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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; Poulson 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 has 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.

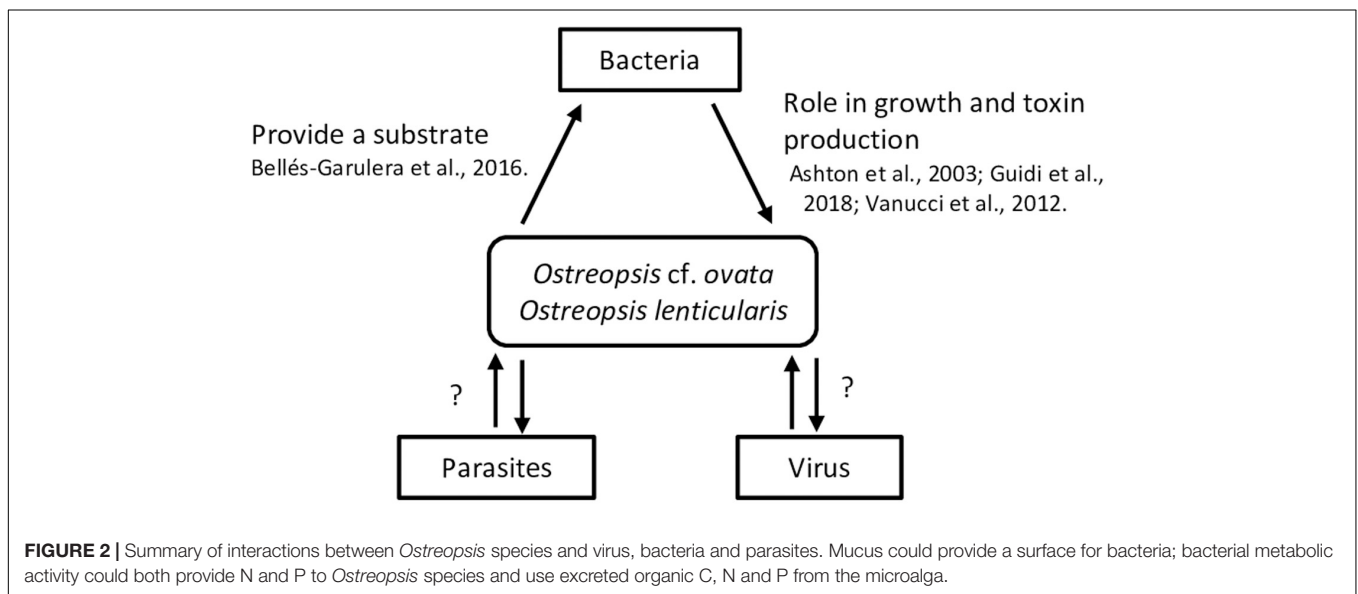
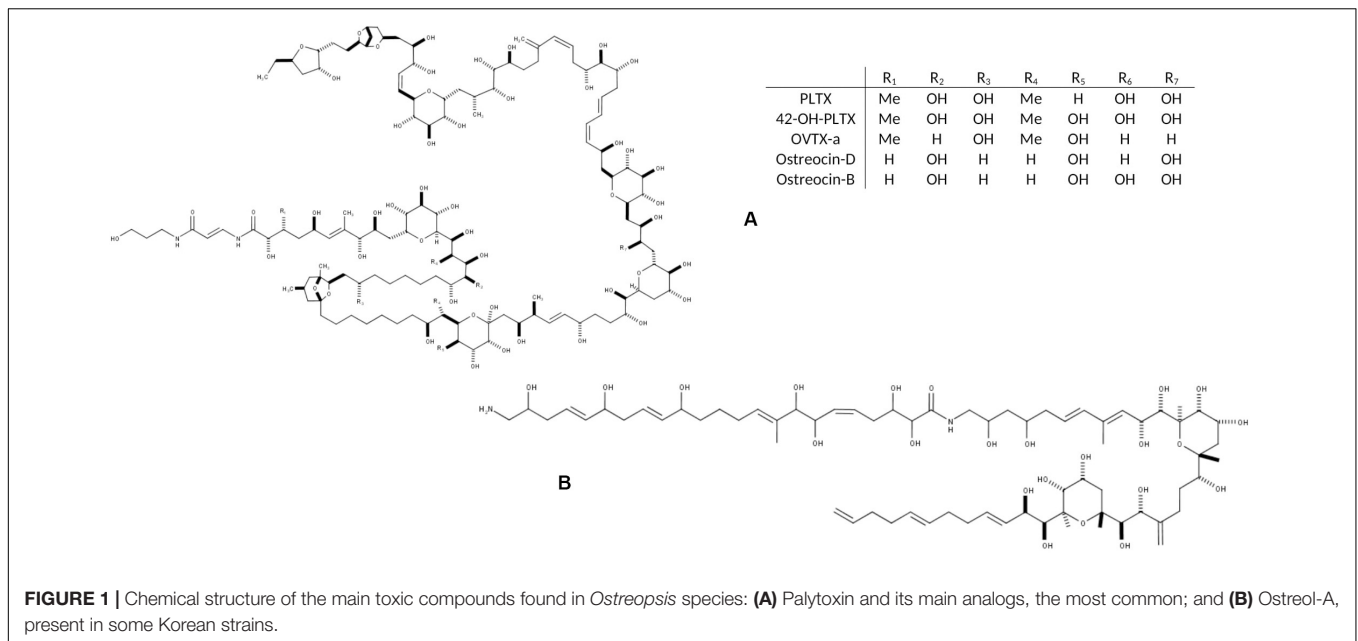
This work aims to review the present knowledge on the MCE concerning the biology and dynamics of blooms of the

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.



