    | *Sarpa salpa* (Linnaeus, 1758) | Toxin quantification  | HNA: 5 to 99 pPLTX µg.kg⁻¹                        |                   |
| **Ostreopsis ovata**              | *Paracentrotus lividus* (Lamarck, 1816) | Toxin quantification  | LC-MS/MS: < LOQ pPLTX µg.kg⁻¹                      | Biré et al., 2015 |
| Field sample - Nice harbour and Villederfranche-sur-Mer, Mediterranean Sea | | | | |
| **Ostreopsis ovata**              | *Paracentrotus lividus* (Lamarck, 1816) | Toxin quantification  | Haemolytic assay: 256.6 µg.kg⁻¹ (WF)               | Biré et al., 2013 |
| Field samples - Rochambeau site, Villederfranche-sur-Mer, Mediterranean Sea | | | | |

(Continued)
### TABLE 3

| Species/Strain | Organisms | Stage | Effects | References |
|----------------|-----------|-------|---------|------------|
| **Interactions with planktonic cells of *Ostreopsis* species** |
| *Ostreopsis ovata* isolated by A. Penna | Paracentrotus lividus (Lamarck, 1816) | Competent larvae | Mortality | $LC_{50-90-20-20}^\circ C = 168 \text{ cells.mL}^{-1}$ |
| *Ostreopsis cf. ovata* CBA29-2012 (Genoa) | Aurelia sp. | Polyp | Reproduction/early stages | Unaffected (100 cells.mL$^{-1}$) |
| *Ostreopsis cf. ovata* Marche coast (Italy NW Adriatic Sea) | Mytilus galloprovincialis (Lamarck, 1819) | Adults | Histological impairments | |
| *Ostreopsis cf. ovata* Field sample from Adriatic Sea (Portonevo & Passetto sites) | Mytilus galloprovincialis (Lamarck, 1819) | Adults | Histological impairments | Inhibition of Na$^+$/K$^+$/ATPase and acetylcholine esterase activity |
| *Ostreopsis cf. ovata* Natural samples (French Mediterranean coasts) | Mytilus galloprovincialis (Lamarck, 1819) | | Toxin quantification | MBA: Qualitative analysis HNA: 33.3 to 97 pPLTX $\mu$g.kg$^{-1}$ |
| *Ostreopsis cf. ovata* Filed samples (Adriatic Sea) | Mytilus galloprovincialis (Lamarck, 1819) | | Toxin quantification | MBA + HNA: Qualitative analysis |
| *Ostreopsis ovata* Field samples (Tyrrhenian Sea) | Mussels | | Toxin quantification | HNA: 103 pPLTX $\mu$g.kg$^{-1}$ LC-MS/MS: < LOQ pPLTX $\mu$g.kg$^{-1}$ - 131 to 228 OVTXa $\mu$g.kg$^{-1}$ |
| *Ostreopsis siamensis* CAWD75 (New Zealand) | Greenshell™ mussels Pacific oysters Scallops | | Toxin quantification | MBA: qualitative analysis HNA: 0.3 pg.eq, PLTX.cell$^{-1}$ |
| *Ostreopsis siamensis* CAWD75 (New Zealand) | Perna canaliculus (Gmelin, 1791) Pecten novaezelandiae (Reeve, 1852) Crassostrea gigas (Thunberg, 1793) | | Toxin quantification | MBA (qualitative analysis): none to death HNA: trace to 1 ng.g$^{-1}$ |
| *Ostreopsis cf. ovata* Field samples - Rochambeau site Villefranche-sur-Mer | Arca noae (Linneaus, 1758) | | Toxin quantification | Haemolytic assay: < 10 $\mu$g.kg (WF) |
| *Ostreopsis cf. ovata* CBA29-2012 (Genoa) | Aurelia sp. | Ephyrae | Reproduction/early stages | |
| *Ostreopsis cf. ovata* ITACS01 | Paracentrotus lividus (Lamarck, 1816) | Eggs | Reproduction/early stages | Gametes: % fertilization decrease; less toxic for eggs than sperms Embryos: no segmentation |

(Continued)
### TABLE 3 | Continued

| Species/Strain | Organisms | Stage | Effects | References |
|----------------|-----------|-------|---------|------------|
| O. ovata (whole cells + lysate) Natural samples (Ionian Sea) | Paracentrotus lividus (Lamarck, 1816) | Embryos | Reproduction/early stages | Whole cells: Developmental delay or anomalous cell division Cell lysate: Growth inhibition at 1.87 mg/mL⁻¹ | Pagliara and Caroppo, 2012 |

### Interactions with surface cells of O. species

| Species/Strain | Field samples | Stage | Effects | References |
|----------------|---------------|-------|---------|------------|
| O. ovata | Field samples | Species/Stage | Toxin quantification | Haemolytic assay: 12.7 µg/kg (WF) | Biré et al., 2013 |
| O. ovata | Nice harbour and Villefranche-sur-Mer | Patella spp. | Toxin quantification | Haemolytic assay: 392.2 µg/kg (DT) | Biré et al., 2015 |
| O. ovata | Field samples - Rochambeau site Villefranche-sur-Mer | Patella spp. | Toxin quantification | LC-MS/MS: 359.1 µg/kg (WF) | |
| O. ovata | Field samples Genoa, Nice, Villefranche-sur-Mer | Paracentrotus lividus (Lamarck, 1816) | Density | Any decrease of P. lividus densities related to high abundances of O. ovata | |
| O. ovata | Patella spp. | | | No significant decrease of densities in Villefranche-sur –mer and Nice; Significant decrease in Genoa potentially linked to O. cf. ovata blooms | |

**EC₅₀**: Half maximal Effective O. Concentration; **DT**: Digestive Tube; **HNA**: Hemolysis Neutralization Assay; **LC₅₀**: Median Lethal Concentration; **LC-MS**: Liquid Chromatography – Mass Spectrometry; **LT₅₀**: median Lethal Time; **MBA**: Mouse BioAssay; **RT**: Remaining Tissue; **WF**: Whole Flesh.

Mangialajo et al., 2011) suggested that O. fragments, mucus, and/or associated biota (including bacteria, cyanobacteria or other pico- or nanoeukaryotes) could be present in the aerosol and cause the health disorders. It should be noted here that symptoms do not occur concurrently with high cell O. densities neither during the bloom, but only in certain periods. Vila et al. (2016) conducting a parallel epidemiology and ecology survey found that symptoms occurred at the end of the exponential phase and initial stationary phase of the bloom, at least in 2013 in a Mediterranean hot spot. This trend has been approximately repeated in the following years in that hot spot (Abós-Herrándiz et al., unpublished). Still an open question is how toxins and/or fragment of O. can be aerosolized and whether these toxins are the causative agent of the disorders.

### Toxicity on Mammalian Cells and Mode of Action

The main biological target of PLTX seems to be the Na⁺/K⁺-ATPase, a plasma membrane pump involved in the maintenance of trans-membrane ionic gradients of animal cells, essential for cellular functions and life (Habermann, 1989; Wu, 2009; Rossini and Bigiani, 2011). Impairment of the membrane pump by PLTX results in its conversion into a non-selective pore for monovalent cations, thereby destroying the transmembrane ionic gradient and triggering several adverse biological effects, some life threatening (Habermann, 1989; Artigas and Gadsby, 2003).

