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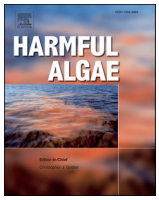

Original Article

Mitigation of harmful algal blooms caused by *Alexandrium catenella* and reduction in saxitoxin accumulation in bivalves using cultivable seaweeds

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ABSTRACT

Alexandrium catenella is a harmful algal bloom (HAB)-forming dinoflagellate that causes significant damage to the cultivation and harvest of shellfish due to its synthesis of paralytic shellfish toxins. To evaluate the potential for macroalgae aquaculture to mitigate *A. catenella* blooms, we determined the effects of three cultivable macroalgae - *Saccharina latissima* (sugar kelp), *Chondrus crispus* (Irish moss), and *Ulva* spp. - on *A. catenella* in culture- and field-based experiments. Co-culture growth assays of *A. catenella* exposed to environmentally realistic concentrations of each macroalgae showed that all species except low levels of *C. crispus* caused cell lysis and significant reductions in *A. catenella* densities relative to control treatments of 17–74% in 2–3 days and 42–96% in ~one week ($p<0.05$ for all assays). In a toxin accumulation experiment, *S. latissima* significantly lessened ($p<0.05$) saxitoxin (STX) accumulation in blue mussels (*Mytilus edulis*), keeping levels (71.80±1.98 μg STX 100 g^{-1}) below US closure limits (80 μg STX 100 g^{-1}) compared to the untreated control (93.47±8.11 μg STX 100 g^{-1}). Bottle incubations of field-collected, bloom populations of *A. catenella* experienced significant reductions in cell densities of up to 95% when exposed to aquaculture concentrations of all three macroalgae ($p<0.005$ for all). The stocking of aquacultured *S. latissima* within mesocosms containing a bloom population of *A. catenella* (initial density: 3.2×10^4 cells L^{-1}) reduced the population of *A. catenella* by 73% over 48 h ($p<0.005$) while *Ulva* addition caused a 54% reduction in *A. catenella* over 96 h ($p<0.01$). Among the three seaweeds, their ordered ability to inhibit *A. catenella* was *S. latissima* > *Ulva* spp. > *C. crispus*. Seaweeds' primary anti-*A. catenella* activity were allelopathic, while nutrient competition, pH elevation, and macroalgae-attached bacteria may have played a contributory role in some experiments. Collectively, these results suggest that the integration of macroalgae with shellfish-centric aquaculture establishments should be considered as a non-invasive, environmentally friendly, and potentially profit-generating measure to mitigate *A. catenella*-caused damage to the shellfish aquaculture industry.

1. Introduction

Harmful algal blooms (HABs) are increasing in range, frequency, and intensity throughout the world, primarily due to anthropogenic factors such as climate change, eutrophication, and anthropogenic transport (Heisler et al., 2008; Anderson et al., 2008, 2012b; Gobler et al., 2017). *Alexandrium catenella* is a HAB-forming dinoflagellate of particular interest due to its production of saxitoxins, compounds that accumulate in shellfish and can result in paralytic shellfish poisoning (PSP) (Anderson, 1997; Kodama, 2010). In addition to presenting a human health hazard, blooms of *A. catenella* can result in substantial economic losses due to the closure of shellfish beds and farms (Lewitus et al., 2012; Anderson et al., 2014; Vandersea et al., 2018). Blooms of *A. catenella* occur across North America, South America, Europe, Asia, and Australia (Lewitus et al., 2012; Anderson et al., 2012a; Campbell et al., 2013; Gu et al., 2013; Toebe et al., 2013; Vandersea et al., 2018; Paredes et al., 2019) causing damage to shellfisheries (Hoagland and Scatasta, 2006). Therefore, there is great interest in developing strategies for the prevention, control, and mitigation (PCM) of these blooms.

Annual global seaweed (henceforth macroalgae) aquaculture production exceeds 32.3 million metric tons, worth >13 billion USD per annum (FAO, 2020; Ferdouse et al., 2018). While North America is not currently a major contributor to this market, there is vast potential for growth, particularly in the cultivation of phaeophyte *Saccharina latissima*, also known as sugar kelp (Kim et al., 2015; Augyte et al., 2017; Kim et al., 2019). Macroalgae are considered a primary component of

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integrated multitrophic aquaculture (IMTA) systems (Chopin et al., 2001; Neori et al., 2004; Neori, 2007; Park et al., 2018), as many cultivated macroalgae have a high assimilative capacity for nitrogen and phosphorus (Ahn et al., 1998; Kim et al., 2014, 2015; Marinho et al., 2015), allowing for effective nutrient mitigation. There is also emerging evidence that aquaculture of macroalgae has the potential to mitigate coastal acidification via rapid CO_2 assimilation (Fernández et al., 2019; Wahl et al., 2018; Young and Gobler, 2018). The nutrient mitigation and potential pH elevation from open-water macroalgal aquaculture both have potential for mitigating HABs. The incidence of HABs may decrease as nutrient management strategies are established to reduce eutrophication (Gobler et al., 2005; Imai et al., 2006b; Paerl et al., 2018), and it has also been shown that many microalgae, including HAB dinoflagellates, may experience reduced growth rates in higher pH waters (Hansen, 2002). Additionally, there are many studies documenting the allelopathic activity of several macroalgae and macroalgal extracts towards HAB dinoflagellates (Gharbia et al., 2017; Nagayama et al., 2003; Nan et al., 2004; Tang et al., 2014; Tang and Gobler, 2011).

Little is known regarding the effects of macroalgae on *Alexandrium* spp. There is some evidence that the ulvalean macroalgae species *Ulva pertusa* and *Ulva lactuca* have allelopathic growth-inhibiting effects on *Alexandrium tamarense* (Jin and Dong, 2003; Nan et al., 2004, 2008). These prior studies of *A. tamarense*, however, were culture-based, performed with a single clonal strain of *A. tamarense* rather than wild populations – a limitation of many studies that have been published regarding the allelopathic effects of macroalgae on HAB microalgae. Moreover, there is no published research documenting the effects of commercially cultivated macroalgae, such as *Saccharina latissima*, on any species of *Alexandrium*. Finally, the effects of macroalgae on *A. catenella* toxin production and subsequent accumulation in shellfish are unknown. Paralytic shellfish toxins are nitrogen-rich molecules (Wong et al., 1971), making it plausible that the N-assimilatory capacity of some macroalgae could result in the co-reduction of growth rates and toxin production in *A. catenella*.

The primary objective of this study was to assess the ability of commercially valuable, cultivable macroalgae to inhibit the growth of and reduce the toxicity of *A. catenella* blooms, with a secondary objective to probe the causative mechanism behind the inhibiting effects. Specifically, we report on (1) the growth-inhibiting effects of three cultivable macroalgae – *S. latissima, Chondrus crispus*, and *Ulva* spp. – on three clonal, saxitoxin-producing cultures of *A. catenella*, (2) the ability of *S. latissima* to lower toxin accumulation in blue mussels (*M. edilus*) fed a diet of cultured, saxitoxin-producing *A. catenella*, and (3) the growth-inhibiting effects of these macroalgae on wild, bloom populations of *A. catenella* at multiple scales. The results demonstrate that the integration of macroalgal aquaculture with shellfish aquaculture has significant potential as a strategy for the prevention, control, and mitigation of *A. catenella* HABs.

2. Materials and methods

2.1. Microalgal cultures

Three strains of *A. catenella* were included in this study, including one strain isolated from Northport Bay, New York (NP8) and two strains isolated from the Bay of Fundy, Canada (CCMP2304, BF-5). All strains were cultured in f/2 media without silicate (Guillard, 1975), made with sterilized and filtered (0.22 μm) seawater with salinity of ~32 PSU. An antibiotic solution (10,000 I.U. penicillin, 10,000 μg mL^{-1} streptomycin; Mediatech. Inc., Hemdon, VA) was added into the medium of all cultures at a final concentration of 0.5% immediately prior to inoculation. Cultures were maintained at 18 °C within exponential growth phase under at bank of fluorescent lights (~100 μmol photons $m^{-2}s^{-1}$) on a 16h:8 h light:dark cycle. All culture transfers were conducted using aseptic techniques in a class-100 laminar flow hood. All strains were confirmed to be axenic via DAPI staining.

2.2. Collection, identification, and maintenance of macroalgae

Three types of macroalgae were included in this study: *Ulva* spp., *Chondrus crispus*, and *Saccharina latissima. Ulva* spp. and *C. crispus* were collected from coastal sites in Shinnecock Bay, NY, and Long Island Sound near the Mattituck Inlet, NY, up to a month prior to experiments. *S. latissima* was grown on an oyster farm on staked ropes in Moriches Bay, NY, and was collected from the growing site several days prior to experiments by cutting the holdfast and removing the stipe and blade. *C. crispus* is one of the most common species of red algae in the Northeastern US and is easily identifiable morphologically. All *S. latissima* used in this study originated in Stony Brook University's kelp hatchery at the Stony Brook - Southampton Marine Sciences Center. In contrast to *C. crispus* and *S. latissima*, identifying *Ulva* spp. across the Northeast US is more challenging due to the co-occurrence of multiple morphologically similar species (Hofmann et al., 2010; Mao et al., 2014; Fort et al., 2020); for the purposes of this study, therefore, we refer to these macroalgae simply as *Ulva* (Young and Gobler, 2016).

Fresh thalli of all macroalgae were examined for lesions or discoloration, with unhealthy thalli discarded. Remaining thalli were liberally rinsed with UV-sterilized filtered (0.22 μm) seawater and then lightly wiped with sterile Kimwipes to remove still-attached grazers and epiphytes. Thalli were then maintained in 20 L polyethylene vessels in f/2 media, illuminated by a bank of fluorescent lights on a 16h:8 h light:dark cycle for up to one month prior to experiments. Media in maintenance vessels was replenished weekly.

2.3. Laboratory experiments

2.3.1. Co-incubation growth assays

Four laboratory assays were conducted to quantify algicidal and/or growth-inhibiting effects of each macroalgae against cultured *Alexandrium catenella* at different temperatures. For each experiment, live portions of macroalgal thalli were administered to *A. catenella* in various concentrations ranging from field densities of macroalgae (bottom coverage of a 1 m deep estuary; 1 m^2 m^{-3}; Tang and Gobler, 2011) to higher concentrations possible in aquaculture. Concentrations of *Saccharina latissima* used to represent aquaculture densities of macroalgae were obtained from measurements of kelp growth on our collaborating farm in Moriches Bay, NY in 2019 and 2020. Kelp growth data in kilograms per meter of line and local tidal ranges were used to extrapolate ranges of kelp concentration (g L^{-1}) in the surrounding water, using a

Table 1
Estimated concentration ranges of *Saccharina latissima* at the growing site in Moriches Bay, NY, accounting for 5 m of separation between individual kelp lines. All kelp for experiments in this study was obtained from this growing site within the dates outlined here.