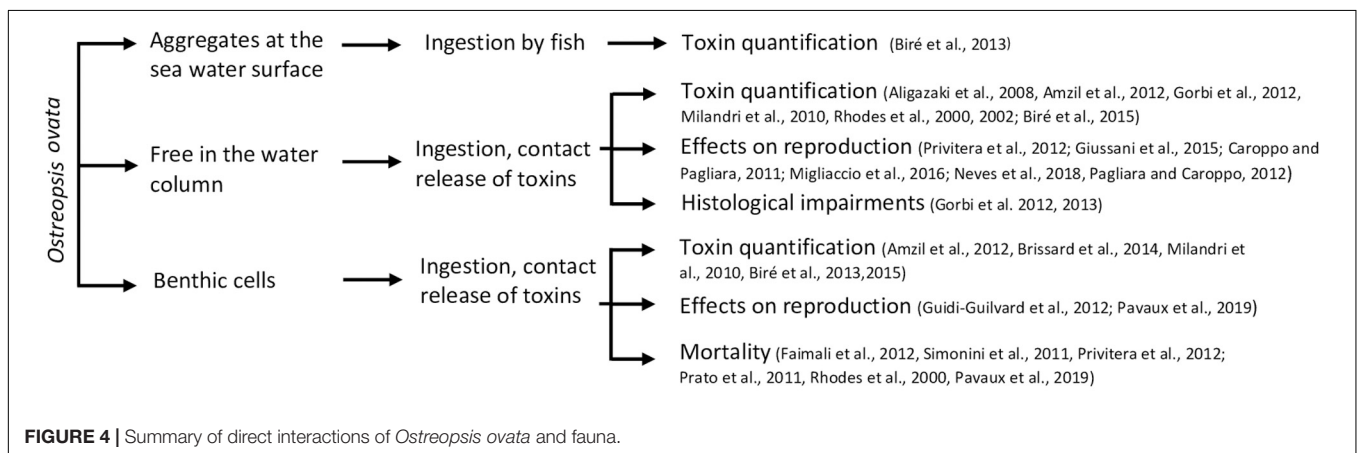
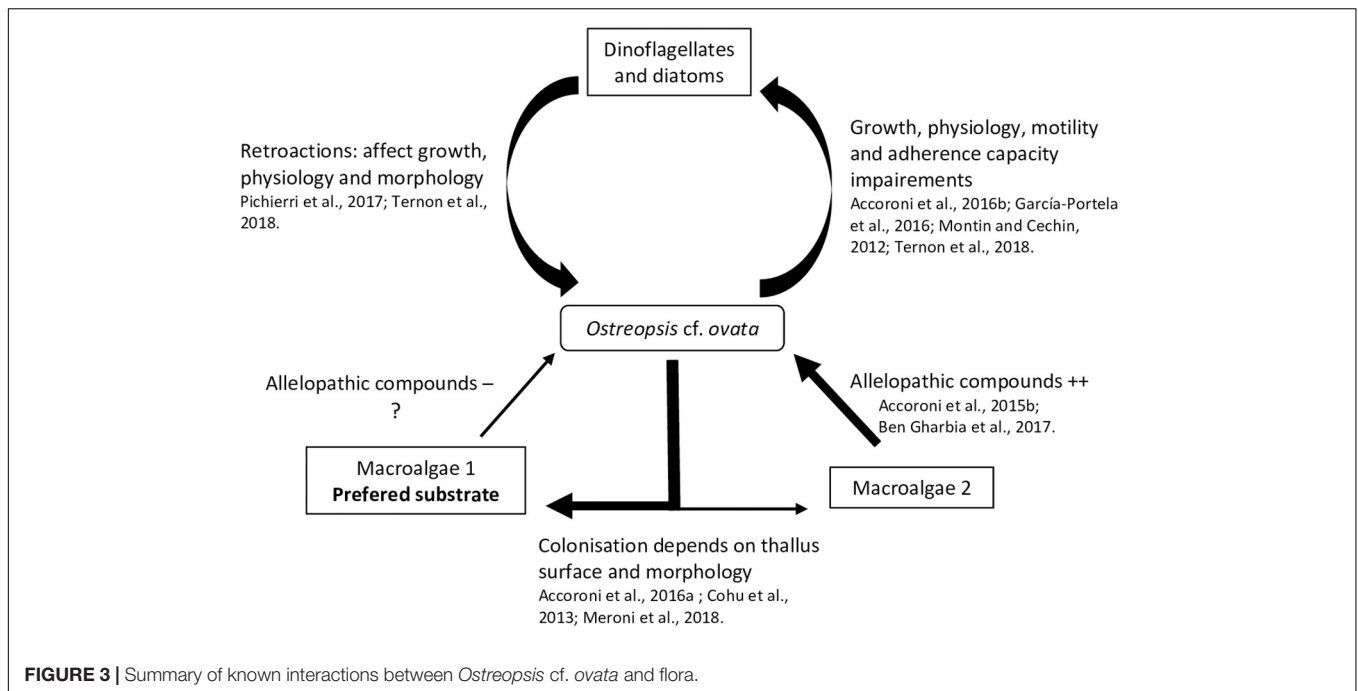
With the most recent progresses in chemical analysis, toxin profile could also become a taxonomic criterion.

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

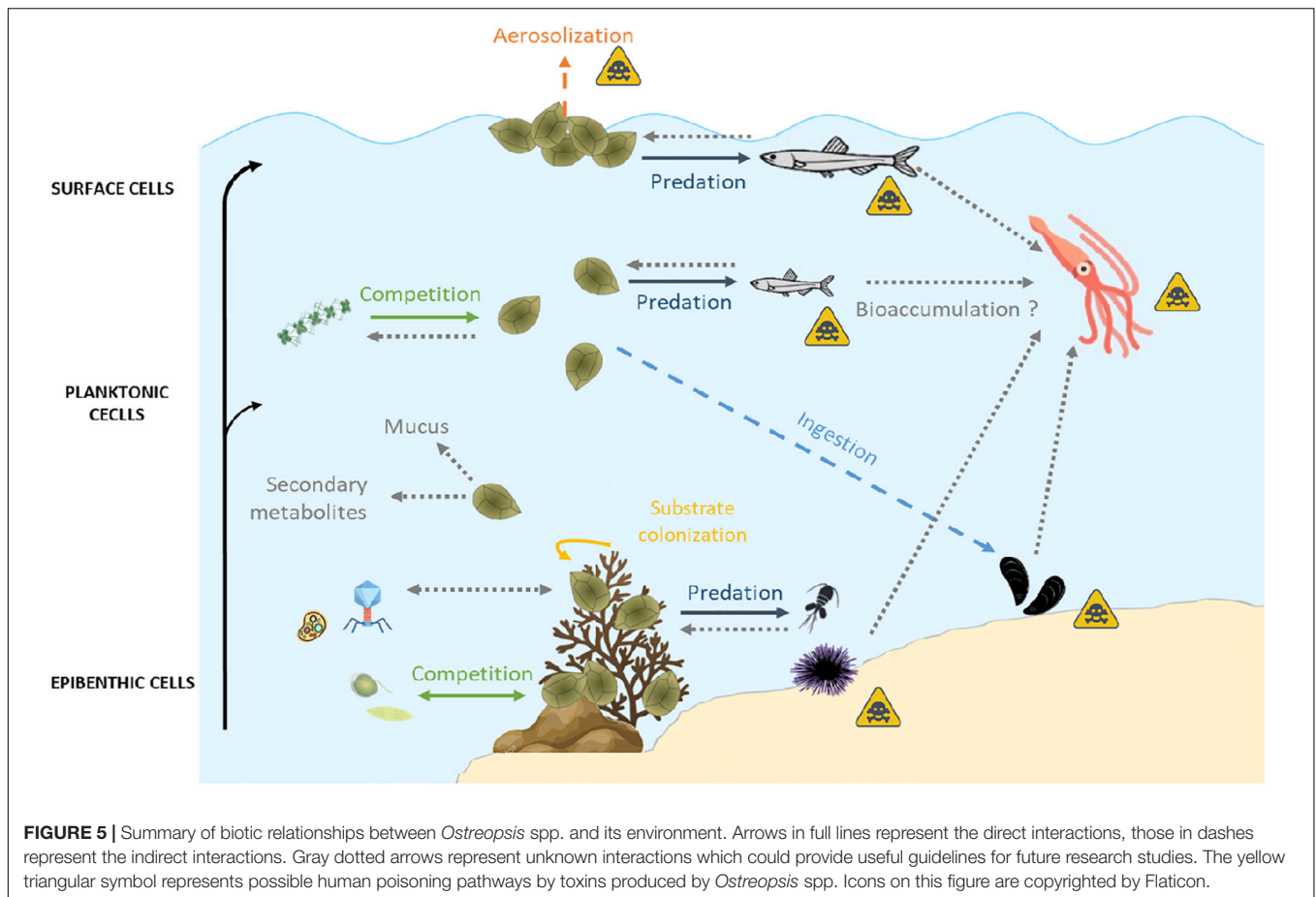
Several species in the *Ostreopsis* genus are considered potentially harmful to humans and other marine organisms due to the