However, these studies have been conducted in vitro on mammalian cell tissues and the actual in vivo toxicity of the molecule is still poorly understood. In the 1970’s, semipurified PLTX was tested in a broad range of animal species through several routes of administration. Thus, a reduced or even increased toxicity of the pure molecule are possible. More recently, high purity PLTX administration in mice showed that toxicity is dependent upon the route of administration (Munday, 2011). Poli et al. (2018) characterized the toxicity and basic histopathological effects of PLTX (derived from Japanese Palythoa tuberculosa), the analog 42-OH-PLTX (from Hawaiian P. toxica) and ovatoxin-a (isolated from a Japanese strain of O. ovata) after intraperitoneal and aerosol administration to rats. All toxin preparations showed similar potency towards mouse erythrocytes in the erythrocyte hemolysis assay and interactions with the anti-PLTX mAb (antibody). Intraperitoneal LD₅₀ values between 0.92 and 3.26 µg·kg⁻¹ consistent with published values, and aerosol LD₅₀ values of 0.031 to 0.063 µg·kg⁻¹ confirmed the potency of PLTX suggested by
the literature. Most commonly affected tissues were the lungs, liver, heart, salivary glands, and adrenal glands.

Mechanisms of Toxins Release in Sea Water and Aerosolization

It is well recognized that microorganisms including some microalgae can be dispersed by air and survive in the aerosols (e.g., Genitsaris et al., 2011; revision by Tesson et al., 2016). Microorganisms become airborne mainly due to drop formation at the water surface microlayer, which is enriched with biological material in all aquatic habitats (Schlichting, 1974; Wilson et al., 2015). Foam drops of a diameter larger than 40 µm are formed by wind friction and breaking wave crests at wind speeds exceeding 7 m·s⁻¹. Bubble bursting due to waves, rainfall, boat traffic, or
supersaturation of gases in the water produces film drops (1 μm to 10 μm diameter), projected in various directions, and vertically emitted jet drops (6 μm to 100 μm diameter). Recreational activities (i.e., waterskiing, using personal watercraft, swimming, or wading) can also generate aerosols. Once emitted, airborne turbulent kinetic energy drags the microorganisms further up into the atmosphere.

The few available studies indicate that microalgae are found at very low concentrations (10^−4 to 10^4 cells per m^−3, Mayol et al., 2014) and with heterogeneous distributions, which requires high-volume sampling technology. High-volume sampling on filters or agar plates can be achieved by different instruments, but high-volume sampling into liquids is more complicated, as high airflows may lead to evaporation and reduce collection efficiency. Once collected, a combination of microscopy and molecular tools contribute to the identification of the airborne microalgae. The main microalgal groups found in bioaerosols are chlorophytes (“green algae”), bacillariophytes (diatoms, mainly small Nitzschia) and cyanobacteria. Airborne microalgae are recognized as allergens and antigens. They are the cause of severe medical issues, including respiratory allergies (e.g., hay fevers), asthmatic attacks, dermatitis and skin lesions, rhinitis, and disturbances in lymphatic systems or vital organs (e.g., protothecosis, see review in Ashok and Gupta, 1998). In addition, certain aerosolized algal toxins, namely, microcystins produced by cyanobacteria (Backer et al., 2010) brevetoxins synthesized by Karenia brevis (Pierce and Henry, 2008; Fleming et al., 2011) and OVTX and PLTX analogs generated by Ostreopsis species, are the causes of further human illnesses.

So far, the detection of Ostreopsis cf. ovata and its related toxins in the aerosol was conducted by Casabianca et al. (2013) and Ciminiello et al. (2014). Casabianca et al. (2013) used air pump samplers (CAV-A/mb, Barcelona, Spain) equipped with 15 cm diameter QM-A quartz filters (Whatman, Maidstone, United Kingdom). Two air samplers located at 0.5 m and 3 m above sea level, respectively, pumped air continuously for 3 days during an O. cf. ovata bloom at a flow rate of 30 m^3·h^−1. Filters were replaced every 6 or 7 h and were divided in two portions to analyze, respectively, the concentration of Ostreopsis cell concentrations by qPCR and toxins by the hemolytic assay and by liquid chromatography with fluorescence detection (LC-FLD). Ostreopsis cells were detected in the aerosol by qPCR, exhibiting a marked variability during the bloom although not always directly related to the concentrations of the epiphytic Ostreopsis in the water; the authors noted that wind and other environmental factors could have affected these findings. In the seawater, epiphytic Ostreopsis contained ca. 1.2 pg total PLTX analogs per cell but toxins were not detected in the aerosol. Different technical aspects (e.g., toxin binding to glass tubes, not efficient retention by the filters) were suggested as potential technical limitation. Ciminiello et al. (2014) also employed AirCube COM2 (Analítica Strumenti srl., Italy) equipped with 47 mm diameter glass/quartz microfiber filters (Whatman, Maidstone, United Kingdom) and SAS PCR VWR International (PBI, Italy). In this case, air and a collecting fluid (50 mL distilled water in 2009, and seawater in 2010) flow together through a nozzle were poured into a vessel with a coil; the collecting fluid was circulated continuously to prolong the contact time with aerosols and to enrich itself in toxins and/or cells. Both air samplers were located 10 m from the seashore and worked continuously for 1.5-6 h. Air flow speed was 10 L·min^−1 in 2009 and 30 L·min^−1 in 2010. The presence of OVTX in the aerosol at levels of 2.4 pg of OVTX per liter of air was confirmed for the first time but PLTX by inhalation exposure toxicological data were not available. Overall, the presence of both cells and toxins in the aerosols provided by these studies opened new possibilities to increase the understanding of the Ostreopsis-related respiratory syndrome.

**MARINE CHEMICAL ECOTOLOGY OF Ostreopsis IN THE AQUATIC ENVIRONMENT**

This section reviews the interactions of *Ostreopsis* cells with different marine organisms and environments as part of the MCE of Ostreopsis.

**Interactions With Bacteria, Viruses and Parasites**

Interactions between microalgae species and bacteria remain poorly investigated although the available studies reveal connections playing important roles in the biology and the ecology of these microorganisms. Bacteria may interact with algae within the phycosphere (Bell and Mitchell, 1972) as free-living bacteria, attached to the algal cell surface or occurring as intracellular symbionts. Algae–bacteria interactions can be synergistic and mutualistic, as commensalism or symbiotic, e.g., by producing cytokinins – phytohormones (Ramanan et al., 2016). Some vitamins and ion chelators produced by bacteria are involved in nutrient recycling facilitating nutrient incorporation by algae, while, in return, bacteria use microalgal exudates (Sarmento and Gasol, 2012). Furthermore, competition, parasitism or antagonist interactions also occur. Bacteria could interfere microalgal life cycle and growth of some HAB species. Bacterial exopolymers can increase the tendency of cells to flocculate and enhance sinking rates and degradation of decaying (harmful and innocuous) blooms (Decho, 1990). In turn, algae could also control bacterial growth by the production of antibiotic or hydroxyl radicals and other selected anti-bacterial growth substances (Bell et al., 1974). Information on these different interactions focused on HAB species can be found, e.g., in Fukami et al., 1992; Oda et al., 1992; Sawayama et al., 1993; Doucette, 1995; Hare et al., 2005; Jasti et al., 2005; Maruyama et al., 2008; Kim et al., 2009; Trick et al., 2011. These interactions exhibit spatio-temporal variability scales (Doucette, 1995) which, in the case of HABs can also involve phylogenetically and metabolically diverse bacterial groups along the bloom dynamics (Mayali et al., 2011). While some bacteria could coexist with microalgal cells during the initiation and exponential phases of the blooms, antagonist or parasitic bacteria would proliferate before the declining period and saprophytic or scavenger bacteria will occur after bloom termination when the availability of phytodetritus is high.
Bacterial communities associated to *Ostreopsis lenticularis* appear to be species and even clone specific (Toestesen et al., 1989) they vary with the bloom phase, and likely, with the habitat. Pérez-Guzmán et al. (2008) identified single species belonging to the *Cytophaga-Flavobacter-Bacteroides* complex. Vanucci et al. (2016) and Guidi et al. (2018) found *Alphaproteobacteria* (83 % relative abundance - genera *Rugeteria, Jannaschia* and *Erythrobacter*), *Gammaproteobacteria* (13%) and *Flavobacteria* (7%) during the early O. *cf. ovata* bloom period, while *Alphaproteobacteria* (66%) and *Flavobacteria* (19%) were predominant in peak bloom phases. In the case of dinoflagellates, bacteria-algae interactions can be very strong given that some microalgae are unable to grow in axenic conditions in culture confirming the predominant role of bacteria in algal cycle. This has also been observed in *Ostreopsis* cultures although not always (Vanucci et al., 2012a).