Date	Kelp concentration, low tide (g L^{-1})	Kelp concentration, high tide (g L^{-1})
April 1st, 2019	1.71 ± 0.46	0.57 ± 0.15
April 19th, 2019	1.94 ± 0.72	0.65 ± 0.24
May 14th, 2019	1.73 ± 0.41	0.58 ± 0.14
April 2nd, 2020	1.76 ± 0.67	0.59 ± 0.22
April 16th, 2020	2.54 ± 0.26	0.85 ± 0.09
April 28th, 2020	2.80 ± 0.21	0.93 ± 0.07
May 12th, 2020	2.93 ± 0.48	0.98 ± 0.16
May 22nd, 2020	3.41 ± 0.80	1.14 ± 0.27
June 1st, 2020	4.39 ± 0.93	1.46 ± 0.31

2.5 m radius away from individual kelp lines to account for spacing between multiple lines (Table 1). Using this data as a guideline, we elected to use 1 g L^{-1} as a target for low/moderate aquaculture densities, and 3 g L^{-1} as a target for high aquaculture densities.

Live thalli of macroalgae were prepared for assays one-to-three days prior to initiation of experiments. Thalli of blade-forming macroalgae (*Ulva, Saccharina latissima*) were cut into circular discs of varied size depending upon targeted concentration (low concentration – 4.52 cm^2, moderate concentration – 8.04 cm^2, high concentration – 11.34 cm^2), and then further trimmed to the target wet mass with a razor blade if necessary. Reproductive tissue was avoided in this preparation by cutting away from discolored margins of *Ulva* thalli (Redmond et al., 2014; Wallace and Gobler, 2014) and avoiding the sorus of mature blades of *S. latissima* when present (Redmond et al., 2014). For the branching macroalga *Chondrus crispus*, portions were excised from the main plant with a razor to obtain the approximate size required. For all macroalgae, cut thalli were rinsed with filtered seawater and spun in a salad spinner to remove excess water and then weighed for wet weight (Young and Gobler, 2016). Thalli were trimmed, when necessary, with a razor to the target wet weight for each treatment in the experiment. Thalli were then stored in sterile f/2 media in the same conditions as *Alexandrium catenella* cultures described earlier until initiation of experiments.

Alexandrium catenella replicate cultures were prepared for assays in 250 mL flasks with sterile f/2 media with 0.5% antibiotics. *A. catenella* was inoculated into flasks at densities observed during blooms (Hattenrath-Lehmann and Gobler, 2011) and densities seen at the onset of exponential growth in cultures (2-10 $\times 10^2$ cells mL^{-1}). Experimental treatments with 3x – 5x replication were prepared with different concentrations and species of macroalgae, while control treatments without macroalgae were established at the same cell density. Cut thalli of macroalgae prepared earlier were added to each treatment after inoculation of cells, and cultures were incubated as described (besides temperature) for 7–15 days. Experiments were performed at 15 °C, 18 °C, and 21 °C including a range of temperatures under which *A. catenella* blooms occur in North America (Hattenrath-Lehmann et al., 2010; Ralston et al., 2014).

Alexandrium catenella cell density was monitored every 1–3 days throughout experiments via microscopic cell counts with a Sedgewick Rafter slide. pH was measured at regular intervals using a Thermo Orion™ Flat Surface pH electrode that was rinsed with sterilized filtered (0.22 μm) seawater in between replicates and calibrated on the National Bureau of Standards (NSB) scale using National Institute of Standards and Technology (NIST) standards. Maximum photochemical quantum yield of PS II (F_V/F_M) was measured at regular intervals on a PhytoPam II fluorometer (Heinz Walz GmbH). Samples were dark-adapted for at least 10 min prior to F_V/F_M measurements to ensure that values were indicative of maximum photosynthetic efficiency rather than dynamic photosynthetic efficiency; lower values therefore correspond to damage to PS II (Kitajima and Butler, 1975; Abreu et al., 2009; Schansker, 2020). In RStudio, one-way ANOVAs were used to compare differences in photosynthetic efficiency, pH, and *A. catenella* cell density on each timepoint of experiments, with post-hoc analysis conducted via Tukey HSD.

A simplified final assay with higher replication ($n = 6$) was conducted with one level of *Ulva* (1.0 g L^{-1}) to collect data on the physiological effects of macroalgae on *A. catenella* that had been observed in prior assays. This assay was conducted as above with an initial cell density of 720 cells mL^{-1} and one timepoint monitoring total *A. catenella* cell density and density of lysed/damaged *A. catenella* cells after 4 days. Samples were preserved in 2% glutaraldehyde and photographed under a 40x objective lens and an oil-immersion 100x objective lens on a Nikon Eclipse E800.

2.3.2. Nutrient amendment experiment

Given that many macroalgae, including *Ulva* spp., have a high assimilatory capacity for nutrients (Neori et al., 2004; Al-Hafedh et al., 2015; Wu et al., 2018), it is possible that one aspect of macroalgal control of HABs is nutrient competition. A laboratory assay was carried out to investigate the contribution of nutrient competition to the inhibition of *Alexandrium catenella* growth by macroalgae. This experiment was conducted using the *A. catenella* strain BF-5 using the culture conditions described in Section 2.1. Treatments consisted of *A. catenella* grown alone and in co-culture with a dense aquaculture concentration of *Ulva* (1.1 g wet weight L^{-1}; prepared as described in 2.3.1.) in standard f/2 media (2000 μM nitrate), f/2 media with added 50 μM ammonium, given the preference of this form of N by *Alexandrium* (Leong et al., 2004; Hattenrath-Lehmann et al., 2010), and f/2 media without nitrogen or phosphate. Each treatment had 5x replication and cell densities and pH were monitored as described above. At experiment conclusion (10 days), an aliquot of each replicate was filtered through combusted (450 °C, 2 h) glass fiber filters for the analysis of dissolved nitrate, ammonium, and phosphate and compared to initial concentrations measured in the same manner. *A. catenella* cell densities at each timepoint were compared between treatments using a two-way ANOVA in RStudio, with presence of *Ulva* and nutrient regime as the factors. Final media concentrations of NO_3^-, NH_4^+, and PO_4^{3-} in *Ulva* and control treatments were compared using Student's *t*-test.

2.3.3. Saxitoxin accumulation experiments

An experiment was conducted to quantify saxitoxin accumulation in blue mussels (*Mytilus edilus*) fed a mixed diet of lab-cultured *Alexandrium catenella* and non-toxic phytoplankton (including *Tetraselmis suecia* and *Tisochrysis lutea/T-iso*), in the presence and absence of aquaculture concentrations of *Saccharina latissima*. This experiment was conducted to assess the potential of macroalgae-bivalve aquaculture integration to mitigate toxin accumulation in shellfish during bloom events. There were two triplicate treatments for the experiment: a control without macroalgae, and a treatment comprised of 1 g L^{-1} *S. latissima*. Mussels 4–6 cm in length were collected from beds in eastern Shinnecock Bay, NY, USA, 24 h prior to experiment initiation in May 2020 when water temperatures were ~18 °C. During the past 15 years of monitoring, elevated densities of *A. catenella* (> 10 cells L^{-1}) have never been observed at this location (C. Gobler, per. obs). Mussels were immediately returned to the laboratory, gently rinsed and cleaned using 0.2μm-filtered seawater and Kimwipes and placed in 0.2μm-filtered seawater at 18 °C for 24 h until experiment initiation. *S. latissima* was collected from staked ropes on an oyster farm in Moriches Bay, NY, USA. Fresh thalli were cleaned and maintained as described in Section 2.2 and maintained in the same environmental chamber as the mussels at 18 °C until experiment initiation.

For experiments, four mussels were added to 8 L polycarbonate vessels filled with 6 L fresh f/2 media made with 0.2 μm filtered seawater and bubbled at a moderate rate with ambient air to maintain phytoplankton suspension and elevated dissolved oxygen levels. *Saccharina latissima* thalli were cut to a wet mass equivalent ~6 g and added to three vessels with mussels while three others served as a control. Vessels were illuminated via a bank of fluorescent lights on a 14h:10h light:dark cycle mimicking day lengths at the time of sugar kelp collection. Replicates were fed by adding 1 L of cultured *Alexandrium catenella* and 1 L of nontoxic phytoplankton. After dilution, these additions resulted in concentrations of algae that represented a dense bloom of *A. catenella* (8-9$\times 10^2$ cells mL^{-1}; (Hattenrath-Lehmann et al., 2010) as well as a level of food needed to sustain blue mussel feeding and growth (*T. suecia* – 2×10^4 cells mL^{-1}, T-iso– 8×10^4 cells mL^{-1}; Helm et al., 2004). During the period 24 h prior to adding the cultures to the experimental vessels with mussels, cultures used for the treatment were exposed to *S. latissima* at an identical concentration used in experiments to establish exposure to macroalgae before consumption by mussels. During the 96 h experiments, mussels were fed once daily the same mixed diet of phytoplankton including *A. catenella* by removing 2 L of experimental water and replacing it with 2 L of cultured algae as described above. Prior to daily feeding, cell counts were conducted on

each of the replicates to quantify consumption of *A. catenella*; in all cases, few if any phytoplankton cells, including A. catenella, remained in every replicate after the 24 h feeding period. *A. catenella* and nontoxic phytoplankton stock cultures were then counted and refed to replicates as described above; densities of *A. catenella* immediately post-feeding were 898±17 cells mL^{-1}, well-above densities known to make blue mussels toxic (i.e., 250 cells mL^{-1}) in as little as one day (Bricelj et al., 1990). After 96 h, mussels from each replicate were removed from experimental vessels, shucked, soft tissue combined and homogenized, and frozen in 50 mL centrifuge tubes. These samples were then shipped to the Bigelow Laboratory for Ocean Sciences in East Boothbay, ME, USA for saxitoxin content analysis using the post-column oxidation (PCOX) method (Van De Riet et al., 2011; Hattenrath-Lehmann et al., 2017). Mean total toxicity (μg STX eq 100 g^{-1}) in each treatment was then compared with a *t*-test using RStudio.

2.3.4. Bottle incubations

To evaluate the effects of macroalgae on wild populations of *Alexandrium catenella*, two sets of bottle incubation experiments with estuarine water collected from blooms were conducted in 1 L polyethylene bottles. The first was conducted using water from a bloom of *A. catenella* in Weesuck Creek, NY, USA, during April 2019 and examined the effects of the three macroalgae (*Ulva, Saccharina latissima*, and *Chondrus crispus*) at a high aquaculture concentration (3 g L^{-1}). The second experiment, conducted with the May 2019 population of A. catenella from Old Fort Pond, NY, USA. This experiment used multiple densities of the two most effective macroalgae from the previous bottle experiment, *Ulva* and *S. latissima*. In all cases, macroalgae were collected and prepared for experiments in an identical manner to the laboratory assays described above.