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 Cimminiello 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, Garcia-Altare 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
<i>O. belizeanus</i> (Faust, 1999)	Unknown		Belize, Caribbean Sea	Faust, 1999
<i>O. caribbeanus</i> (Faust, 1999)	Unknown		Puerto Rico, Belize, Caribbean Sea	Faust, 1999
<i>O. fattorussoi</i> (Accoroni et al., 2016a)	isoPLTX C ₁₂₉ H ₂₂₃ O ₅₄ N ₃ (2) Ovatoxin-a C ₁₂₉ H ₂₂₃ N ₃ O ₅₂ (1 & 2) Ovatoxin-d C ₁₂₉ H ₂₂₃ N ₃ O ₅₃ (1 & 2) Ovatoxin-e C ₁₂₉ H ₂₂₃ N ₃ O ₅₃ (1 & 2) Ovatoxin-i C ₁₃₁ H ₂₂₅ O ₅₃ N ₃ (2) Ovatoxin-j1 C ₁₃₁ H ₂₂₅ O ₅₄ N ₃ (2) Ovatoxin-j2 C ₁₃₁ H ₂₂₅ O ₅₄ N ₃ (2) Ovatoxin-k C ₁₃₁ H ₂₂₅ O ₅₅ N ₃ (2)	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-Zabala et al., 2019
<i>O. heptagona</i> (Norris et al., 1985)	Unknown but extracts described as toxic to mice (in Accoroni et al., 2016b)		Knight Key, Florida, Gulf of Mexico	Norris et al., 1985; Rhodes, 2011
<i>O. labens</i> (Faust and Morton, 1995)	Unknown but described as toxic in Rhodes et al. (2002)	Artemia assay Death of 24h old larvae of <i>Artemia</i> in standard assay	Belize, Caribbean Sea, Malaysia, Japan	Faust and Morton, 1995; Rhodes, 2011
<i>O. lenticularis</i> (Fukuyo, 1981). Includes the cryptic species <i>Ostreopsis</i> sp. 5 in Chomérat et al., 2019	No toxic (1) Ostreotoxin 1 (2) Ostreotoxin 3 (2)	N2a analysis: EC ₅₀ (PLTX) = 1191 ± 175 pg.mL ⁻¹ (O ⁻ condition) (1) LC-UV-MS/MS analysis: nd (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-Zabala et al., 2019
<i>O. marinus</i> (Faust, 1999)	Unknown	No pPLTX activity by HA using sheep erythrocytes	Caribbean, Indian Ocean, Vietnam	Faust, 1999; Carnicer et al., 2015a
<i>O. mascarenensis</i> (Quod, 1994)	Mascarenotoxin–A C ₁₂₇ H ₂₂₁ N ₃ O ₅₀ Mascarenotoxin–B nd	HPLC–ESI–MS/MS: 0.04 pg eq.PLTX/cell Mouse bioassay: LD ₅₀ = 900 μg.kg ⁻¹ (intraperitoneal injection)	Rodrigues and Reunion Islands, Indian Ocean	Lenoir et al., 2004; Ramos and Vasconcelos, 2010; Chomérat et al., 2020
<i>O. ovata</i> (Fukuyo, 1981)	pPLTX C ₁₂₉ H ₂₂₃ N ₃ O ₅₄ (2) Ovatoxin-a C ₁₂₉ H ₂₂₃ N ₃ O ₅₂ (2) Ovatoxin-b C ₁₃₁ H ₂₂₇ N ₃ O ₅₃ (2) Ovatoxin-c C ₁₃₁ H ₂₂₇ N ₃ O ₅₄ (2) Ovatoxin-d C ₁₂₉ H ₂₂₃ N ₃ O ₅₃ (2) Ovatoxin-e C ₁₂₉ H ₂₂₃ N ₃ O ₅₃ (2) Ovatoxin-f C ₁₃₁ H ₂₂₇ N ₃ O ₅₂ (1)	LC–HRMS pPLTX: 0.02 to 3.6 pg eq. PLTX/cell OVTX a: 1.26 to 42.2 pg eq. PLTX/cell OVTX b: 9 to 9.4 pg eq. PLTX/cell OVTX c: 1.6 to 2 pg eq. PLTX/cell OVTX d+e: 4 pg eq. PLTX/cel Hemolytic test 1.93 to 18.1 ng SnE.cell ⁻¹ (3)	Australia, Belize, Brazil, China, Cook Islands, Caribbean, French Polynesia, Hawaii, Indian Ocean, Japan, Malaysia, Mediterranean, New Caledonia, New Zealand, Puerto Rico, Reunion, Rodrigues Island, Venezuela, Vietnam	Penna et al., 2005; Ciminiello et al., 2008, 2006, 2011, 2012; Guerrini et al., 2010; Granéli et al., 2011; Rhodes, 2011