Some studies indicate that bacteria could directly or indirectly modulate production and degradation of microalgal toxins (Albinsson et al., 2014) although the results appear study- and species-dependent and contradictory. While associated bacteria were linked to the production of paralytic shellfish toxin by *Alexandrium* spp. (Gallacher et al., 1997) higher toxin levels were found in bacteria-free than in non-axenic cultures of *Alexandrium tamarense* (Hold et al., 2001) and *A. lusitanicum* (Wang et al., 2004). Ashton et al. (2003) reported a toxicity loss of *Ostreopsis lenticularis* when exposed to elevated temperature and explained it by the reduction of *Ostreopsis* associated *Pseudomonas* and *Alteromonas* bacteria. Axenic cultures of *Ostreopsis cf. ovata* (Vanucci et al., 2012a) were also characterized by lower toxin content in late stationary phase compared to non-axenic cultures. *Ostreopsis cf. ovata* cell concentration along a bloom was correlated with the abundance of planktonic, free-living *Vibrio* (Bellés-Garulera et al., 2016) and a high proportion of *Vibrio* were found attached to particles, suggesting that *Ostreopsis* bloom could provide biological colonizable surfaces (fragments of thecae or mucilage) for bacteria. The study suggested that bacteria could be involved in wound infections reported by beach users during *Ostreopsis* blooms. In fact, *Ostreopsis* blooms were reported in heavily antropogenically impacted environments (Cen et al., 2019). However, the role of bacteria, potentially colonizing the mucus produced by *Ostreopsis* (a mucilaginous matrix, described as a network of trichocysts embedded with acidic polysaccharides filaments by Honsell et al., 2013) in the respiratory irritations associated to the microalgal bloom has not been clarified yet.

Parasite infection may play critical roles in the regulation of HABs. It has been already described for the planktonic toxic dinoflagellate *Alexandrium fundyense* which presented an up-regulation of genes associated to defense against the parasite *Amoeobophrya* and thus controlling host mortality (Garcés et al., 2013a; Lu et al., 2016, 2014). *Ostreopsis* spp. (among other phytoplankton species) was infected by the generalistic parasitoid *Parvilucifera sinerae* (Garcés et al., 2013b).

To our knowledge, there has been no research on the interactions between *Ostreopsis* species and viruses while viruses have been proposed as natural agents to control HABs. This is the case of the virus HcRNAV, specific of the dinoflagellate *Heterocapsa circularisquama* (Nagasaki and Yamaguchi, 1997; Nagasaki et al., 2004; Nakayama and Hamaguchi, 2016).

### Interactions With Heterotrophic Protists and Ciliates

Heterotrophic dinoflagellates (HTDs) and ciliates have been described as effective grazers on HAB species (Matsuyama et al., 1999; Tillmann, 2004; Jeong et al., 2015). However, so far, only one study has investigated feeding on *Ostreopsis cf. ovata* by a ciliate and various HTDs, all them potentially able to ingest it based on cell size criteria (Yoo et al., 2015). O. *cf. ovata* was ingested by *Gyrodinium dominans, G. moestrupii, Oxyrrhis marina*, and *P. kofoidii* by engulfment and by *Pfiesteria piscicida* using a peduncle. The study suggested that these HTDs can feed on *O. cf. ovata* by enzymes involved in the detection, capture, ingestion and digestion of toxic dinoflagellates. In contrast, lack of these enzymes in the naked ciliate *Strombiliidium sp.* and the HTDs *Gyrodinium spirale, Proteotetidium bipes, and Stoeckeria algicida* would impede feeding on *O. cf. ovata*. Overall, information on microzooplankton grazing on *Ostreopsis* species in the field are lacking, and there is a major uncertainty on whether the success of this benthic microalga is caused by lack of effective predation. It has also been suggested that the mucus could be deterrent agent.

### Interactions With Flora

A relatively small but recent number of studies focus on interactions between *Ostreopsis* species and flora, microphytobenthos and macrophytes, suggesting different allelopathic interactions during the dinoflagellate bloom dynamics. In these studies, the degree of interaction has been measured using different physiology and morphology parameters of the tested organisms, namely, growth rate (García-Portela et al., 2016; Ben et al., 2017) fluorescence (Ben et al., 2017; Ternon et al., 2018) swimming speed (Yoo et al., 2015) adherence capability (García-Portela et al., 2016) cysts formation (Accoroni et al., 2016b) cellular integrity (variation of shape, size, nucleus position using lipid and nuclear staining; Pichierri et al., 2017) and toxin production (Ben et al., 2017). The interactions with micro- and macroalgae are presented next and summarized in the Figure 3.

### Microalgae

Some studies have shown that particular secondary metabolites i.e., low molecular weight compounds (as opposed to peptides or proteins) not directly involved in basic life processes, could considerably affect HABs dynamic and growth (Uchida et al., 1999; Fistarol et al., 2003; Prince et al., 2008; Yamasaki et al., 2010). These sorts of interactions have also been addressed concerning the impact of *Ostreopsis cf. ovata* on diatom and other dinoflagellates, as well as the retroactions of these microalgae on *O. cf. ovata*.

A strong inhibitory effect of *O. cf. ovata* on microalgae was observed in the in situ study of Accoroni et al. (2016b). In particular, it was manifested as a significant decrease in the diversity index and an increase of motile diatoms abundance during the *O. cf. ovata* bloom. Motile life diatom phase would...
be favored by the Ostreopsis mucous matrix, illustrating the importance of the mucus in the interactions between O. cf. ovata and its environment. Recently, Ternon et al. (2018) using co-cultures assays (with diatoms) suggested a contact-mediated toxicity of Ostreopsis cells, probably by the mucus, which could retain the toxins and other compounds and avoid their dilution in the surrounding environment.

Monti and Cecchin (2012) observed weak effects on the growth of the dinoflagellates Coilia mononis and Prorocentrum minimum when exposed to filtrates of O. cf. ovata cultures obtained during its exponential phase. This highlights the importance of growth stages considered in the experiments. Indeed, variation of the toxin content among the growth stage has been described in different studies (Vanucci et al., 2012a; Brissard et al., 2014; Pezzolesi et al., 2014) on Ostreopsis cf. ovata cultures, with a trend of higher concentration in the stationary phase.

García-Portela et al. (2016) using mixed cultures of different Ostreopsis strains and toxic and non-toxic dinoflagellates, demonstrated differences of toxicity among Ostreopsis strains. Indeed, O. cf. ovata was more toxic than O. sp. «Lanzarote type», highlighting the necessity to study the intraspecific variability of the interactions of Ostreopsis species with other organisms. The chemical compounds involved in the negative interaction of Ostreopsis and other microalgae (specially diatoms) are poorly known and secondary metabolites other than the OVTXs group could play a role, as suggested by Ternon et al. (2018).