Bottles were randomly arranged in an environmental chamber set to the temperature of the water in the field at time of collection, with illumination at ~100 μmol photons $m^{-2}s^{-1}$ on a 12:12 h L:D cycle, a day length slightly shorter than ambient at the time of collection (14 h). Bottles were gently aerated with filtered air to maintain pH at ambient levels (~8.1). Two treatments were established using the bloom water: a treatment that received daily nutrient supplementation (5 μM nitrate, 0.3 μM orthophosphate, mimic nutrient loading rates in NY estuaries (Kinney and Valiela, 2011)), and a treatment that received the same levels of nutrients and the macroalgae. At the conclusion of experiments, samples for *Alexandrium catenella* cell density were collected. To differentiate *A. catenella* from other dinoflagellates, samples were preserved in formaldehyde and then methanol prior to hybridization with a probe specific for the NA1 North American (Group I) ribotype *A. fundyense/catenella/tamarense* with Cy3 dye conjugated to the 5′ terminus (5′-/5Cy3/AGT GCA ACA CTC CCA CCA-3′). Cells were then enumerated using a Nikon epifluorescent microscope with a Cy3™ filter cube (Anderson et al., 2005). Final timepoint pH was measured using a Thermo Orion™ Flat Surface pH electrode, and final timepoint dissolved nutrient samples were collected from each replicate. For the first experiment, FV/FM was also measured on a PhytoPam II fluorometer as described earlier. *A. catenella* cell densities, nutrient concentrations, and pH were compared using one-way ANOVAs conducted in RStudio, with post-hoc comparisons between groups via Tukey's HSD.

2.3.5. Mesocosm experiments

Finally, mesocosm experiments were conducted to provide an ecosystem level representation of macroalgae effects on *Alexandrium catenella* populations. The Stony Brook – Southampton Mesocosm Facility, which has been used previously to explore various estuarine processes (Wall et al., 2008, 2011; Harke et al., 2011), was used to conduct mesocosm incubations of wild populations of *A. catenella* with both *Ulva* and *Saccharina latissima*. For each experiment, polyethylene mesocosms (Nalgene©; volume 300 L, inner diameter 60 cm, depth 1.2 m) were anchored to a floating dock in Old Fort Pond at the Stony Brook – Southampton Marine Science Center. Mesocosms were ~90% immersed during experiments, maintaining prevailing temperature, light, and wind conditions typical of NY estuaries on the south shore of Long Island.

Alexandrium catenella bloom water for the first mesocosm experiment, conducted in April 2019, was collected from Weesuck Creek, NY, using submersible pumps that transferred water to holding tanks on the *R/V Peconic* which were transported to the mesocosm site. The second mesocosm experiment in May 2019 was conducted during an intense bloom of *A. catenella* at the mesocosm site, and bloom water was pumped directly into the mesocosms from the surrounding water. In all cases, small amounts of water (~20 L) was progressively and randomly added to mesocosms to ensure equal distribution of potentially patchy plankton populations.

In each experiment, there were three treatment groups, with triplicate replication in the first experiment and quadruplicate replication in the second experiment. The first treatment was a control, containing only the bloom water. In the second treatment, nutrients were administered as described for bottle experiments. In the final treatment, nutrients were administered and macroalgae (1 g L^{-1}) was added to the mesocosms. Macroalgae for these experiments were either intertwined in, or grown on, ropes strung across the surface of the mesocosms, mimicking an aquaculture setting. The first experiment used field-collected Ulva while the second used aquacultured *Saccharina latissima* intertwined into ropes. A laminar circulation pump (Rio® 180 Mini; 450 L h^{-1}) was fitted inside each mesocosm a few centimeters below the surface to ensure adequate mixing of water column (Wall et al., 2008, 2011).

Experiments persisted for 48 – 96 h during which time data were collected at the same time each morning to minimize the effect of diel patterns. Water (2 L) was collected from each mesocosm for the analysis of dissolved nutrients, chlorophyll *a*, and *A. catenella* cell densities. Nutrient samples were filtered as described above. Chlorophyll *a* samples were obtained using 0.2 μm polycarbonate filters and analyzed using a Trilogy Fluorometer (Turner Designs™) using standard, non-acidification methods (Welschmeyer, 1994). At the end of each experiment, concentrated water samples were preserved for molecular confirmation of *A. catenella* cell density using a fluorescent in-situ hybridization (FISH) probe described by Anderson et al. (2005). These samples were processed in an identical manner as the bottle incubation experiments. *A. catenella* cell densities, pH, and concentrations of NO_3^-, NH_4^+, and PO_4^{3-} were compared using one-way ANOVAs with post-hoc comparison between groups conducted via Tukey HSD using RStudio.

3. Results

3.1. Co-incubation growth assays

The addition of fresh thalli of *Ulva* spp., *Chondrus crispus*, and *Saccharina latissima* to cultured *Alexandrium catenella*, in all tested concentrations but one (lowest concentration of *C. crispus*), resulted in significantly lower densities of *A. catenella* compared to control treatments during incubations at all three temperatures tested (15 °C, 18 °C, 21 °C) (Fig. 1,2). In all cases but one, macroalgae addition at any concentration resulted in not only growth inhibition but distinct morphological changes in *A. catenella*. These changes were characterized by cell shrinkage within theca, chlorosis, and ultimately lysis, as shown in samples exposed to 1 g L^{-1} *Ulva* for 96 h (Fig. 3). In the first assay conducted at 21 °C (strain CCMP2304; Fig. 1A), all three levels of Ulva addition (0.7 g L^{-1}, 1.1 g L^{-1}, 1.8 g L^{-1}) resulted in a significant reduction in *A. catenella* cell density of 42–70% relative to the control by day 4 (Fig. 1A, $p<0.01$, ANOVA), with the highest concentration of Ulva resulting in significantly lower *A. catenella* within 2 days (Fig. 1A, $p<0.01$, Tukey HSD), and the middle concentration having significant effect within 3 days (Fig. 1A, $p<0.01$, Tukey HSD). In the second assay conducted at 18 °C (strain NP8; Fig. 1B), the *Ulva* addition (0.9 g L^{-1}) and the two higher levels of *C. crispus* (1.8 g L^{-1}, 2.4 g L^{-1}) significantly

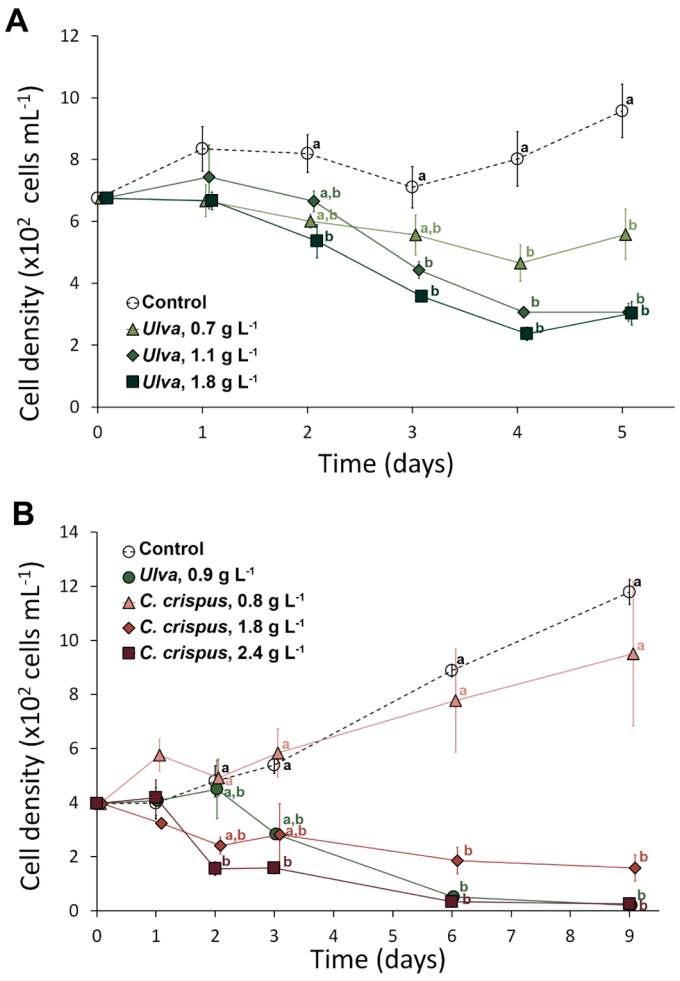

Fig. 1. Densities of *A. catenella* exposed to multiple concentrations of macroalgae at different temperatures. (A) *A. catenella* strain CCMP2304 incubated with different levels of *Ulva* at 21 °C; (B) *A. catenella* strain NP8 incubated with different levels of *C. crispus* at 18 °C. Data points are means ± SE ($n = 3$). Letters represent significantly different groups formed by pairwise comparison between treatments using Tukey HSD.

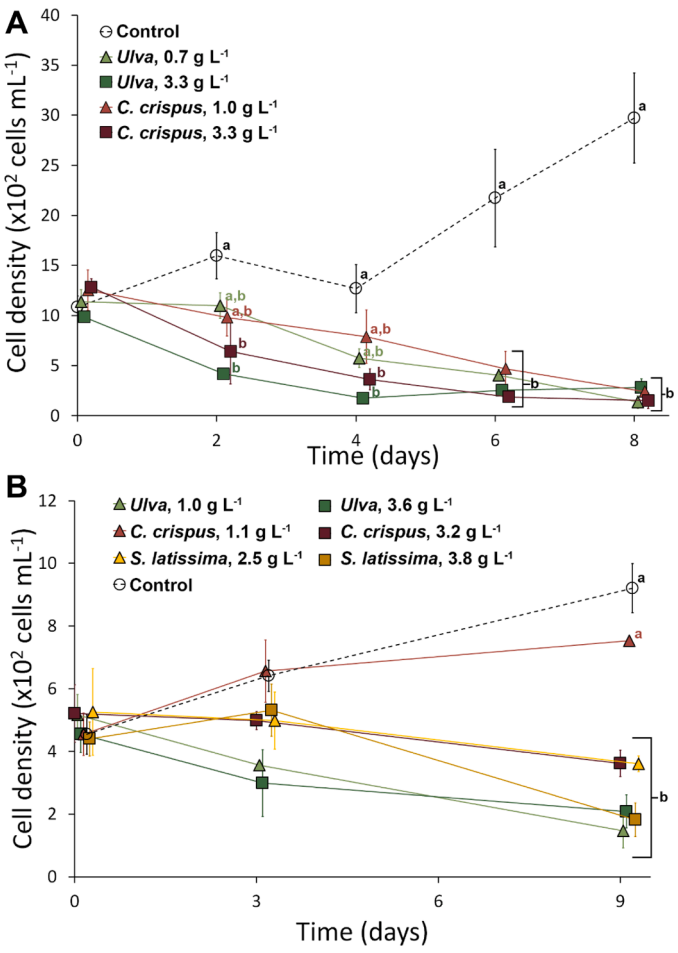

Fig. 2. Densities of *A. catenella* exposed to multiple concentrations of macroalgae at different temperatures. (A) *A. catenella* strain CCMP2304 incubated with multiple levels of *Ulva* and *C. crispus* at 18 °C; (B) *A. catenella* strain CCMP2304 incubated with multiple levels of *Ulva, C. crispus*, and *S. latissima* at 15 °C. Data points are means ± SE ($n = 3$). Letters represent significantly different groups formed by pairwise comparison between treatments using Tukey HSD following ANOVA.