(Continued)

TABLE 1 | Continued

Species	Toxins/Formula	Quantification	Distribution	References
<i>O. cf. ovata</i>	pPLTX C ₁₂₉ H ₂₂₃ N ₃ O ₅₄ Ovatoin-a C ₁₂₉ H ₂₂₃ N ₃ O ₅₂ Ovatoin-b C ₁₃₁ H ₂₂₇ N ₃ O ₅₃ Ovatoin-c C ₁₃₁ H ₂₂₇ N ₃ O ₅₄ Ovatoin-d C ₁₂₉ H ₂₂₃ N ₃ O ₅₃ Ovatoin-e C ₁₂₉ H ₂₂₃ N ₃ O ₅₃ Ovatoin-f C ₁₃₁ H ₂₂₇ N ₃ O ₅₂ (2) Ovatoin-g C ₁₂₉ H ₂₂₃ N ₃ O ₅₁ (3) Ovatoin-h C ₁₂₉ H ₂₂₅ N ₃ O ₅₁ (1) Ostreol A C ₆₇ H ₁₁₂ N ₂ O ₂₃ (4) Mascarenotoxin-a C ₁₂₇ H ₂₂₁ N ₃ O ₅₀ (5) Mascarenotoxin-c C ₁₂₉ H ₂₂₁ N ₃ O ₅₁ (5)	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 f: nd - 17 pg eq. PLTX/cell OVTX g: 0.35 to 24.8 pg eq. PLTX/cell	Australia, Brazil, China, Canary Islands, Caribbean, Egypt, Hawaii, Indonesia, Japan, Korea, Malaysia, New Caledonia, New Zealand, Madeira, Mediterranean Sea, Thailand, South West Indian Ocean, Vietnam	Rossi et al., 2010; David et al., 2013; Honsell 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-Altare et al., 2015; Giussani et al., 2015; Ben et al., 2017
<i>O. rhodesae</i> (Verma et al., 2016)	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
<i>O. siamensis</i> (Schmidt, 1901)	Ostreocin-A C ₁₂₇ H ₂₁₉ N ₃ O ₅₄ Ostreocin-D C ₁₂₇ H ₂₁₉ N ₃ O ₅₃ Ostreocin-E1 C ₁₂₇ H ₂₁₇ N ₃ O ₅₂ Ostreocin-B C ₁₂₇ H ₂₁₉ N ₃ O ₅₃	Haemolysis Neutralization Assay 0.3 pg PLTX eq/cells (Rhodes, 2011)	Belize, Gulf of Siam, Iriomote 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
<i>O. cf. siamensis</i>	Ostreocin-D C ₁₂₇ H ₂₁₉ N ₃ O ₅₃ Ostreocin-B C ₁₂₇ H ₂₁₉ N ₃ O ₅₃	LC-MS/MS: 0.17 pg. eq PLTX. cell ⁻¹ (1) Mouse bioassay: LD ₅₀ = 25.1 mg.kg ⁻¹ (intraperitoneal injection) (2)	Atlantic, Australia, Belize, Canary Islands, Caribbean, 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 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-ESI-MS/MS: High-Performance Liquid Chromatography-Electrospray Ionization tandem Mass Spectrometry; OVTX: Ovatoin; 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-Altare et al., 2015).

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.

TABLE 2 | Reports of mild respiratory, cutaneous and/or general malaise symptoms in humans after exposure to aerosols in *Ostreopsis* spp. blooms affected beaches.

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

Seafood Borne PLTX Poisonings

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, restlessness, 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 21st 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 $\mu\text{g}\cdot\text{kg}^{-1}$ of whole flesh, exceeding the threshold of 30 $\mu\text{g}\cdot\text{kg}^{-1}$ 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**). Symptoms include rhinorrhea, pharyngeal pain, dry or mildly productive cough, nose irritation, general malaise, headache, fever ($\leq 38^\circ\text{C}$), eye irritation and/or dermatitis (Durando et al., 2007; Tichadou et al., 2010). Most of the symptoms disappeared within a few hours without specific medication when people moved away from the affected area in the vicinity of the *Ostreopsis* bloom; only a few severe cases required hospitalization (Durando et al., 2007). A metallic taste has also been reported by people when snorkeling and windsurfing, or by researchers (including the authors of this review) when sampling *Ostreopsis* blooms (Pfannkuchen et al., 2012). It has been hypothesized that PLTX analogs could be the most plausible agent causing the observed symptoms, in part because the observed signs were similar, although much milder, to those experienced by people exposed to aerosols from home aquaria containing zoanthids (Deeds and Schwartz, 2010). Indeed, culturing *Palythoa* corals have become popular among aquarists. Unfortunately, potent irritative compounds released after pouring boiling water or bleach in aquaria with the aim to eliminate a colony of zoanthids caused within 20 min after exposure, rhinorrhoea, coughing, difficult breathing and light headedness which progressed to severe fits of coughing and chest pain 4h later. At the local hospital the patient was administered an anti-inflammatory corticosteroid and pain medication, an inhaled steroid treatment and cough suppressant for one month. A follow-up examination by a pulmonary specialist two weeks post exposure diagnosed the patient with asthma-like symptoms of bronchial inflammation and bronchoconstriction. Similar cases have been reported in the last years (see **Tables 4 and 5** in Tubaro et al., 2011) one last case affecting a whole family, with three little kids in the UK in August 2019. Metallic taste was also reported by people when snorkeling and windsurfing in coral reefs containing *Palithoa*-like corals.

However, during *Ostreopsis* blooms OVTX-a and isoPLTX (putative) have been only rarely found in the aerosol and in very low concentrations (2.4 pg ovatoxins per liter of air by Ciminiello et al., 2014) and not coinciding with respiratory symptoms in humans. Several studies (Brescianini et al., 2006;

TABLE 3 | Noxious effects of direct interaction of *Ostreopsis* species on different fauna.