In turn, it has been observed that planktonic and benthic diatoms can negatively affect O. cf. ovata physiology, morphology and growth. An inhibition of its growth rate by 57 % and 78 % was reported in cultures exposed to, respectively, filtrates of the planktonic diatoms Skeletonema marinoi and Thalassiosira sp., and similar growth inhibition, deleterious effects and genotoxic damages were also observed when exposed to filtrates of other benthic diatoms (e.g., Tabularia affinis, Proschkinia complanatoïdes and Navicula sp.) (Pichiri et al., 2017). These studies suggested the production of allelopathic compounds by macroalgae are still poorly known but could mainly include phenols and polyunsaturated fatty acids (PUFAs - Ben et al., 2017).

**Macrolalgae**

Biotic substrate preferences of Ostreopsis species has been demonstrated in several studies (Totti et al., 2010). Substrate choice could be explained in part, by the macroalgal thallus surface and morphology: complex, three dimensional flexible and branched thalli favored Ostreopsis cell attachment (Cohu et al., 2013; Accoroni et al., 2016a; Meroni et al., 2018). These thalli would also be more suitable for O. cf. ovata (Vila et al., 2001; Accoroni et al., 2012) resistance to wave action. Higher abundances of O. cf. ovata were also found on the turf dominated community i.e., in a complex intricate matrix of small Corallinales, Ceramiales (both Florideophyceae) and other filamentous algae (Meroni et al., 2018) as reported in Vila et al. (2001) for Ellisoldandia elongata and in Blanfuné et al. (2015) for Jania rubens. Lee and Park (2018) also showed that Ostreopsis sp. ingested rhodophytes because of their soft cell membrane containing microfibrillar and sulfated galactans (see section 4.2).

The production of allelopathic compounds by macroalgae could also explain Ostreopsis species substrate preferences. Macrolalgae are known to produce a large number of secondary metabolites sometimes used in biotechnology as antibiofouling coatings (Hellio et al., 2002) or as a way to control HABs (Hu and Hong, 2008; Tang et al., 2015). Thus, it is reasonable to hypothesize that these metabolites could selectively determine substrate preference of Ostreopsis species. Rhodymenia pseudopalma (Florideophyceae) had little effect on Ostreopsis growth and only in powder form (Accoroni et al., 2015). The seagrasses Zostera noltei and Cymodocea nodosa has also a low impact on O. cf. ovata growth although Z. noltei have been described as a producer of phenolic acids inhibiting the growth of Alexandrium catenella (Laabir et al., 2013). Ulva rigida (Ulvolphyceae) and Dycytota dichotoma (Phaeophyceae) had a strong effect on O. cf. ovata by decreasing its growth, physiology, morphology, toxin production and behavior with a decrease of cell adherence (Accoroni et al., 2015; Ben et al., 2017). The potential allelochemical compounds produced by this macroalgae are still poorly known but could mainly include phenols and polyunsaturated fatty acids (PUFAs - Ben et al., 2017).

**Interactions With Fauna**

Toxins produced by Ostreopsis have been documented in various marine organisms suggesting the potential bioaccumulation among the trophic web reaching levels above the alert threshold recommended by EFSA. The toxin transfer, which could be analogous to that of Gambierdiscus species synthesized ciguatoxins and maitotoxins (Ledreux et al., 2014), requires more research. Meanwhile, the few existing studies have reported strong differences of sensitivity (e.g., replicotoxicity potentially leading to changes in benthic communities) between organisms exposed to Ostreopsis toxins, suggesting unknown mechanisms of acclimation and detoxification.

**Impacts of Ostreopsis Blooms on Fauna in Tropical and Temperate Areas**

As indicated above, human intoxications have been reported in tropical areas mainly due to the consumption of fish or crustaceans contaminated with PLTX or its analogs without any indication of the effects of these toxins on the vector organisms. This suggests a direct ingestion, at least by herbivorous ingesting macroalgae supporting Ostreopsis cells. Even if no human intoxication due to the consumption of fish or crustaceans was reported in temperate areas, massive mortality of invertebrates occurred during Ostreopsis sp. bloom. Mass mortalities of sea urchins were reported in Italy (Vale and Ares, 2007) Algeria
(Illoul et al., 2012) Brazil (Granéli et al., 2002) New Zealand (Shears and Ross, 2009) Spain (Vila et al., 2008) and France (Blanfuné et al., 2012). Impacts on other sessile and mobile benthic organisms such as cirripeds, mussels, limpets and cephalopods were also observed (Ciminiello et al., 2006; Totti et al., 2010). Even if the role of oxygen depletion and high seawater temperature could be involved in those mass mortalities (Shears and Ross, 2009) more and more authors rather suggest that these mortalities were a consequence of some ecotoxic effects associated to *Ostreopsis* sp. blooms (Sansoni et al., 2003; Simoni et al., 2003; Vila et al., 2008).

### Direct Interactions Between Marine Fauna and *Ostreopsis* Species

*Ostreopsis* is an epibenthic genus, growing attached to macroalgae or rocks (Totti et al., 2010; Cohu et al., 2013, 2011; Penna et al., 2014; Carnicer et al., 2015a) thanks to the production of a mucilaginous matrix (Honsell et al., 2013; Escalera et al., 2014). Cells are also released in the water column, even if the link between planktonic and benthic abundances exhibits a high variability (Mangialajo et al., 2011) and can also aggregate on the water surface, forming what was called “sea-flowers”. *Ostreopsis* cells could thus have different impacts on marine ecosystems depending on whether cells are benthic, planktonic or aggregated at surface. These interactions are summarized in Figure 4.

### Interactions of fauna with benthic *Ostreopsis* cells

When *Ostreopsis* cells attach on benthic substrates, they can interact with its surrounding community and notably with meiobenthic organisms. Indeed, these benthic organisms live in close contact with *Ostreopsis* cells and could potentially feed on this toxic dinoflagellate. To study the impact of *O. cf. ovata* on benthic organisms, bioassays are commonly used (Table 3). For instance, the benthic copepod *Tigriopus fulvus* and the amphipod *Corophium insidiosum* are both sensitive organisms since their *Ostreopsis* median lethal concentration (LC50) values after 96 hours of exposure are, respectively, 10.11 et 11.81 cell·mL−1 (Prato et al., 2011). Other organisms, such as the harpacticoid copepod *Sarsamphiascus cf. propinquus*, co-occurring with *O. cf. ovata* in summer, has been demonstrated as very resistant to toxins produced by *O. cf. ovata* (Pavaux et al., 2019) with LC50 (48h) values higher than 20,000 cells·mL−1 so. These numbers are at least 250 times higher than those reported for another benthic copepod, *Tigriopus fulvus* (Faimali et al., 2012) suggesting potential acclimation phenomenon to the presence of *Ostreopsis*. However, these studies are difficult to compare since they used different life stages of the targeted organism, different parameters to determine the sensitivity, and different determination of LC50 values, e.g., at 24, 48, or 96 h, the experimental conditions (e.g., temperature) during LC50 determination. As an example, Faimali et al. (2012) showed that toxicity increased with the temperature of culture: LC50 values of the barnacle *Amphibalanus amphitrite* were 1416.95 and 192.26 at 20 and 25°C, respectively. This overall situation suggests the need of standardizing the methods to test the toxicity of *Ostreopsis* species on benthic organisms.