reduced *A. catenella* density in 6 days by 79–96% (Fig. 1B, $p<0.01$, ANOVA), with only the highest concentration of *Chondrus crispus* significantly decreasing *A. catenella* prior to that (Fig. 1B, 2 days, $p<0.01$, Tukey HSD). The third assay (strain CCMP2304; Fig. 2A), conducted at 18 °C with high and low concentrations of both *Ulva* (0.7 g L^{-1}, 3.3 g L^{-1}) and *C. crispus* (1.0 g L^{-1}, 3.3 g L^{-1}), showed *A. catenella* densities significantly reduced by 60–74% in both high macroalgae concentration treatments after 2 days and by 88–91% after 6 days (Fig. 2A, $p<0.01$, Tukey HSD), with the lower concentration treatments showing significant reductions of 78–81% only after 6 days (Fig. 2A, $p<0.01$, ANOVA). The fourth assay (strain CCMP2304; Fig. 2B), testing high and low concentrations of Ulva (1.0 g L^{-1}, 3.6 g L^{-1}), *S. latissima* (2.5 g L^{-1}, 3.8 g L^{-1}), and *C. crispus* (1.1 g L^{-1}, 3.3 g L^{-1}) at 15 °C, showed significant inhibition only by the high concentration of *Ulva* in 3 days (53% reduction) and by all macroalgae treatments except the low concentration of *C. crispus* in 9 days, with *A. catenella* densities reduced by 61%–84% (Fig. 2B, $p<0.0001$, ANOVA, Tukey HSD). Except for the low-concentration (0.8–1.1 g L^{-1}) of *C. crispus* in the second and fourth assays, the addition of all species and concentrations of macroalgae significantly reduced density of *A. catenella* in culture.

In the fifth assay (strain CCMP2304 at 18 °C), *Alexandrium catenella* cell density after four days was reduced significantly by Ulva to 350 ± 171 cells mL^{-1} compared to the control (1258 ± 235 cells mL^{-1}; $p<0.0001$; *t*-test), with a significantly higher prevalence of cell lysis in the *Ulva* treatment (39.9%±31.6% lysed) compared to the control (2.2%±1.8% cells lysed; $p<0.05$; *t*-test). As observed with other macroalgae in previous experiments, *A. catenella* exposed to *Ulva* took on a distinct morphology before undergoing cell lysis, with the cell shrinking within the theca and losing pigmentation prior to lysis (Fig. 3). While some lysed and damaged cells along with cellular debris were visible in the control treatment, these cells did not exhibit loss of pigmentation or reduced cell size.

Across the assays in which it was measured, maximum photochemical quantum yield of PS II (F_V/F_M) of *Alexandrium catenella* was significantly inhibited by *Ulva* and to a lesser extent by *C. crispus* ($p<0.01$, ANOVA, Fig. 4). In an assay with two concentrations of *C. crispus* and *Ulva* (Fig. 4), the high concentration of *Ulva* caused a precipitous and significant drop in F_V/F_M from 0.6 to 0.1 by day 4 (Fig. 4, $p<0.01$, ANOVA), with the lower concentration of *Ulva* displaying a similar effect by day 6 (Fig. 4, $p<0.01$, ANOVA). The higher concentration of *C. crispus* showed a significantly decreased F_V/F_M (0.2) by days 6 and 8 (Fig. 4, $p<0.01$, ANOVA). Similarly, in the fourth assay, the higher dose of *Ulva* caused a significant reduction in F_V/F_M by the third day ($p<0.001$, Tukey HSD), with the smaller dose of *Ulva* showing a smaller reduction in yield compared to the other macroalgae treatments and control; by the ninth day, both *Ulva* treatments significantly

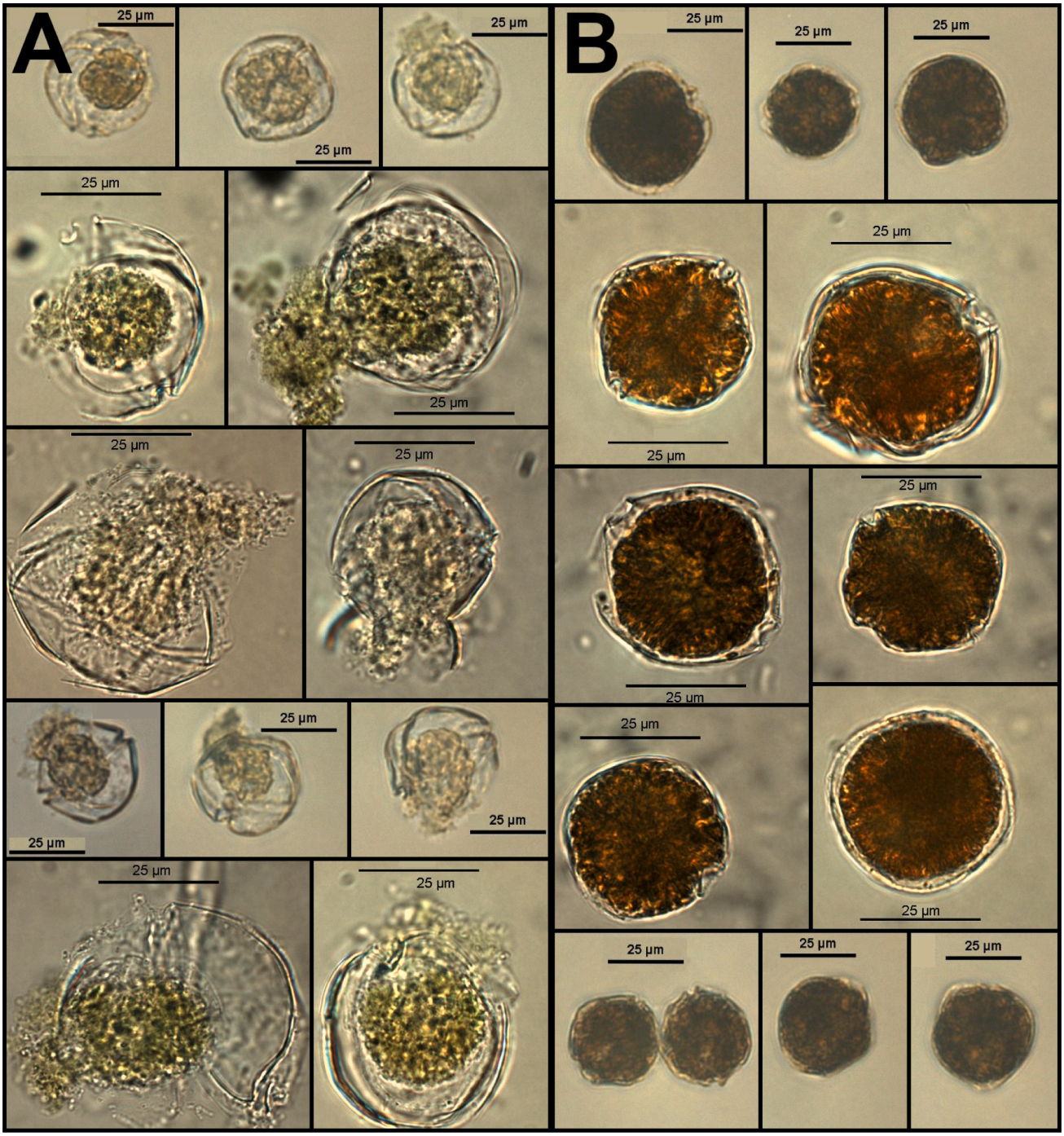

Fig. 3. Light microscopy images of *A. catenella* cells under 40x or 100x objective lens. Side A: after 96 h incubation with 1 g L^{-1} *Ulva* tissue; Side B: after 96 h incubation without macroalgae.

reduced F_V/F_M ($p<0.01$, Tukey HSD) while other macroalgae did not (Table 2). These results suggest that *Ulva* has a strong, dose-dependent negative effect on F_V/F_M in *A. catenella*, while the photochemical effects induced by *C. crispus* were comparatively more subtle.

In all assays, macroalgae significantly increased pH in a dose-dependent manner, although the magnitude of the pH effect was dependent upon the macroalgae species. Across assays, control pH levels remained between 8.0–8.3 across experiments (Fig. 5). *Ulva* had the greatest effect on pH, typically causing elevation to the 9.0–9.5 range but sometimes exceeding 10, while *C. crispus* (8.4–9.0) and *Saccharina latissima* (8.8–9.0) had more modest effects. A combined analysis of pH across all four experiments using a two-way ANOVA using macroalgae species and concentration as factors showed that macroalgae species was highly significant ($p<0.0001$), while macroalgae concentration was not. There was a significant interactive effect between macroalgae species and concentration (Fig. 5, $p<0.01$) likely due to the species-specific dose-responses of pH. Regression analyses showed that the concentrations of *Ulva* ($R^2=0.29$, $p<0.01$, linear regression) and *C. crispus* ($R^2=0.87$, $p<0.0001$, linear regression) were significantly correlated with pH, while the concentrations of *S. latissima* were not.