Species/Strain	Organisms	Stage	Effects	References	
Interactions with epibenthic cells of <i>Ostreopsis</i> species					
<i>Ostreopsis ovata</i> isolated by A. Penna	<i>Tigriopus fulvus</i> (Fisher, 1860)	I-II stage Nauplii	Mortality	LC _{50-48h-20°C} = 1486.74 cells.mL ⁻¹ LC _{50-48h-25°C} = 250.12 cells.mL ⁻¹	Faimali et al., 2012
<i>Ostreopsis cf. ovata</i>	<i>Tigriopus fulvus</i> (Fisher, 1860)		Mortality	LC _{50-24h-20°C} > 4000 cells.mL ⁻¹	Giussani et al., 2016
<i>Ostreopsis ovata</i> isolated by A. Penna	<i>Amphibalanus amphitrite</i> (Darwin, 1854)	II-III stage Nauplii	Mortality	LC _{50-48h-20°C} = 1416 cells.mL ⁻¹ LC _{50-48h-25°C} = 192 cells.mL ⁻¹	Faimali et al., 2012
<i>Ostreopsis cf. ovata</i>	<i>Amphibalanus amphitrite</i> (Darwin, 1854)		Mortality	LC _{50-24h-20°C} > 4000 cells.mL ⁻¹	Giussani et al., 2016
<i>Ostreopsis cf. ovata</i> Natural samples, Ligurian Sea (44°3'27"N; 9°55'43"E)	<i>Dinophylus gyrociliatus</i> (Schmidt, 1857)	Juveniles	Mortality	LT _{50-24°C} (3500 cells.mL ⁻¹) = 2h LT _{50-24°C} (1500 cells.mL ⁻¹) = 3.4h LT _{50-24°C} (200 cells.mL ⁻¹) = 12.25h ± 3.18	Simonini et al., 2011
<i>Ostreopsis ovata</i> isolated by A. Penna	<i>Paracentrotus lividus</i> (Lamarck, 1816)	Juveniles	Mortality	LC _{50-48h-20°C} = 168 cells.mL ⁻¹	Privitera et al., 2012
<i>Ostreopsis cf. ovata</i> Natural samples, Gulf of Taranto, Ionian Sea	<i>Tigriopus fulvus</i> (Fisher, 1860)	Nauplii	Mortality	LC _{50-96h-25°C} = 10.11 cell.mL ⁻¹	Prato et al., 2011
	<i>Corophium insidiosum</i> (Crawford, 1937)	2-4 mm body length	Mortality	LC _{50-96h-25°C} = 11.81 cell.mL ⁻¹	
	<i>Sphaeroma serratum</i> (Fabricius, 1787)	2-4 mm body length	Mortality	LC _{50-96h-25°C} = 214.81 cell.mL ⁻¹	
<i>Ostreopsis siamensis</i> CAWD73/74/75/96	<i>Haliotis virginea</i> (Gmelin, 1791)	Larvae	Mortality	Not lethal within 24h	Rhodes et al., 2000
<i>Ostreopsis cf. ovata</i> MCCV 054	<i>Sarsamphiascus cf. propinquus</i> (Sars G.O., 1906)	Adults	Mortality	LC _{50-24h-24°C} > 20 000 cell.mL ⁻¹	Pavaux et al., 2019
<i>Ostreopsis cf. ovata</i> Natural samples from French and Italian NW Med. Coasts	Phytopl meiofauna		Community composition	72 % decrease of nauplii	Guidi-Guilvard et al., 2012
<i>Ostreopsis cf. ovata</i> MCCV 054	<i>Sarsamphiascus cf. propinquus</i> (Sars G.O., 1906)	Females	Reproduction	Decrease of fertility and fecundity rations	Pavaux et al., 2019
<i>Ostreopsis cf. ovata</i> Natural samples (French Mediterranean coasts)	<i>Paracentrotus lividus</i> (Lamarck, 1816)		Toxin quantification	LC-MS/MS: 77 to 361 µg eq PLTX.kg ⁻¹	Amzil et al., 2012
	<i>Sarpa salpa</i> (Linnaeus, 1758)		Toxin quantification	LC-MS/MS: 33 to 152 µg.kg ⁻¹	
<i>Ostreopsis ovata</i> Field samples (Tyrrhenian Sea)	Sea urchins		Toxin quantification	HNA: 5 to 99 pPLTX µg.kg ⁻¹ LC-MS/MS: < LOQ pPLTX µg.kg ⁻¹ 87 to 164 OVTXa µg.kg ⁻¹	Milandri et al., 2010
<i>Ostreopsis cf. ovata</i> Field samples Nice harbour and Villefranche-sur-Mer, Mediterranean Sea	<i>Paracentrotus lividus</i> (Lamarck, 1816)		Toxin quantification	Haemolytic assay: 256.6 µg/kg (WF) LC-MS/MS: 192.5 µg/kg (WF)	Biré et al., 2013
	<i>Sarpa salpa</i> (Linnaeus, 1758)		Toxin quantification	Haemolytic assay: 230.0 µg/kg (DT) LC-MS/MS: 191.2 µg/kg (WF)	
<i>Ostreopsis cf. ovata</i> Field samples - Rochambeau site, Villefranche-sur-Mer, Mediterranean Sea	<i>Paracentrotus lividus</i> (Lamarck, 1816)		Toxin quantification	Haemolytic assay: 159.2 µg/kg (DT)	Biré et al., 2015
	<i>Sarpa salpa</i> (Linnaeus, 1758)		Toxin quantification	Haemolytic assay: 361.0 µg/kg (DT)	

(Continued)