Additionally, a reprotoxic (negative effect on reproduction) effect of *O. cf. ovata* has been suggested by the significant decrease of the number of copepod nauplii described in the in situ study of Guidi-Guilvard et al. (2012) and confirmed by laboratory experiments by Pavaux et al. (2019). The two studies showed a decrease of fecundity and fertility ratios of the benthic copepod *Sarsamphiascus cf. propinquus*. These reprotoxic effects lead to changes in benthic communities by decreasing the number of nauplii.

By forming aggregates that cover macroalgae, *Ostreopsis* cells are also ingested by macroherbivores such as sea urchins or herbivorous fish. Using biological assays (HNA) or toxin analysis by HPLC-MS, several studies have already quantified PLTX and analogs of these two groups in these herbivorous (Milandri et al., 2010; Amzil et al., 2012; Biré et al., 2013, 2015; Brissard et al., 2014). *Paracentrotus lividus* (an edible and herbivorous sea urchin) and *Sarpa salpa* (an herbivorous fish) accumulated high concentrations of PLTX-group toxins (respectively, 423 and 361 µg·kg−1), making these organisms good sentinel species for the presence of PLTXs in marine organisms (Biré et al., 2015). Bioaccumulation of toxins seems to be organ-dependent: no toxins were found in sea urchin gonads although it reached up to 423 µg eq PLTX·kg−1 in the digestive tract (Brissard et al., 2014). However, Bauder et al. (2001) described different affinity of diarrheic shellfish toxins (DST) produced by *Prorocentrum lima* for tissues leading to a quicker detoxification in the gonads. This low affinity of toxins for tissues except for viscera, could explain the absence of toxins in sea urchin gonads documented in the work of Biré et al. (2015, 2013). Neves et al. (2018) also reported that the ingestion of *O. cf. ovata* cells by adult sea urchins had an impact on their offspring (dead and abnormal larvae, arrest of embryonic development – Table 3). These development anomalies persist at least 8 months after the exposition to *O. cf. ovata* and seems to be transmitted from the female gonads with the involvement of the nitric oxide pathway since the transcription of several genes directly or indirectly modulated by nitric oxide showed transcription variations (Neves et al., 2018; Tibiriçá et al., 2019).

### Interactions of fauna with planktonic *Ostreopsis* cells

During its planktonic phase, *Ostreopsis* cf. *ovata* could reach cell concentrations in the range of 10^5–10^6 cell·L−1 (Mangialajo et al., 2011) and thus affect planktonic organisms but also bivalves and other benthic filter-feeders. Some monitoring of toxin concentration in bivalves (*Mytilus galloprovincialis*) varied from 28 to 228 µg·kg−1 (Table 3). Quantities of toxins found in other filter-feeders such as the mussel *Perna canaliculus* or the bivalve *Arca noae* were well below and frequently found only in trace amounts (Rhodes et al., 2000, 2002) probably due to the use of biological assays to quantify...
toxins in these organisms leading to an underestimation of toxin concentration.

Mechanisms of toxicity have been addressed by exploring histological impairments on *Mytilus galloprovincialis* adults (Gorbi et al., 2012, 2013). These studies showed a limited role of oxidative stress and suggested that toxic effects of the compounds produced by *Ostreopsis* species could be rather mediated by immune response than oxidative stress. Finally, toxins produced by *Ostreopsis cf. ovata* had a strong impact on the planktonic ephyrae larvae of the jellyfish *Aurelia* sp. (Giussani et al., 2016) and embryos and eggs of the sea urchin *Paracentrotus lividus* (Caroppo and Pagliara, 2011; Pagliara and Caroppo, 2012; Migliaccio et al., 2016). The sea urchin *Lytechinus variegatus* also showed reduced fertilization success and arrest ofembryonic development at the gastrula stage when exposed to *Ostreopsis cf. ovata* cells (Neves et al., 2018). In summary, planktonic *Ostreopsis* cells can affect filter feeders but also meroplanktonic larvae.

**Interactions of fauna with sea-surface *Ostreopsis* cells**

Toxins quantified both in the digestive tract and in the whole flesh of the mullet *Mugil cephalus* were high and reached to 392.5 µg·kg⁻¹ of flesh fresh which can be explained by the grazing behavior of this animal that feeds directly on *Ostreopsis cf. ovata* cells aggregates on the water surface (Biré et al., 2013). Other organism from the mediterrial coastal area such as the limpets *Patella* spp. are also exposed to surface cells of *O. cf. ovata* and up to now, studies have mainly focused on toxin quantification in the whole flesh that reached up to 12.7 µg·kg⁻¹, well below the threshold value established by the EFSA (Efsa Panel on Contaminants in the Food Chain, 2009). The study of Blanfuné et al. (2012) reported a significant decrease of *Patella* spp. densities during the 2008 *O. cf. ovata* bloom in Genoa, attributed to the poisoning of the shellfish by ingestion of *O. cf. ovata* cells.

**Indirect Interactions Between *Ostreopsis* and Marine Fauna**

Toxin concentrations found in carnivorous and omnivorous organisms (Table 4) suggested transfer and bioaccumulation of toxins within the trophic web (Milandri et al., 2010; Faimali et al., 2012; Pezzolesi et al., 2012; Biré et al., 2013, 2015; Giussani et al., 2016). Toxins quantified in both the crab *Eriphia verrucosa* (carnivorous) and the gastropod *Stramonita haemastoma* (carnivorous) accounted for up to 58.6 and 26.4 µg·kg⁻¹ (Fresh Weight) respectively. Octopuses also accumulated more than 446 µg·kg⁻¹ (Milandri et al., 2010) suggesting a bioaccumulation of toxins among the trophic web which might have played a role in the ecosystem suffering with stranding of octopuses. However, mussels and other predators such as copepods have already been demonstrated as a vector for toxin transfer through both benthic and planktonic food webs (Furlan et al., 2013; Boisnoir et al., 2020).

Other studies reported a strong sensitivity of *Dicentrarchus labrax* fish juveniles to *O. cf. ovata* raising the question of the impact on the structure of marine ecosystems (Faimali et al., 2012; Pezzolesi et al., 2012; Giussani et al., 2016). Indeed, as mentioned by the authors, these fish are unable to eat *Ostreopsis* cells, the observed toxicity was exclusively due to contact with *Ostreopsis* cells.

**OVERALL PERSPECTIVE OF THE IMPACTS OF *Ostreopsis* SPECIES ON ECOSYSTEM STRUCTURE AND FUNCTIONING**

The studies described above allow to extract a general vision of the chemical ecology of *Ostreopsis* and the gaps in knowledge that are concentrated on three main levels: 1) the ecotoxic impacts, 2) the importance of the mucus in the biological interactions and 3) the regulation of the *Ostreopsis* blooms by biologic interactions.

**Ecotoxic Impacts**

The available information shows negative effects of this dinoflagellate on different trophic levels and suggests subsequent negative impacts on the structure of the ecosystems. At the level of primary producers, *Ostreopsis* species seem to have a strong competitive capacity as revealed by the negatively impact on diatoms and other dinoflagellates with which they co-occur, regardless of the exposure pathway (extracellular released compounds or whole living cells) leading to changes in microphytobenthic communities composition and succession. For secondary producers, a strong reptrotoxic effect has also been reported. Herbivorous organisms feeding on *Ostreopsis* species (e.g., the benthic copepod *Sarsamphiascus cf. propinquus*) or organisms feeding on macroalgae supporting *Ostreopsis* populations (e.g., sea urchins *Paracentrotus lividus* or fish *Sarpa salpa*) could accumulate high quantity of toxins without short term lethal effects. Despite several studies reported invertebrate mass mortalities (Shears and Ross, 2009; Totti et al., 2010) research is needed to determine whether they can genuinely be attributed to toxins produced by *Ostreopsis* spp.