3.2. Nutrient amendment experiment

An experiment was performed assessing the effects of *Ulva* on

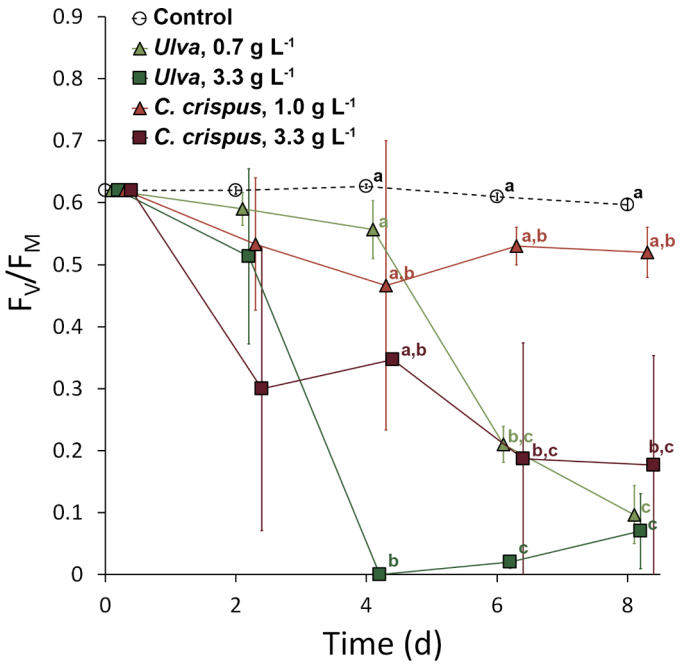

Fig. 4. Dark-adapted maximum photochemical quantum yield (F_V/F_M) of *A. catenella* co-cultured with two densities of *Ulva* and *C. crispus* over the eight-day laboratory assay depicted in Fig. 2A. Error bars are ±SE ($n = 3$), and letters represent significantly different groups formed by pairwise comparison between treatments at each timepoint using Tukey HSD following ANOVA.

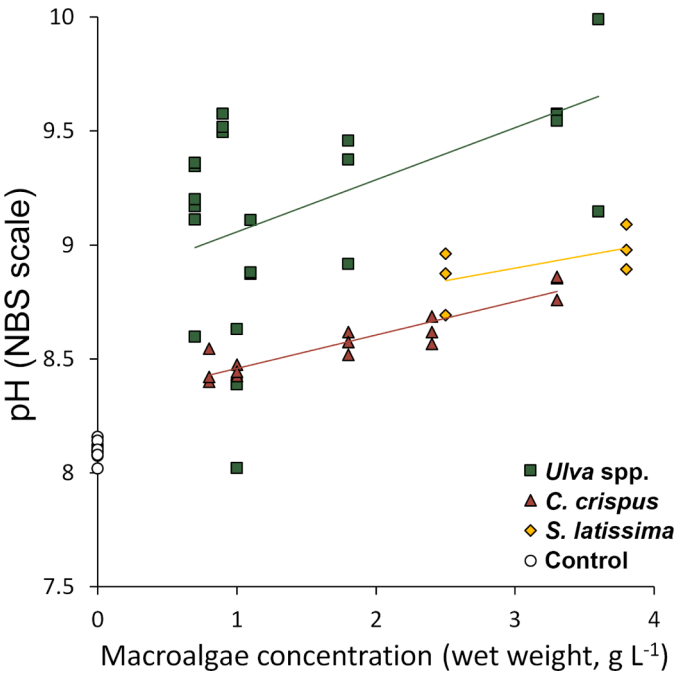

Fig. 5. All pH values obtained in laboratory assays, measured at the end of each experiment. Regression analyses on each individual macroalgae species showed that the concentration of both *Ulva* (R^2=0.29, p<0.01) and *C. crispus* (R^2=0.87, p<0.0001) significantly correlated with pH.

Table 2
Dark-adapted maximum photochemical quantum yield (F_V/F_M) of *A. catenella* co-cultured with two densities of *Ulva, C. crispus*, and *S. latissima* over a nine-day laboratory assay at timepoints $t = 3$ d and $t = 9$ d ($n = 3$). Values for F_V/F_M are mean ± standard deviation.

Treatment	F_V/F_M(t = 3 d)	p value(vs control; Tukey HSD)	F_V/F_M(t = 9 d)	p value(vs control; Tukey HSD)
Control	0.63 ± 0.04	n/a	0.63 ± 0.02	n/a
Ulva (1.0 g L^{-1})	0.51 ± 0.07	$p > 0.05$	0.00 ± 0.00	$p < 0.0001$
Ulva (3.6 g L^{-1})	0.36 ± 0.10	$p < 0.001$	0.18 ± 0.24	$p < 0.01$
C. crispus (1.1 g L^{-1})	0.64 ± 0.01	$p > 0.05$	0.64 ± 0.02	$p > 0.05$
C. crispus (3.2 g L^{-1})	0.62 ± 0.02	$p > 0.05$	0.53 ± 0.12	$p > 0.05$
S. latissima (2.5 g L^{-1})	0.63 ± 0.01	$p > 0.05$	0.59 ± 0.02	$p > 0.05$
S. latissima (3.8 g L^{-1})	0.63 ± 0.01	$p > 0.05$	0.62 ± 0.04	$p > 0.05$

Alexandrium catenella grown under high (f/2), high with ammonium supplementation (f/2 + 50 μM NH_4^+), and low nutrient levels (no N or P added). Of the three nutrient regimes, only the high nutrient treatment (standard f/2 media) resulted in exponential growth in the control, with both NH_4^+ supplementation and nutrient starvation resulting in slower growth in the controls (strain BF-5; Fig. 6). The presence of *Ulva* was a significant factor in growth rate reduction (p<0.0001, Two-way ANOVA), while nutrient regime was not (Fig. 6). In all cases, treatments exposed to *Ulva* grew significantly slower than the respective control, with significantly lower *A. catenella* density at nearly every timepoint (Fig. 6, p<0.05, Tukey HSD).

Nutrient concentrations at the end of this experiment were lower in *Ulva* treatments compared to their control counterparts (Table 3). In the f/2 media group, *Alexandrium catenella* without *Ulva* addition utilized

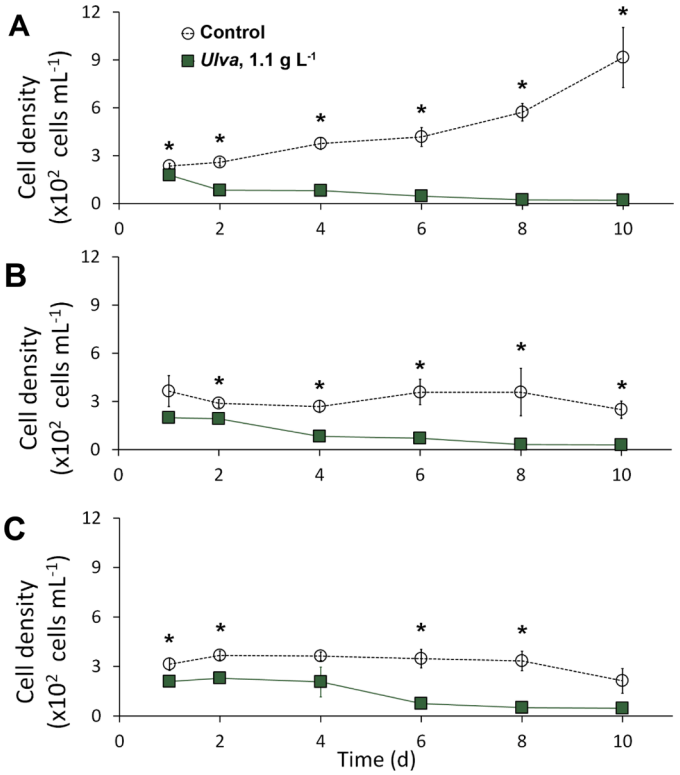

Fig. 6. Cell densities of *A. catenella* exposed to *Ulva* in different nutrient regimes (A) f/2 media, (B) f/2 media with 50 μM ammonium, (C) f/2 media without added N or phosphate. Data points are means±SE ($n = 4$), asterisks indicate significant differences in *A. catenella* density at individual timepoints (p<0.05, ANOVA).

3.8% of initial NO_3^- and 9.8% of available PO_4^{3-} over the 10-day

Table 3
Nutrient measurements of initial media for nutrient amendment. Initial measurements are of culture media, while final measurements were taken of each replicate for each treatment ($n = 4$). Mean final treatment concentrations are shown with standard deviation in parentheses.

Treatment	Initial media concentration (μM)			Final concentration (μM)		
	NO_3^-	NH_4^+	PO_4^{3-}	NO_3^-	NH_4^+	PO_4^{3-}
f/2	799.6	1.5	33.6	769.3 (3.6)	1.2 (1.1)	30.3 (0.5)
f/2, *Ulva*				314.8 (49.8)	0.8 (0.1)	2.0 (2.0)
f/2 + NH_4^+	693.2	51.3	35.2	831.7 (17.0)	15.8 (7.5)	31.4 (0.6)
f/2 + NH_4^+, *Ulva*				269.3 (98.9)	0.9 (0.1)	2.0 (0.5)
f/2 -N, -P	23.7	1.3	3.3	1.4 (1.5)	0.7 (0.4)	0.8 (0.4)
f/2 -N, -P, *Ulva*				4.2 (7.3)	1.6 (0.6)	0.4 (0.1)

incubation, while the combined *A. catenella* and *Ulva* treatment utilized 60.6% of available NO_3^- and 94.2% of available PO_4^{3-} over the same period with NO_3^- ($p < 0.0001$, *t*-test) and PO_4^{3-} ($p<0.0001$, *t*-test) levels being significantly lower than the control without *Ulva*. In the ammonium media group, *A. catenella* without *Ulva* addition utilized 69.2% of initial NH_4^+ and 10.8% of initial PO_4^{3-} over the 10 day incubation, with the concentration of NO_3^- increasing by 20%; in the *Ulva* treatment, NH_4^+ was reduced by 98.2%, PO_4^{3-} by 94.3%, and NO_3^- by 61.2% with the final concentrations of NO_3^- ($p<0.0001$, *t*-test), NH_4^+ ($p<0.01$, *t*-test), and PO_4^{3-} ($p<0.0001$, *t*-test) being significantly lower than the control without *Ulva*. Finally, in the nutrient starved group, *A. catenella* without *Ulva* utilized 94.1% of NO_3^- and 75.8% of PO_4^{3-} over the 10-day incubation, while the *Ulva* treatment utilized 82.3% of NO_3^- and 87.9% of PO_4^{3-}. In the nutrient starved group, differences in nutrient concentrations between the *Ulva* and no *Ulva* treatments were not significant.

3.3. Toxin accumulation experiment

At the end of a four-day exposure to *Alexandrium catenella* (strain BF-5), total toxicity (μg saxitoxin equivalents 100 g^{-1} tissue) of mussels grown together with 1 g L^{-1} *Saccharina latissima* was significantly (23%) lower (71.80±1.98 μg STX diHCl eq 100 g^{-1}) than in the control treatment grown without macroalgae (93.47±8.11 μg STX diHCl eq 100 g^{-1}) (Fig. 7, $p<0.05$, ANOVA).