TABLE 3 | Continued

Species/Strain	Organisms	Stage	Effects		References
Interactions with planktonic cells of <i>Ostreopsis</i> species					
<i>Ostreopsis ovata</i> isolated by A. Penna	<i>Paracentrotus lividus</i> (Lamarck, 1816)	Competent larvae	Mortality	LC _{50-48h-20°C} = 168 cells.mL ⁻¹	Privitera et al., 2012
<i>Ostreopsis</i> cf. <i>ovata</i> CBA29-2012 (Genoa)	<i>Aurelia</i> sp.	Polyp	Reproduction/early stages	Unaffected (100 cells.mL ⁻¹)	Giussani et al., 2015
<i>Ostreopsis</i> cf. <i>ovata</i> Marche coast (Italy NW Adriatic Sea)	<i>Mytilus galloprovincialis</i> (Lamarck, 1819)	Adults	Histological impairments	<u>Immune system</u> : - Decrease of granulocytes Phagocytosis activity decrease Reduced lysosomal membrane stability <u>Histology</u> : - Decrease of the digestive gland wall thickness Dilatation of tubules Haemocytes infiltration into digestive gland Decrease of neutral lipids quantity <u>Oxidative stress</u> : limited role	Gorbi et al., 2013
<i>Ostreopsis</i> cf. <i>ovata</i> Field sample from Adriatic Sea (Portonevo & Passetto sites)	<i>Mytilus galloprovincialis</i> (Lamarck, 1819)	Adults	Histological impairments	Inhibition of Na ⁺ /K ⁺ ATPase and acetylcholine esterase activity <u>Immune system</u> : Reduced lysosomal membrane stability <u>Oxidative stress</u> : limited role	Gorbi et al., 2012
<i>Ostreopsis</i> spp. Cultures + field samples (North Aegean coasts)	<i>Mytilus galloprovincialis</i> (Lamarck, 1819) <i>Venus verrucosa</i> <i>Odiolus barbatus</i>		Toxin quantification	MBA: Qualitative analysis HNA: 33.3 to 97 pPLTX μg.kg ⁻¹	Aligizaki et al., 2008
<i>Ostreopsis</i> cf. <i>ovata</i> Natural samples (French Mediterranean coasts)	<i>Mytilus galloprovincialis</i> (Lamarck, 1819)		Toxin quantification	LC-MS/MS: 28 to 217 μg eq PLTX.kg ⁻¹	Amzil et al., 2012
<i>Ostreopsis</i> cf. <i>ovata</i> Filed samples (Adriatic Sea)	<i>Mytilus galloprovincialis</i> (Lamarck, 1819)		Toxin quantification	MBA + HNA: Qualitative analysis	Gorbi et al., 2012
<i>Ostreopsis ovata</i> Field samples (Tyrrhenian Sea)	Mussels		Toxin quantification	HNA: 103 pPLTX μg.kg ⁻¹ LC-MS/MS: < LOQ pPLTX μg.kg ⁻¹ - 131 to 228 OVTXa μg.kg ⁻¹	Milandri et al., 2010
<i>Ostreopsis siamensis</i> CAWD75 (New Zeland)	Greenshell TM mussels Pacific oysters Scallops		Toxin quantification	MBA: qualitative analysis HNA: 0.3 pg eq. PLTX.cell ⁻¹	Rhodes et al., 2000
<i>Ostreopsis siamensis</i> CAWD75 (New Zeland)	<i>Perna canaliculus</i> (Gmelin, 1791) <i>Pecten novaezalandiae</i> (Reeve, 1852) <i>Crassostrea gigas</i> (Thunberg, 1793)		Toxin quantification	MBA (qualitative analysis): none to death HNA: trace to 1 ng.g ⁻¹	Rhodes et al., 2002
<i>Ostreopsis</i> cf. <i>ovata</i> Field samples - Rochambeau site Villefranche-sur-Mer	<i>Arca noae</i> (Linnaeus, 1758)		Toxin quantification	Haemolytic assay: <10 μg/kg (WF)	Biré et al., 2015
<i>Ostreopsis</i> cf. <i>ovata</i> CBA29-2012 (Genoa)	<i>Aurelia</i> sp.	Ephyrae	Reproduction/early stages	% Alteration of Pulsation Frequency EC _{50-24h} = 5.32 cells.mL ⁻¹ Immobility EC _{50-24h} = 10.50 cells.mL ⁻¹	Giussani et al., 2015
<i>Ostreopsis</i> cf. <i>ovata</i> ITAC501	<i>Paracentrotus lividus</i> (Lamarck, 1816)	Eggs	Reproduction/early stages	Gametes: % fertilization decrease; less toxic for eggs than sperms Embryos: no segmentation	Caroppo and Pagliara, 2011

(Continued)

TABLE 3 | Continued

Species/Strain	Organisms	Stage	Effects	References	
<i>Ostreopsis</i> cf. <i>ovata</i> Natural samples (Gaiola MPA, Italy)	<i>Paracentrotus lividus</i> (Lamarck, 1816)	Embryos	Reproduction/early stages	Fertilization and developmental impairments Alteration of several marker genes	Migliaccio et al., 2016
<i>Ostreopsis</i> cf. <i>ovata</i> Strain UNR-05 Armação dos Búzios (Rio de Janeiro)	<i>Lytechinus variegatus</i> (Lamarck, 1816)	Embryos	Reproduction/early stages	Stronger effect on larvae than on fertilization success: - Reduced fertilization - Arrest of embryonic development (gastrula stages at 400 cells.mL ⁻¹) - Increase of dead and abnormal larvae	Neves et al., 2018
<i>Ostreopsis</i> cf. <i>ovata</i> (whole cells + lysate) Natural samples (Ionian Sea)	<i>Paracentrotus lividus</i> (Lamarck, 1816)	Embryos	Reproduction/early stages	<u>Whole cells</u> : Developmental delay or anomalous cell division <u>Cell lysate</u> : Growth inhibition at 1.87 mg.mL ⁻¹	Pagliara and Caroppo, 2012
Interactions with surface cells of <i>Ostreopsis</i> species					
<i>Ostreopsis</i> cf. <i>ovata</i> Field samples Nice harbour and Villefranche-sur-Mer	<i>Patella</i> spp. <i>Mugil cephalus</i> (Linnaeus, 1758)		Toxin quantification Toxin quantification	Haemolytic assay: 12.7 µg/kg (WF) Haemolytic assay: 392.2 µg/kg (DT) LC-MS/MS: 359.1 µg/kg (WF)	Biré et al., 2013
<i>Ostreopsis</i> cf. <i>ovata</i> Field samples - Rochambeau site Villefranche-sur-Mer	<i>Patella</i> spp.		Toxin quantification	Haemolytic assay: <10 µg/kg (WF)	Biré et al., 2015
<i>Ostreopsis</i> cf. <i>ovata</i> Field samples Genoa, Nice, Villefranche-sur-Mer	<i>Paracentrotus lividus</i> (Lamarck, 1816) <i>Patella</i> spp.		Density	Any decrease of <i>P. lividus</i> densities related to high abundances of <i>O. cf. ovata</i> No significant decrease of densities in Villefranche-sur-mer and Nice; Significant decrease in Genoa potentially linked to <i>O. cf. ovata</i> blooms	Blanfuné et al., 2012

EC₅₀: Half maximal Effective *Ostreopsis* 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 *Ostreopsis* 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 *Ostreopsis* 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 *Ostreopsis* 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, semi-purified 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 *Ostreopsis 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

TABLE 4 | Effects on organisms exposed indirectly to *Ostreopsis* species.