Overall, toxin transfer through the food webs poses a risk of seafood poisoning in humans; although not reported in temperate areas yet, some dramatic cases in tropical areas unfortunately occurred. However, the specific mechanisms of *Ostreopsis* toxin transfer through the marine foodwebs are unknown. Toxins could circulate from benthic unicellular algae to herbivorous fish as it has been demonstrated for ciguatoxins (Ledreux et al., 2014). Zooplankton, and more especially copepods or fecal pellets, could also be intermediate vectors, as described for microcystins (Smith and Haney, 2006) nodularin (Lehtiniemi et al., 2002) domoic acid (Baustian et al., 2018) okadaic acid (Maneiro et al., 2000) and paralytic shellfish toxin (Teegarden and Cembella, 1996).

Some organisms could be able to protect themselves from the presence of *Ostreopsis* by different mechanisms such as production of secondary metabolites or adaptation and aclimation process. Detoxification and storage mechanisms have been described in some organisms exposed to certain toxic dinoflagellates (Bricelj and Shumway, 1998; Bauder et al., 2001;
Colin and Dam, 2002; Walid et al., 2010; Jauffrais et al., 2012; García-Lagunas et al., 2013). Analogous studies are lacking in the case of *Ostreopsis* species.

**Importance of the Mucus in *Ostreopsis* Biological Interactions**

The functional role of the mucilaginous matrix produced by *Ostreopsis* sp. is still unknown. Mucus production is considered as an adaptation to benthic life (Parsons et al., 2012; Escalera et al., 2014) and described as a complex structure composed by a network of long fibers, deriving from trichocysts extruded through thecal pores and by an amorphous matrix of acid polysaccharides (Honsell et al., 2013). Production of mucilaginous matrix is common in benthic dinoflagellates (MacKenzie et al., 2002) and plays a role in cellular adhesion to surfaces with the formation of a transparent film embedding many cells, providing a clear example of ecosystem engineering (Escalera et al., 2014). Its role in defense against grazers, in increasing buoyancy and metabolic self-regulation has been investigated in other microalgae (Reynolds, 2007). The role of the mucilaginous matrix as a method of defense against grazers or to capture larger organisms has also been documented for other heterotrophic (*G. ovata*; Kiørboe and Titelman, 1998) and mixotrophic dinoflagellates (*A. pseudogonyaulax*; Blossom et al., 2012).

For *Ostreopsis*, the role of the mucilage in species competition and predation has been also argued. The toxicity of the mucus was first documented by Giussani et al. (2015) with experiments of *O. cf. ovata* on *Artemia salina* and supported by images obtained by atomic force microscopy. More recently, Ternon et al. (2018) observed a toxic effect of *O. cf. ovata* on co-occurring diatom mediated by direct contact between cells. Based on this, the study suggested that the mucus could facilitate toxins storage, avoiding their dilution in the environment and thus contributing to the *Ostreopsis* competition capacity.

The role of this mucilaginous matrix in mixotrophic behavior was also suggested (Barone, 2007). Mixotrophy is a common way of nutrition in harmful algal species (Burkholder et al., 2008) and several studies have investigated this nutritional capacity in *Ostreopsis*, although not completely demonstrated yet. Faust and Morton (1995) observed *Ostreopsis labens* cells with large ingested particles within the cytoplasm. In 2012, Fraga et al. (2012) linked the presence of reddish round inclusions inside *Ostreopsis* cells (detected through light microscopy) to the mixotrophic behavior. Almada et al. (2017) showed evidence of phagotrophy using LysoSensor staining even if the prey inside the cells were not discernable. More recently, using molecular approaches, Lee and Park (2018) defined the red bodies as digestive vacuoles containing ingested red macroalgae (Class Florideophyceae).

The mucilage, rich in organic carbohydrates, appears also as biologically colonizable surface for the growth of some bacteria (Vanucci et al., 2016; Guidi et al., 2018) including *Vibrio* (Bellés-Garavela et al., 2016). This positive association for pathogenic bacteria increases the risk of health impacts posed by *Ostreopsis* to human populations.

**Regulation of *Ostreopsis* Bloom by Biotic Interactions**

There is a growing awareness that HABs may have been increasing globally in the last 40 years and may continue to increase under the fast-coming scenarios of global warming (Wells et al., 2019). HABs have strong impacts on human health and economy (Hoagland et al., 2002; Larkin and Adams, 2007; Adams et al., 2018). Hence the necessity to better understand factors and mechanisms favoring bloom formation and maintenance which is a complex result of biotic factors combined with chemical (salinity, nutrients,...) and physical processes (currents, upwelling, freshwater runoff,...) and, in some cases, associated to anthropogenic forcings including eutrophication and alteration of coastal habitats (Sellner et al., 2003). This review highlights the number, the importance and the complexity of interactions between *Ostreopsis* and its environment. The question is whether or not these biotic interactions could also regulate *Ostreopsis* blooms initiation, maintenance and decline. Many harmful bloom-forming species produce toxins whose adaptive significance is still unclear. Toxins could constitute a main chemical signal or cue, in the case of HAB species. It has been suggested that toxins confer some advantages in reaching very high cell densities (Anderson et al., 1998) by providing a defense against pathogens, grazers and parasites. This hypothesis is supported by the study of Selander et al. (2006) describing that toxin-producing species are less preferred by predators and that predator presence induces toxin production. In the case of *O. cf. ovata*, it has been noted that benthic copepods are able to actively select non-toxic diatoms in a microalgae mixture (Pavaux et al., 2019). Here, the information concerning the role of allelopathy, predation and parasitism in the *Ostreopsis* blooms dynamics is discussed.

It has been suggested that allelopathy could favor HABs by suppressing the growth of competitors (Smayda, 1997). Allelopathy mechanisms could include oxidative damage, loss of competitor mobility, inhibition of photosynthesis, inhibition of enzymes and membrane damage (Legrand et al., 2003). The production of allelochemicals could explain in particular the success of *Karenia brevis* blooms (Kubanek et al., 2005; Prince et al., 2008) but demonstrating such mechanisms in the field is difficult (Prince et al., 2008). Meta-analysis conducted by Jonsson et al. (2009) indicate that the significant effect of allelopathic mechanisms would only occur at high cell densities since at the beginning of a bloom, cell abundances are too low to concentrate enough infochemicals. Toxins could play a role as phytochemicals. However, Tillmann and John (2002) showed that toxins produced by *Alexandrium* spp. are not involved in allelochemical defense mechanism. In the case of *Ostreopsis*, Ternon et al. (2018) demonstrated the importance of the toxins in negative effects on diatoms (mediated by the mucus) and the potential involvement in the chemical control by *O. cf. ovata* on its competitor. These results are promising, and suggest that future studies in this line can contribute to clarify the conflicting about the role of the toxins as allelochemicals. As in many other situations, the response may be species specific.
The balance between growth- and loss-promoting factors determine the abundance of harmful species. Predation by zooplankton is the largest mortality factor for phytoplankton (Calbet and Landry, 2004). Factors such as size, shape, nutritional value are traditionally suggested to explain predation pressure. However, the production of chemical deterrents can also affect predation pressure. The few conducted studies on predation of Ostreopsis by meiofauna have shown low ingestion rate of this dinoflagellate by benthic copepods (Pavaux et al., 2019) while heterotrophic ciliates seem to be active predators of O. cf. ovata (Matsuyama et al., 1999). Thus, predation pressure mediated by heterotrophic ciliates on Ostreopsis could potentially participate in population decline, already demonstrated by Solé et al. (2006) on other HABs. However, contradictory results have been documented by the theoretical study of Mitra and Flynn (2006) describing predatory activation as a factor promoting HAB. Overall, more studies need to be conducted to clarify the role of predation as a control mechanism of Ostreopsis blooms.