3.4. Bottle incubations

The first bottle incubation was conducted April 2019 with bloom water from Weesuck Creek, NY, USA. In all three macroalgae-added treatments, *Alexandrium catenella* cell densities at the end of the four day incubation were significantly higher in the nutrient-supplemented control ($2.9\times10^3 \pm 1.5\times10^3$ cells mL^{-1}) compared to the nutrient-supplemented treatments exposed to *Ulva* (157±87 cells mL^{-1}), *Chondrus crispus* (573±329 cells mL^{-1}), and *Saccharina latissima* (143±38 cells mL^{-1}) (Fig. 8A, $p<0.01$, Tukey HSD). At the conclusion of the experiment, pH was elevated relative to the nutrient control (8.14±0.05) in the *Ulva* (8.77±0.33), *C. crispus* (8.52±0.07), and *S. latissima* (8.17±0.11) treatments, but was significantly different from the control in the *Ulva* and *C. crispus* treatments only (Fig. 8B, $p<0.0001$, Tukey HSD). There were no significant differences in concentrations of NO_3^-, NH_4^+, or PO_4^{3-} at the conclusion of the experiment (Fig. 8C, ANOVA). F_V/F_M of the phytoplankton community was significantly reduced only by *Ulva* (Fig. 8D, $p<0.0001$, Tukey HSD).

The second bottle incubation experiment examined two levels of *Ulva* and *Saccharina latissima* during May 2019 using water from Old Fort Pond, NY, USA when *Alexandrium catenella* cell densities were 2.7×10^3 cells mL^{-1}. At the end of the four-day incubation *A. catenella* cell densities were significantly and 80±21% lower in the macroalgae

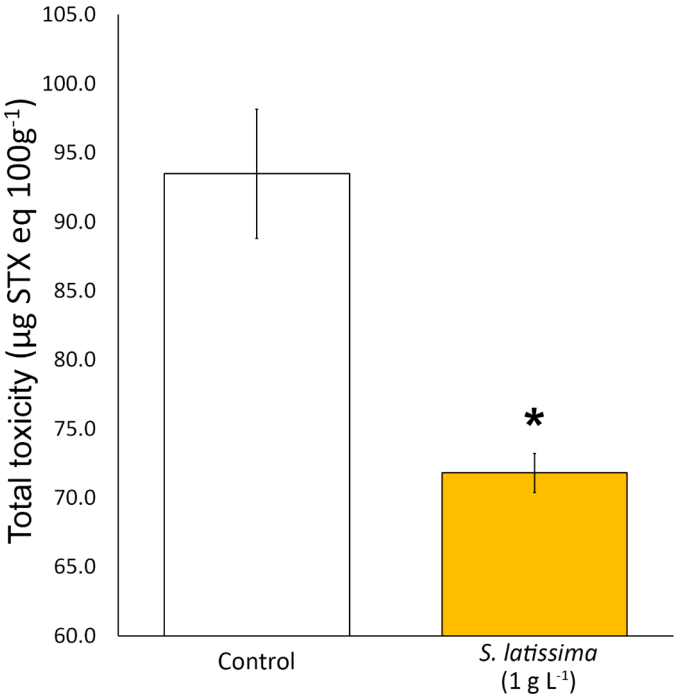

Fig. 7. Saxitoxin concentration in mussels fed *A. catenella* over 96 h with and without *S. latissima*. *S. latissima* significantly reduced toxicity of mussels ($p<0.05$, ANOVA).

treatments than the control, but there were no significant differences between macroalgae treatments (Fig. 9A, $p<0.0001$, Tukey HSD). While the higher concentrations of *Ulva* and *S. latissima* (6 g L^{-1}) resulted in lower *A. catenella* cell densities (84 ±10% reduction) than the lower concentrations (3 g L^{-1}; 76±29% reduction; Fig. 9A), differences were not statistically significant. pH was significantly elevated by *Ulva* in a dose-dependent manner, with the denser treatment of *Ulva* resulting in a significantly higher pH (9.22±0.23) than the lower density of *Ulva* (8.70 ± 0.22; Fig. 9B, $p<0.0001$, ANOVA, Tukey HSD). The lower density *S. latissima* treatment also caused significantly elevated pH (8.50 ± 0.08; Fig. 9B, $p<0.05$, ANOVA, Tukey HSD), while value from the higher density treatment were not available. There were no differences in ammonium or phosphate concentrations across treatments; however, in both *Ulva* treatments, nitrate was significantly reduced compared to the control (73±26% reduction; Fig. 9C, $p\leq0.01$, Tukey HSD). There was also a large, 63% nitrate reduction in the high-density *S. latissima* treatment, but this was not statistically significant (Fig. 9C, $p>0.05$, Tukey HSD).

3.5. Mesocosm experiments

The first mesocosm experiment was performed in April 2019 with *Alexandrium catenella* bloom water collected from Weesuck Creek, NY, USA, with an initial density of ~485 *A. catenella* cells L^{-1} and persisted for 4 days (Fig. 10). Without *Ulva*, daily supplementation with nutrients resulted in a significant increase in *A. catenella* cell density over the course of the experiment; however, the same supplementation regime together with addition of 1 g L^{-1} *Ulva* resulted in a decline in *A. catenella* nearly identical to the nutrient-starved control (Fig. 10A, $p<0.01$, Tukey HSD). Compared to the nutrient treatment, the addition of *Ulva* resulted in a 54% reduction in *A. catenella* bloom density over the 96 h experiment. The *Ulva* treatment with nutrients had significantly lower concentrations of NO_3^- and PO_4^{3-} than the nutrient treatment (Fig. 10B, $p<0.05$, Tukey HSD). There were no differences in total chlorophyll *a* between the control (11.60±3.74 mg L^{-1}), nutrient (9.38±1.64 mg L^{-1}), and Ulva (14.67±3.12 mg L^{-1}) treatments.

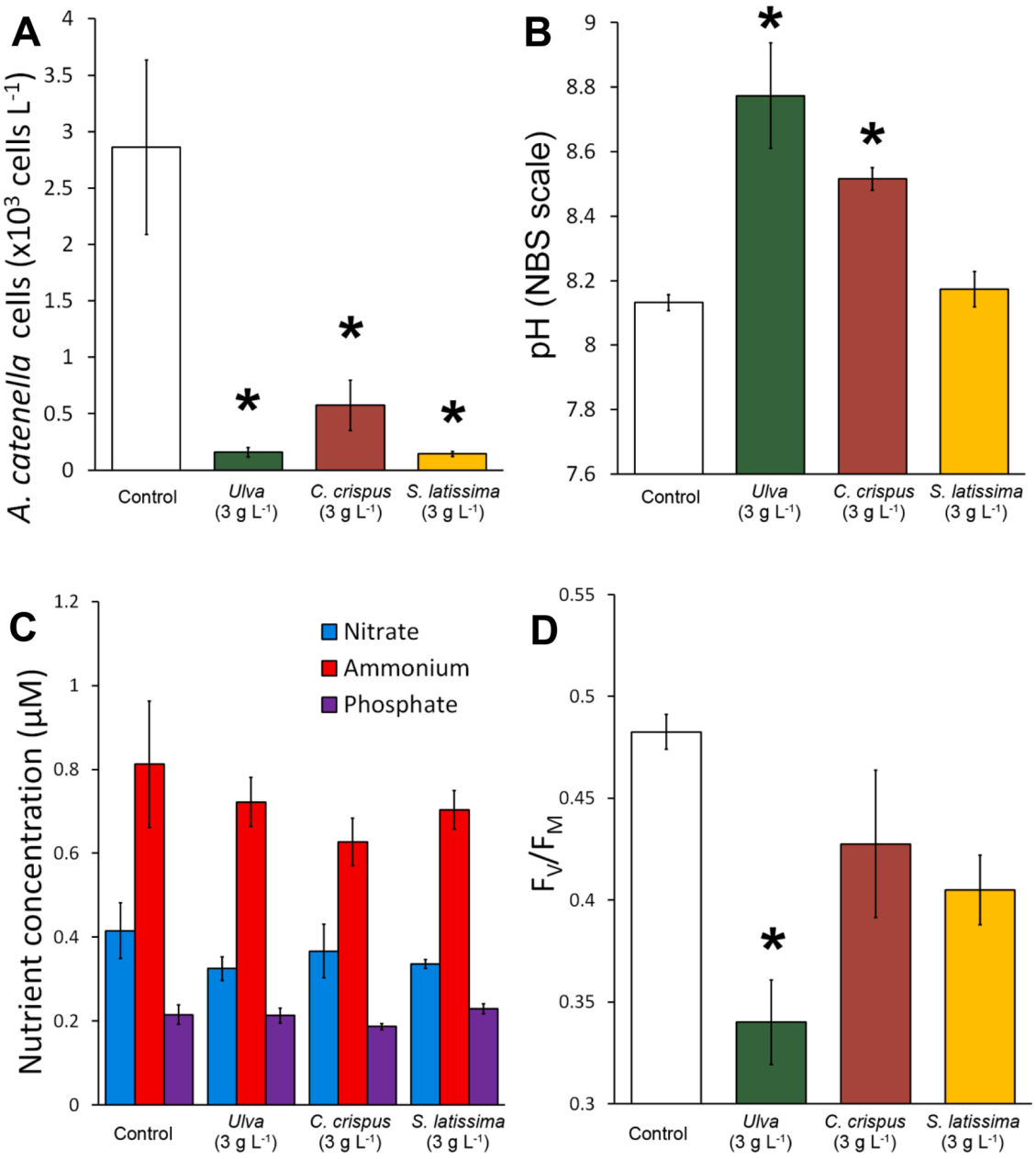

Fig. 8. . Field-based bottle incubation experiment (96 h), April 2019: (A) FISH-probe enumerated *A. catenella* cell density, (B) pH (NBS scale), (C) concentration of nitrate, ammonium, and phosphate, and (D) phytoplankton community F_V/F_M. Bars are means ± SE (n = 4); asterisks indicate significant differences from the control (ANOVA).

The second mesocosm experiment occurred in May 2019 with *Alexandrium catenella* bloom water collected from Old Fort Pond, NY, USA, with an initial density of ~3×10^5 A. catenella cells L^{-1} and persisted for 48 h (Fig. 11). *A. catenella* densities in the *Saccharina latissima* (1 g L^{-1}) with nutrients treatment were 73% lower than the nutrient only treatment (Fig. 11A, $p<0.005$, Tukey HSD). pH was significantly elevated in the *S. latissima* plus nutrient treatment (7.80±0.05) compared to both the control (7.58±0.04) and nutrient only treatments (7.59±0.01; Fig. 11B, $p<0.005$, Tukey HSD). The *S. latissima* + nutrients treatment had significantly lower concentrations of NO_3^- ($p<0.001$, Tukey HSD), NH_4^+ ($p<0.01$, Tukey HSD), and PO_4^{3-} ($p<0.001$, Tukey HSD) than the nutrient treatment (Fig. 11C). There were no differences in chlorophyll *a* between the control (3.12±1.04 mg L^{-1}), nutrient (3.21±2.21 mg L^{-1}), and *S. latissima* (3.90±1.47 mg L^{-1}) treatments.