Species/Strain	Organisms	Authority	Effects	References	
<i>Ostreopsis ovata</i> Field samples (Tyrrhenian Sea)	<i>Octopuses</i>		Toxin quantification	HNA: 446 pPLTX $\mu\text{g.kg}^{-1}$ LC-MS/MS: 115 pPLTX $\mu\text{g.kg}^{-1}$ 971 OVTXa $\mu\text{g.kg}^{-1}$	Milandri et al., 2010
<i>Ostreopsis cf. ovata</i> Field samples	<i>Diplodus annularis</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: 10.6 $\mu\text{g/kg}$ (DT)	Biré et al., 2013
Nice harbour and Villefranche-sur-Mer (Mediterranean Sea)	<i>Diplodus sargus</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: 5.1 $\mu\text{g/kg}$ (DT)	
	<i>Eriphia verrucosa</i>	Forskål, 1775	Toxin quantification	Haemolytic assay: 38.4 $\mu\text{g/kg}$ (WF) LC-MS/MS: 58.6 $\mu\text{g/kg}$ (WF)	
	<i>Maja squinado</i>	Herbst, 1788	Toxin quantification	Haemolytic assay: 8.3 $\mu\text{g/kg}$ (WF)	
	<i>Mullus surmuletus</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: < LOQ	
	<i>Muraena helena</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: < LOQ	
	<i>Octopus vulgaris</i>	Cuvier, 1797	Toxin quantification	Haemolytic assay: 18.5 $\mu\text{g/kg}$ (RT)	
	<i>Scorpaena porcus</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: 3.7 $\mu\text{g/kg}$ (DT)	
	<i>Serranus scriba</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: < LOQ	
	<i>Stramonita haemastoma</i>	Linnaeus, 1767	Toxin quantification	Haemolytic assay: 34.1 $\mu\text{g/kg}$ (WF) LC-MS/MS: 26,4 $\mu\text{g/kg}$ (WF)	
	<i>Symphodus tinca</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: 1.8 $\mu\text{g/kg}$ (DT)	
<i>Ostreopsis cf. ovata</i> Field samples	<i>Coris julis</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	Biré et al., 2015
Rochambeau site, Villefranche-sur-Mer	<i>Diplodus vulgaris</i>	Geoffroy Saint-Hilaire, 1817	Toxin quantification		
	<i>Eriphia verrucosa</i>	Forskål, 1775	Toxin quantification	Haemolytic assay: 13.0 $\mu\text{g/kg}$ (WF)	
	<i>Hexaplex trunculus</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: 40.4 $\mu\text{g/kg}$ (WF)	
	<i>Gobiidae</i>		Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Maja squinado</i>	Herbst, 1788	Toxin quantification	Haemolytic assay: 51.3 $\mu\text{g/kg}$ (WF)	
	<i>Mullus surmuletus</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Muraena helena</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Octopus vulgaris</i>	Cuvier, 1797	Toxin quantification	Haemolytic assay: 19.9 $\mu\text{g/kg}$ (RT)	
	<i>Saurida undosquamis</i>	Richardson, 1848	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Scorpena porcus</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Serranus scriba</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Symphodus melops</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: < 10 $\mu\text{g/kg}$ (WF)	
	<i>Symphodus ocellatus</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Symphodus roissali</i>	Risso, 1810	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Symphodus rostratus</i>	Bloch, 1791	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Symphodus tinca</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Thalassoma pavo</i>	Linnaeus, 1758	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
	<i>Xantho poressa</i>	Olivi, 1792	Toxin quantification	Haemolytic assay: <10 $\mu\text{g/kg}$ (WF)	
<i>Ostreopsis ovata</i> isolated by A. Penna	<i>Dicentrarchus labrax</i>	Linnaeus, 1758	Mortality	LC _{50-48h-20°C} = 540 cells.mL ⁻¹	Faimali et al., 2012
<i>Ostreopsis cf. ovate</i>	<i>Dicentrarchus labrax</i>	Linnaeus, 1758	Mortality	LC _{50-48h-20°C} = 679 cells.mL ⁻¹	Giussani et al., 2016
<i>Ostreopsis cf. ovata</i> Strain OOAN0601	<i>Dicentrarchus labrax</i>	Linnaeus, 1758	Mortality	100% mortality after 45 to 72 h exposed to <i>O. cf. ovata</i> (between 425 to 2367 cells.mL ⁻¹)	Pezzolesi et al., 2012

EC₅₀: Half maximal Effective *Ostreopsis* Concentration; LC₅₀: Median lethal concentration; LT₅₀: Median lethal time.

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 to 11 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 microalga. 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 $30 \text{ m}^3 \cdot \text{h}^{-1}$. 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 (Analitica 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 $10 \text{ L} \cdot \text{min}^{-1}$ in 2009 and $30 \text{ L} \cdot \text{min}^{-1}$ 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 ECOLOGY 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 (Sarmiento 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 (Tosteson 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 *Ruegeria*, *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 tamarensis* (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 anthropogenically 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 *Amoebophrya* 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 *Parvilicifera 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 *Strombilidium* sp. and the HTDs *Gyrodinium spirale*, *Protoperidinium 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 *Coolia monotis* 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 complanatoides* and *Navicula* sp.) (Pichierri et al., 2017). These studies suggested the production of allelopathic compounds by all tested diatoms, especially released after *Ostreopsis* cell destruction (Pohnert et al., 2007). These diatoms are well known to produce a large family of polyunsaturated aldehydes (PUAs - Wichard et al., 2005). Pichierri et al. (2017) found that exposure to a range of PUAs (2E,4E-decadienal, 2E,4E-octadienal and 2E,4E-heptadienal) concentrations (from 3 to 36 $\mu\text{mol}\cdot\text{L}^{-1}$) caused *O. cf. ovata* growth inhibition, decrease in photosynthesis efficiency, increase of abnormal cells (motionless, decrease in dimensions, contraction of cytoplasm and formation of abnormal vesicle-like structure) and a decrease in cell integrity (chromatin dispersion, lack of autofluorescence of the chlorophyll and larger lipid bodies).

Macroalgae

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 *Ellisolandia 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. Macroalgae 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 preference of *Ostreopsis* species. *Rhodymenia pseudopalmata* (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* (Ulvophyceae) and *Dyctyota 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., reprotoxicity 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 exposition 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 diarrhetic 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; Tibiriça 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 10⁵–10⁶ 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 is conducted to prevent sanitary impacts during these toxic events (Efsa Panel on Contaminants in the Food Chain, 2009; Accoroni et al., 2011; Amzil et al., 2012; Lemée et al., 2012). Concentrations of toxins quantified in mussels (*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 of embryonic 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 $392.5 \mu\text{g}\cdot\text{kg}^{-1}$ 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 mediolittoral 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 $12.7 \mu\text{g}\cdot\text{kg}^{-1}$, 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; Pezsolesi 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 $26.4 \mu\text{g}\cdot\text{kg}^{-1}$ (Fresh Weight) respectively. Octopuses also accumulated more than $446 \mu\text{g}\cdot\text{kg}^{-1}$ (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; Pezsolesi 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 reprotoxic 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 acclimation 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 (*Noctiluca scintillans*; KiØrboe and Titelman, 1998) and mixotrophic dinoflagellates (*Alexandrium pseudogonyaulax*; Blossom et al., 2012).