Eukaryotic microparasites infecting bloom-forming dinoflagellates, belonging to Parvilucifera (Perkinszoa) and Amoebophrya (Synindiales) genus, have been reported in the literature (Park et al., 2004). In the case of Ostreopsis, different strains have been proved sensitive to the infection by Parvilucifera sinarae (Garcés et al., 2013a,b) but the role during natural blooms has not been described yet.

PERSPECTIVES AND NEW TOOLS TO STUDY MCE OF Oestreopsis

This review summarized how blooms of Ostreopsis, that may last a relatively short time (4-6 weeks in the case of O. cf. ovata blooms in the Ligurian Sea, Mediterranean Sea), affect the different components of the marine ecosystems and this their structure and functioning. It can be envisaged that, in a context of global change leading to an intensification of Ostreopsis blooms, these effects could increase, uprisin the ecosystem imbalances already posed by anthropogenic pressures in the coastal zone. A key open question is whether the ecosystems will adapt to increased Ostreopsis blooms, for instance through developing detoxification strategies and outcompetition by other microalgae. It is also important to understand the factors conducting to Ostreopsis blooms in order to minimize their occurrence and protect the environment and human health as much as possible.

To address these open questions and objectives the next studies should combine the technical approaches indicated next.

Harmonization of Ostreopsis Studies Including Ecotoxic Bio-Assays

Most field and experimental studies have been conducted on Oestreopsis cf. ovata, in part because its wide presence and recurrent blooms in the Mediterranean. However, the impacts of other Oestreopsis species need to be investigated, specially given their detection and blooms in many other areas, some of them pristine and that could constitute observatories of the climate change (Fernández-Zabala et al., 2019).

In order to better estimate the influence of Oestreopsis on marine ecosystems, experiments should be run to clarify the effect of the direct and/or indirect contact of Oestreopsis on different organisms, using realistic (i.e., naturally occurring) Oestreopsis cell concentrations, and following ecologically realistic tests are key. To understand the role of the mucus produced by Oestreopsis, it is necessary to efficiently separate it from the cells.

Several studies have documented the extreme sensitivity of Artemia franciscana and A. salina when exposed to Oestreopsis cells, cell filtrates, and toxin extracts, highlighting the relevance of Artemia as a model organism for ecotoxic studies (Table 5). In order to compare the toxicity of strains, cell filtrates and toxin extracts, a harmonized protocol is required in terms of temperature used, measured response parameters and units (i.e., median lethal concentration - LC50 - at 24/48/96 hours, lethal time -LT50 or Effect Concentration - EC50 expressed in mg·mL⁻¹ or cells·mL⁻¹) and selected larval stages. Indeed, Faimali et al. (2012) demonstrated strong differences of toxicity of Oestreopsis ovata strains cultivated at 20 or 25°C with a higher toxicity of strains maintained at 25°C. This bioassay presents a wide range of advantages compared to other bioassays such as the Mouse Bioassay (MBA) in terms of ethics, cost, time and simplicity. However, the responses of Artemia sp. exposed to toxins produced by Oestreopsis sp. are not specific since our studies (Pavaux et al., 2020). The Artemia bioassay can be a pre-screening test of Oestreopsis strains toxicity for OVTX analogues and other toxic metabolites produced by these dinoflagellates. Indeed, the production of other toxic compounds that do not belong to the OVTX family was suggested by Ternon et al. (2018) and confirmed by Pavaux et al. (2020) because toxicity on Artemia was caused by Oestreopsis cf. ovata’s fractions free of OVTXs. This highlights the importance of this bioassay for a pre-screening of toxic fractions before conducting the most costly and complex toxin analysis by HPLC-MS/MS. Most of the time, the quantification of toxins produced by Oestreopsis sp. is done by targeted analysis, i.e., by the quantification of ions belonging to the OVTXs family (three transitions per analog are monitored for OVTX-a to -f and isoPLTX: [M+2H]²⁺, [M+2H-H₂O]²⁺ and [M+3H-H₂O]³⁺; Brissard et al., 2014). Thanks to this bioassay, it would be more interesting to do untargeted analysis on fragments previously shown as toxic by the bioassay.

Use of Metabolomics and Other «Omics» Tools

The development of “omics” techniques, which allows the simultaneous and large-scale study of genes, transcripts, proteins and metabolites without knowing a priori their biological functions, also constitute an important tool for the study of new toxic compounds. In the field of MCE, metabolomics approaches are the most commonly used (Prince and Pohnert, 2010; Kuhlisch and Pohnert, 2015; Poulin and Pohnert, 2019). This recent technique allows the analysis of a wide range of low molecular weight metabolites of a cell, an organism in a given context (Fiehn et al., 2007). One of the distinctive features of the metabolomics approach is that, due to strong diversity of physico-chemical properties of molecules produced by an
organism, it is today impossible to describe exhaustively the metabolome with the present analytic techniques. A method currently used in metabolomics combines LC-MS/MS and molecular networking and it is employed as a rapid analytical method to detect toxins (Watrous et al., 2012; Yang et al., 2013; Allard et al., 2016; Quin et al., 2017). Mass spectrometry-based molecular networking relies on the principle that structurally similar molecules share similar MS/MS fragmentation patterns, thus giving a visual representation of molecular relatedness of compounds in a sample (Watrous et al., 2012). For instance, this technique allowed the quantitative identification of the lipopeptide malyngamide C by different strains of cyanobacteria (Winnikoff et al., 2014). More and more studies are applying metabolomic approaches to investigate biotic interactions between HAB species and their environment (Giacometti et al., 2013; Poulson-Ellestad et al., 2014; Poulin et al., 2018). The review of McLean (2013) on “omics” tools demonstrates the relevance of genomics, transcriptomics and proteomics approaches to