4. Discussion

4.1. Overview

Previous studies have reported that living macroalgae can reduce the growth rate of, and have algicidal activity towards, HAB-causing phytoplankton. Overwhelmingly, these studies have focused on *Ulva* spp. including *U. lactuca* (Nan et al., 2008; Tang and Gobler, 2011), *U. pertusa* (Jin and Dong, 2003; Nan et al., 2004; Jin et al., 2005; Wang et al., 2007), and *U. linza* (Jin et al., 2005), and have been conducted using clonal laboratory cultures of phytoplankton. These studies have shown that anti-algal properties of macroalgae are highly specific to the target phytoplankton species, with the same concentrations of *Ulva* causing slight reductions in growth rate in some phytoplankton, and overwhelming algicidal activity in others (Jin and Dong, 2003; Nan et al., 2004, 2008; Wang et al., 2007; Tang and Gobler, 2011; Tang et al.,

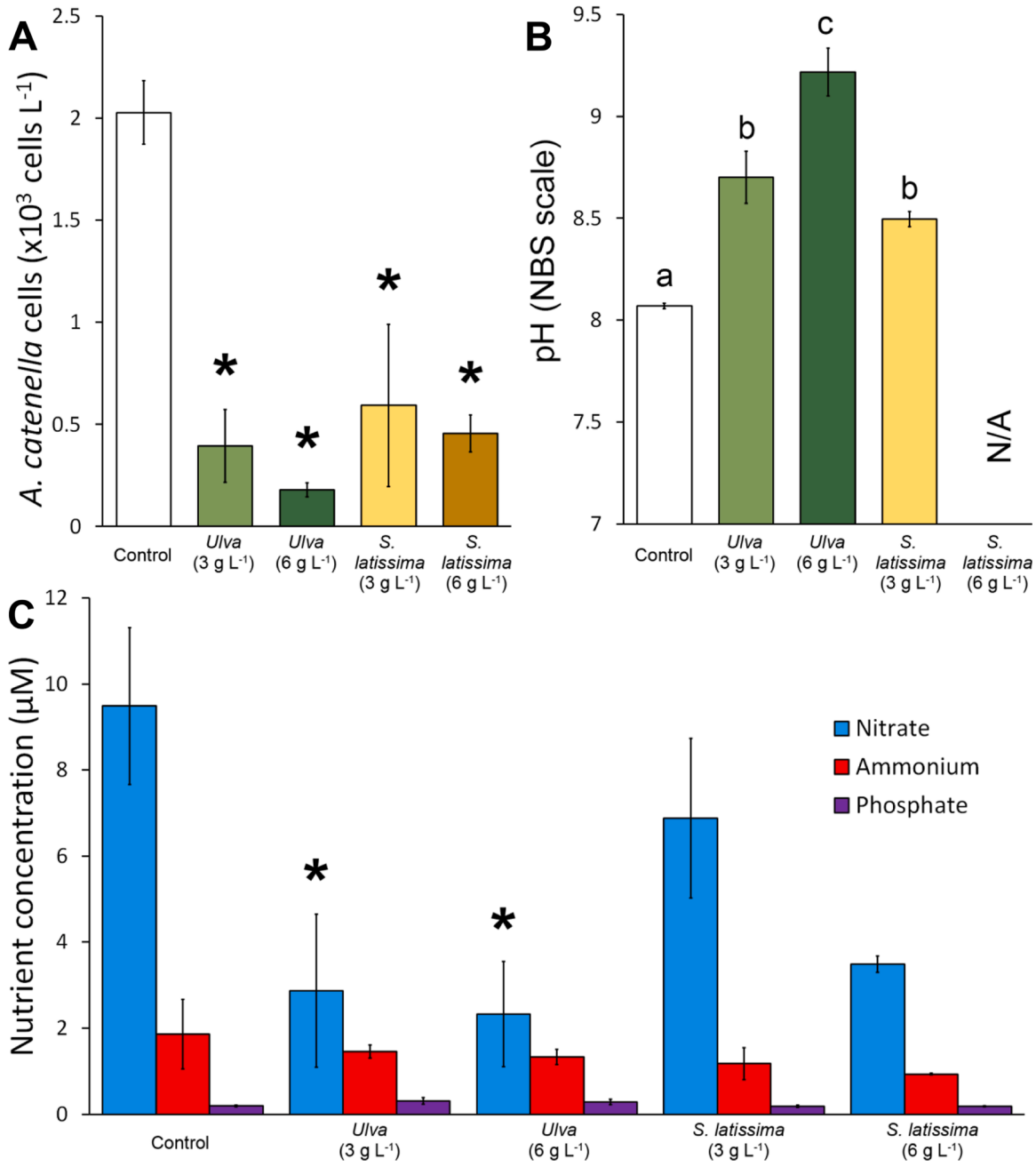

Fig. 9. Field-based bottle incubation experiment (96 h), May 2019: (A) FISH-probe enumerated *A. catenella* cell density, (B) pH, (C) concentration of nitrate, ammonium, and phosphate. Bars represent mean ± SE ($n = 4$), and asterisks indicate significant differences from the control according to ANOVA. Letters in the pH figure represent results of pairwise comparisons between groups using Tukey HSD. N/A indicates data not available.

2014). To mitigate the effects of HABs with seaweed aquaculture, it is therefore necessary to investigate the effectiveness of aquaculture-suitable seaweeds on individual target HABs. Our results demonstrate that *Alexandrium catenella*, one of the most dangerous and costly HAB species on the planet (Anderson et al., 2012a; Lewitus et al., 2012; Vandersea et al., 2018), experiences strong algicidal effects when exposed to aquaculture appropriate concentrations of *Saccharina latissima* (sugar kelp) and *Chondrus crispus*, two macroalgae species with established aquaculture protocols (Redmond et al., 2014), in addition to *Ulva*. All three macroalgae inhibited growth and caused cell lysis in three North American strains of *A. catenella*, and in diverse bloom populations of *A. catenella* within mixed phytoplankton communities from multiple NY estuaries. Furthermore, *S. latissima* co-incubated with blue mussels (*Mytilus edilus*) significantly reduced saxitoxin concentrations in mussel tissues relative to the control experiments with cultured *A. catenella*. Collectively, these results bring novel insight into the manner in which the aquaculture of seaweeds may be useful for the mitigation of HABs caused by *A. catenella*.

4.2. Mechanisms for Alexandrium catenella inhibition

Exposure to macroalgae not only caused significant reduction in *A. catenella* cell densities, but observable lysis of *A. catenella* cells following the development of a distinct damaged morphology. When co-incubated with macroalgae, *A. catenella* cells visibly shrank within the theca and developed a lighter, yellowish-green coloration compared to the deep orange-black pigmentation observed in healthy cells from control treatments. These macroalgae-exposed cells ultimately lysed

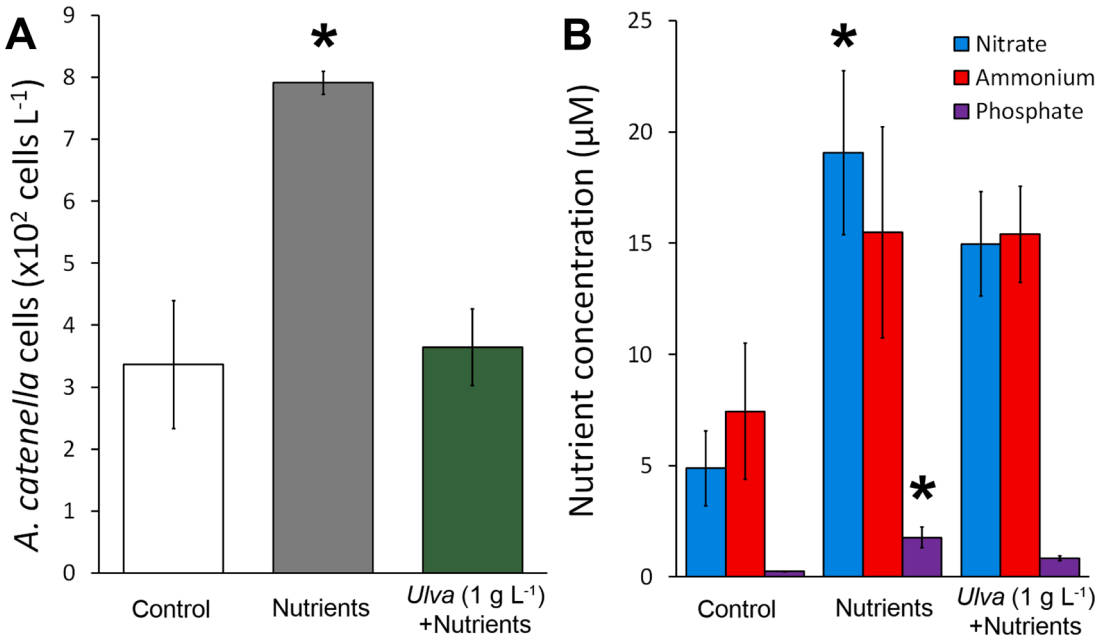

Fig. 10. . Mesocosm experiment (96 h) performed during April 2019 (A) FISH-probe enumerated *A. catenella* cell density ($p = 0.006$), (B) concentration of nitrate, ammonium, and phosphate. Bars represent mean ± SE ($n = 3$), and asterisks indicate significant differences from the control according to ANOVA.

with the cell contents spilling out of the ruptured theca. There are multiple ways macroalgae can cause these growth-inhibiting and algicidal effects, including allelopathy, nutrient competition, pH elevation, and algicidal bacteria; our results provide insight as to the relative contribution of these phenomena within the context of this study.