For *Ostreopsis*, the role of the mucus 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 mucus, 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-Garulera 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* (Perkinsozoa) and *Amoebophrya* (Syndiniales) 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 *Ostreopsis*

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 thus 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, uprisng 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 *Ostreopsis cf. ovata*, in part because its wide presence and recurrent blooms in the Mediterranean. However, the impacts of other *Ostreopsis* 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 *Ostreopsis* on marine ecosystems, experiments should be run to clarify the effect of the direct and/or indirect contact of *Ostreopsis* on different organisms, using realistic (i.e., naturally occurring) *Ostreopsis* cell concentrations, and following ecologically realistic tests are key. To understand the role of the mucus produced by *Ostreopsis*, 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 *Ostreopsis* 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 *Ostreopsis 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 *Ostreopsis* sp. are not specific since our studies (Pavaux et al., 2020). The *Artemia* bioassay can be a pre-screening test of *Ostreopsis* 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 *Ostreopsis 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 *Ostreopsis* 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

TABLE 5 | *Artemia* bio-assay for *Ostreopsis* species toxicity.

Species/Strain	Organisms	Stage	Effects	References
<i>Ostreopsis ovata</i> isolated by A. Penna	<i>Artemia salina</i> (Linnaeus, 1758)	II-III stage nauplii	LC _{50-48h-20°C} = 12 cells.mL ⁻¹ LC _{50-48h-25°C} < 4 cells.mL ⁻¹	Faimali et al., 2012
<i>Ostreopsis</i> cf. <i>ovata</i> Isolated from Lazio & Marche	<i>Artemia</i> sp.	Nauplii	EC ₅₀ calculated but not expressed	Guerrini et al., 2010
<i>Ostreopsis</i> cf. <i>ovata</i>	<i>Artemia salina</i> (Linnaeus, 1758)	Nauplii	LC _{50-24h-20°C} = 15 cells.mL ⁻¹	Giussani et al., 2016
<i>Ostreopsis</i> cf. <i>ovata</i> CBA29-2012	<i>Artemia salina</i> (Linnaeus, 1758)	II – III stages larvae	LC _{50-48h-20°C} = 24.83 / 16.67 / <4 cells.mL ⁻¹ (exponential, stationary and late stationary phase)	Giussani et al., 2015
<i>Ostreopsis</i> cf. <i>ovata</i>	<i>Artemia salina</i> (Linnaeus, 1758)	Nauplii	Immobility EC _{50-48h-20°C} < 4 cells.mL ⁻¹	Giussani et al., 2016
<i>Ostreopsis</i> cf. <i>ovata</i> UNR-05	<i>Artemia salina</i> (Linnaeus, 1758)	Adults	LT _{50-24°C} (200 cells.mL ⁻¹) = 3h	Neves et al., 2017
<i>Ostreopsis</i> cf. <i>ovata</i> (cell lysate) Natural samples (Ionian Sea)	<i>Artemia salina</i> (Linnaeus, 1758)	Nauplii (24h after hatching)	LC _{50-24h-25°C} = 0.03 mg.mL ⁻¹	Pagliara and Caroppo, 2012
<i>Ostreopsis</i> cf. <i>ovata</i> Strain OOAN0601 (Marche Region)	<i>Artemia</i> sp.	Nauplii	LC _{50-24h-20°C} (live cells) = 8 cells.mL ⁻¹ ± 5 = 115 pg.mL ⁻¹ ± 72 LC _{50-24h-20°C} (lysed cells) = 96 cells.mL ⁻¹ ± 6 = 1376 pg.mL ⁻¹ ± 86 LC _{50-24h-20°C} (extract) = 80 cells.mL ⁻¹ ± 7 = 1146 pg.mL ⁻¹ ± 272	Pezzolesi et al., 2012
<i>Ostreopsis</i> cf. <i>ovata</i> Natural samples Gulf of Taranto	<i>Artemia franciscana</i> (Kellogg, 1906)	II – III stages larvae	LC _{50-48h-25°C} = 1.63 cell.mL ⁻¹	Prato et al., 2011
<i>Ostreopsis siamensis</i> CAWD73/74/75/96	<i>Artemia salina</i> (Linnaeus, 1758)		LT ₅₀ (250 cells.mL ⁻¹) = 24h Time until Morbidity ₅₀ (250 cells.mL ⁻¹) = 4h	Rhodes et al., 2000
<i>Ostreopsis ovata</i> Mediterranean Sea	<i>Artemia salina</i> (Linnaeus, 1758)		Correlation (p < 1%) between <i>O.</i> cf. <i>ovata</i> concentration and death of <i>A. salina</i>	Simoni et al., 2003
<i>Ostreopsis ovata</i> Mediterranean Sea	<i>Artemia salina</i> (Linnaeus, 1758)		Correlation between <i>A. salina</i> mortality after 24 h and the number of <i>O. ovata</i> cells	Vale and Ares, 2007; Ramos and Vasconcelos, 2010
<i>Ostreopsis</i> cf. <i>ovata</i> (MCCV 054/055) <i>Ostreopsis fattorussoi</i> (MCCV 057/058) Mediterranean Sea	<i>Artemia franciscana</i> (Kellogg, 1906)	II – III stages larvae	LC _{50-24h} (MCCV 054) = 81.96 ± 63.3 cells.mL ⁻¹ LC _{50-24h} (MCCV 055) = 0.25 ± 0.90 cells.mL ⁻¹ LC _{50-24h} (MCCV 057) = 0.0012 ± 0.00033 cells.mL ⁻¹ LC _{50-24h} (MCCV 058) = 0.023 ± 0.039 cells.mL ⁻¹ LC _{50-24h} (Dissolved OVTXs) = 5.96 ± 2.12 cells.mL ⁻¹ LC _{50-24h} (Dissolved PLTX) = 48.42 ± 14.23 cells.mL ⁻¹	Pavaux et al., 2020.

LC₅₀: Median Lethal Concentration; LT₅₀: Median lethal time.

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; Quinn 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 malnygamide 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

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 through 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.).

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- 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.

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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.

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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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