| TABLE 5 | Artemia bio-assay for Ostreopsis species toxicity. |
|-----------------------------------------------|
| **Species/Strain** | **Organisms** | **Stage** | **Effects** | **References** |
|--------------------|--------------|-----------|-------------|----------------|
| Ostreopsis ovata   | Artemia salina (Linnaeus, 1758) | II-III stage | LC<sub>50</sub>-24h = 12 cells.mL<sup>-1</sup> | Faimali et al., 2012 |
| isolated by A. Penna | | nauplii | LC<sub>50</sub>-24h = 4 cells.mL<sup>-1</sup> | |
| Ostreopsis cf. ovate | Artemia sp. | Nauplii | EC<sub>50</sub> calculated but not expressed | Guerrini et al., 2010 |
| isolated from Lazio & Marche | | | | |
| Ostreopsis cf. ovate | Artemia salina (Linnaeus, 1758) | Nauplii | LC<sub>50</sub>-24h = 15 cells.mL<sup>-1</sup> | Giussani et al., 2016 |
| CBA29-2012 | | | | |
| Ostreopsis cf. ovate | Artemia salina (Linnaeus, 1758) | II – III stages | LC<sub>50</sub>-24h = 24.83 / 16.67 / <4 cells.mL<sup>-1</sup> | Giussani et al., 2015 |
| Ostreopsis cf. ovate | Artemia salina (Linnaeus, 1758) | Nauplii | Immobility EC<sub>50</sub>-24h = < 4 cells.mL<sup>-1</sup> | Giussani et al., 2016 |
| UNR-05 | | | | |
| Ostreopsis cf. ovate (cell lysate) | Artemia salina (Linnaeus, 1758) | Adults | LT<sub>50</sub>-24h = (200 cells.mL<sup>-1</sup>) = 3h | Neves et al., 2017 |
| Natural samples (Ionian Sea) | | | | |
| Ostreopsis cf. ovate Strain OCANO601 (Marche Region) | Artemia sp. | Nauplii | LC<sub>50</sub>-24h = 8 cells.mL<sup>-1</sup> | Pezzolesi et al., 2012 |
| | | (live cells) | 5 ± 115 pg.mL<sup>-1</sup> ± 72 | |
| | | (lysed cells) | 96 cells.mL<sup>-1</sup> ± 1376 pg.mL<sup>-1</sup> ± 86 | |
| | | (extract) | 80 cells.mL<sup>-1</sup> ± 1146 pg.mL<sup>-1</sup> ± 272 | |
| Ostreopsis cf. ovate | Artemia franciscana (Kellogg, 1906) | II – III stages | LC<sub>50</sub>-24h = 1.63 cell.mL<sup>-1</sup> | Prato et al., 2011 |
| Natural samples Gulf of Taranto | | larvae | | |
| Ostreopsis siamensis | Artemia salina (Linnaeus, 1758) | | LT<sub>50</sub> (250 cells.mL<sup>-1</sup>) = 24h | Rhodes et al., 2000 |
| CAWD73/74/75/96 | | | Time until Morbidity<sub>50</sub> (250 cells.mL<sup>-1</sup>) = 4h | |
| Ostreopsis ovata | Artemia salina (Linnaeus, 1758) | | Correlation (p < 1%) between O. cf. ovata concentration and death of A. salina | Simoni et al., 2003 |
| Mediterranean Sea | | | | |
| Ostreopsis ovata | Artemia salina (Linnaeus, 1758) | | Correlation between A. salina mortality after 24 h and the number of O. ovata cells | Vale and Ares, 2007; Ramos and Vasconcelos, 2010 |
| Mediterranean Sea | | | | |
| Ostreopsis cf. ovate (MCCV 054/055) | Artemia franciscana (Kellogg, 1906) | II – III stages | LC<sub>50</sub>-24h (MCCV 054) = 81.96 ± 63.3 cells.mL<sup>-1</sup> | Pavaux et al., 2020. |
| Mediterranean Sea | | larvae | LC<sub>50</sub>-24h (MCCV 055) = 0.25 ± 0.90 cells.mL<sup>-1</sup> | |
| | | | LC<sub>50</sub>-24h (MCCV 057) = 0.0012 ± 0.00033 cells.mL<sup>-1</sup> | |
| | | | LC<sub>50</sub>-24h (MCCV 058) = 0.023 ± 0.039 cells.mL<sup>-1</sup> | |
| | | | LC<sub>50</sub>-24h (Dissolved OVTXs) = 5.96 ± 2.12 cells.mL<sup>-1</sup> | |
| | | | LC<sub>50</sub>-24h (Dissolved PLTX) = 48.42 ± 14.23 cells.mL<sup>-1</sup> | |

<sup>LC<sub>50</sub></sup>: Median Lethal Concentration; <sup>LT<sub>50</sub></sup>: Median lethal time.
advance our understanding on the ecology of HABs. These techniques could give insights in metabolic and regulatory pathways involved in toxins and other secondary metabolites production and the mechanisms of action of these metabolites in the target organisms. Proteomic and metabolomics coupled-analyses lead to a better understanding of allelopathy interactions between the HAB planktonic dinoflagellate *Karenia brevis* and co-occurring species (Poulson-Ellestad et al., 2014) and open a positive perspective to be applied to *Ostreopsis* spp. Indeed, it has been applied for the first time to *Ostreopsis cf. ovata* by Ternon et al. (2018). Using notably untargeted metabolomics approach, this study reported the production of organic compounds not linked to OVTXs family, underlining the urgent need to characterize *Ostreopsis* metabolome.

**Isolation and Toxicity Evaluation of the Different PLTX Analogs**

To date, only pure PLTX standard is commercialized and no OVTX standard is available, which restricts our knowledge on bioactivity and structure of PLTX analogs. Indeed, these studies on *Ostreopsis* toxins need large amounts of pure toxin standards. Poli et al. (2018) have reported differences of toxicity between PLTX and some of its analogs (42-OH-PLTX and OVTXa) by exposing rats to these toxins trough intraperitoneal routes and aerosol exposures and confirmed results already published by others colleagues (Tubaro et al., 2011; Ciminiello et al., 2013). noted huge differences of toxicity between OVTX a and PLTX: OVTX-a is 10 to 100 times less potent than the other but data obtained by Poli et al. (2018) showed only minimal differences. Such differences could explain the difficulties to compare toxin analogs concentrations from NW Mediterranean and Adriatic strains.

**CONCLUSION**

This review highlights the complexity of the interactions between *Ostreopsis* and its environment, summarized in Figure 5.

Some potential avenues for future research on the interactions between *Ostreopsis* and its environment consist on:

- Increasing the research on all *Ostreopsis* species; so far 90% of studies documented in this review have been focused on *Ostreopsis cf. ovata*. This will allow to compare the potential harmful impacts on the different marine environments.
- Clarifying the role of the known toxins and other secondary metabolites in the chemical interactions of *Ostreopsis* and other organisms (predator deterrence, allelopathy, competition, etc.).
- Understand the factors affecting toxin production and clarify the toxicity of all *Ostreopsis* species (Table 1).
- Identifying the effects of ecologically realistic doses of toxic metabolites on the growth, reproduction and survival of the marine organisms exposed to *Ostreopsis* blooms.
- Clarifying the role of the mucus on the chemical interactions, as trap for preys, physical defence against predators, storage of toxins (or other metabolites), etc.
- Exploring the defence mechanisms of organisms exposed to *Ostreopsis* blooms, e.g., storage or detoxification processes, adaptation or acclimation processes.
- Elucidating the potential mechanism of toxic compounds transfer through the food web up to top predators and humans as already described for other HABs such as *Gambierdiscus* spp.
- Investigating the mechanisms involved in toxin aerosolization causing respiratory irritations in areas affected by *Ostreopsis* blooms.

Innovative approaches can contribute to address these questions and increase the knowledge of *Ostreopsis* spp. chemical interactions with its environment with potential consequences on human health.

**AUTHOR CONTRIBUTIONS**

A-SP wrote and prepared the original draft. EB and RL wrote, reviewed, and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

**FUNDING**

This work was supported by the French ANR project (OCEAN 15: *Ostreopsis* Chemical Ecology and Allelopathy Network; project ANR-15-CE35-0002) and the project GoCliME [which is part of ERA4CS, an ERA-NET initiated by JPI Climate, and funded by EPA (IE), ANR (FR), BMBF (DE), UFESCDI (RO), RCN (NO), and FORMAS (SE), with co-funding by the European, Union; Grant 6904462], endorsed to the international programme of IOC UNESCO and SCOR GlobalHAB (www.globalhab.info). French authors are members of the French National GdR PhycoTox.

**ACKNOWLEDGMENTS**

We thank Dr. Rafael Abós-Herrándiz for providing information for Table 1.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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