Macroalgae have an enormous assimilatory capacity for nutrients (Valiela et al., 1997; Neori et al., 2004) and are deployed purposefully in many parts of the world to reduce nutrient loads in coastal waters (Chopin et al., 2001; Neori et al., 2004; Carmona et al., 2006). Given that many HABs, including *Alexandrium catenella*, can be promoted by nutrients (Hattenrath-Lehmann et al., 2010; this study), the observed inhibitory effects may be a result of nutrient competition. Rapid nutrient assimilation did indeed occur in our experiments, with NO_3^- concentrations being reduced from >~770 μM to ≤~300 μM in treatments with *Ulva* and *A. catenella* cultured for 10 days. Across all culture experiments, however, DIN (NH_4^++NO_3^-) levels were never reduced below 5.8 μM in any *Ulva* treatment. The half saturation constant (K_s) for nitrogenous nutrients (NH_4^+, NO_3^-) of *Alexandrium* spp. has been reported as 1.5 – 3.2 μM N (Smayda, 1997; Leong et al., 2004), indicating that even in treatments with macroalgae, N was likely not limiting in culture experiments. In the field-based experiments, there was evidence that nutrient limitation could have contributed toward anti-algal effects, at least in the case of *Ulva*: in the second bottle incubation, mean total DIN was reduced to 4.3±3.38 μM N in the 3 g L^{-1} and 3.6±2.8 μM N in the 6 g L^{-1} *Ulva* treatments. N levels were higher, however, in the *Saccharina latissima* treatments of this experiment(3 g L^{-1}: 8.1±4.0 μM N; 6 g L^{-1}: 4.4±0.4 μM N), and there were no significant differences between the anti-algal effects of *Ulva* and *S. latissima*. Similarly, in the mesocosm experiment conducted with *Ulva*, the *Ulva* treatment had significantly lower NO_3^- (but not NH_4^+) than the nutrient control; however, all treatments including the nutrient control had a much higher concentration of DIN (NO_3^-+NH_4^+) than the half-saturation constant. Furthermore, final concentrations of N in all treatments of the first bottle incubation were below K_s with no significant differences between treatments and the control, but there was still very high reduction in *A. catenella* density by all macroalgae relative to the control, especially by *Ulva* (95% reduction) and *S. latissima* (95% reduction). These findings indicate that nutrient limitation by macroalgae – especially *Ulva* – may have played a role in *A. catenella* inhibition in one of the field-based experiments in this study. However, it was not the primary driver behind the growth-inhibiting effects observed, especially in the case of *S. latissima*, as *S. latissima* always significantly reduced *Alexandrium* cell densities, but never reduced N concentrations below the K_s of *Alexandrium* in any experiments in which the control did not also have N concentrations below K_s.

There have been reports of high pH (>9) limiting the growth of phytoplankton (Hansen, 2002). Since macroalgae cause elevation of pH by rapid photosynthesis reducing PCO2 (Axelsson, 1988), it is possible that this effect contributed to the anti-algal activity observed in this study. Of the macroalgae studied, however, pH levels >9.0 were only regularly observed with *Ulva*, with higher concentrations of *Ulva* even pushing the pH close to 10.0 in the later stages of some culture experiments. The anti-algal activity of seaweeds, however, was observed in the absence of such extreme pH elevation with other macroalgae, most notably *Saccharina latissima* and *Chondrus crispus*. Furthermore, even with an extremely high concentration of *Ulva* used in the first bloom incubation experiment (3 g L^{-1}), mean pH in that treatment was ~8.7 and very high levels of anti-algal activity towards *A. catenella* were still observed. Because of this, we cannot attribute the anti-algal effects of macroalgae towards *A. catenella* solely or even primarily to pH elevation.

In experiments where the maximum photochemical quantum yield of photosystem II (F_V/F_M) was measured, it was significantly reduced by *Ulva* in a dose-dependent manner, but by-and-large not by other macroalgae. Reduced F_V/F_M is indicative of damage to photosystem II (Suggett et al., 2003). Given that *Ulva* also showed a dose-dependent effect on pH, and increased pH far higher than other tested macroalgae, it is possible that the increased pH contributed toward the reduction of F_V/F_M by *Ulva*. A more plausible explanation for the reduced F_V/F_M, however, is the production of allelochemicals by *Ulva* that contributed toward the chlorosis of cells observed during this study. Many more secondary metabolites with wide-ranging anti-algal activity have been isolated from *Ulva* spp. than either *C. crispus* or *S. latissima* and related species (Sun et al., 2019), and most studies documenting the allelopathic effects of live macroalgae and/or macroalgal extracts on phytoplankton have been done using *Ulva* spp. (Nan et al., 2004, 2008; Alamsjah et al., 2008; Tang and Gobler, 2011; Gharbia et al., 2017; Sun et al., 2018). The scarcity of data regarding anti-algal secondary

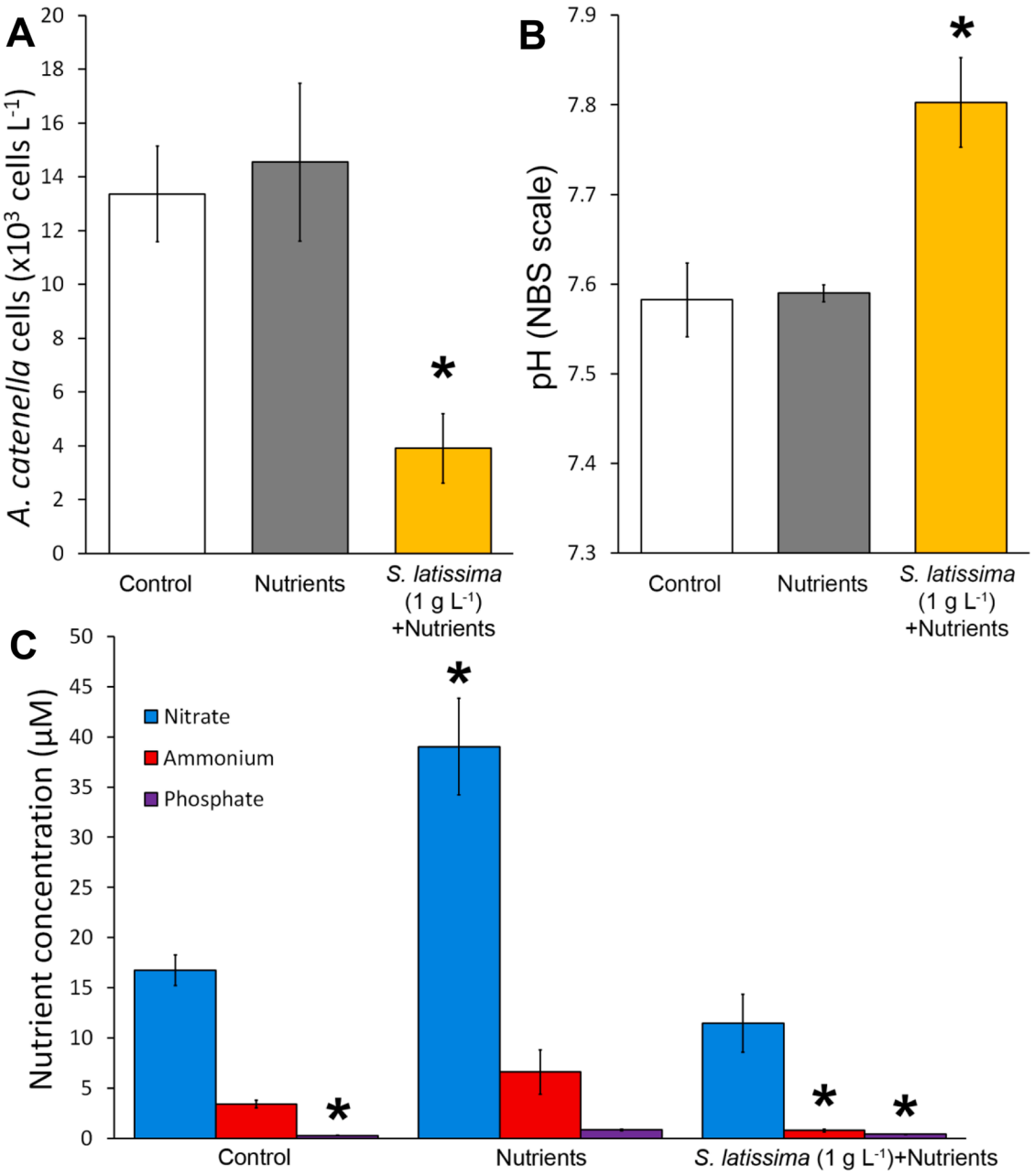

Fig. 11. . Mesocosm experiment (48 h) performed during May 2019. (A) FISH-probe enumerated *A. catenella* cell density, (B) pH, (C) concentration of nitrate, ammonium, and phosphate. Bars represent mean ± SE (n = 4), and asterisks indicate significant differences from the control according to ANOVA.

metabolites produced by more viable aquaculture candidates such as *S. latissima* makes it difficult to conclusively assert that Ulva produces more such compounds.

Finally, biofilms of marine macrophytes, including macroalgae and seagrass, have been shown to be enriched in bacteria with growth-inhibiting and algicidal properties towards some HAB phytoplankton (Imai et al., 2002, 2006a, 2017, ; Inaba et al., 2017, 2020). In the experiments performed in this study, precautionary measures were taken to prevent strong influence from macroalgae-attached heterotrophic bacteria during the experiments, including liberal rinsing of macroalgae with sterile seawater, physically wiping thalli before introduction into experiment vessels, and the inclusion of an antibiotic solution at 1–2% concentration (for laboratory experiments). While these measures may have provided relief from bacteria at the beginning of assays, it is likely that the bacterial community recovered over the course of the experiments. In a study by Onishi et al. (2021) in the Akkeshi-ko Estuary, Japan, bacteria that specifically inhibited the growth of cultured *Alexandrium catenella* were 3–4 orders of magnitude more concentrated in seagrass biofilms than in the surrounding water, and the macrophyte biofilm was hypothesized to be the source of these growth-inhibiting bacteria in the entire estuary. Despite this, the seagrass-attached bacteria showed only growth-inhibiting activity (as opposed to algicidal activity) against *A. catenella* after a 2-week exposure period (Onishi et al., 2021). Furthermore, many bacteria with reported algicidal effects on *A. catenella* only showed significant algicidal activity with the addition of the largest tested volumes of bacterial culture supernatant to *A. catenella* cultures, and not with the addition of live bacterial cells (Amaro et al., 2005; Wang et al., 2010; Bai et al., 2011). Bacteria that did show algicidal effects when added directly to *A. catenella* culture only did so in the presence of additional organic nutrients from bacterial culture broth (Bai et al., 2011; Yang et al., 2014). In these studies, algal-derived DOM was not sufficient for the synthesis of algicidal

compounds, as washed bacterial cultures added to cultures of *A. catenella* in f/2 medium showed no algicidal or growth-inhibiting activity (Bai et al., 2011; Yang et al., 2014). In our study, all laboratory experiments were conducted in f/2 media, and macroalgae treatments resulted in clear algicidal rather than growth-inhibiting activity on *A. catenella*. Despite this evidence, the interactions between phytoplankton and marine macrophytes have been shown to be highly species-specific, so the potential contribution of macroalgae-attached bacteria towards anti-HAB activity by macroalgae should not be minimized based on this study. For example, seagrass biofilms did display direct algicidal activity against harmful raphidophyte *Chattonella antiqua* in a laboratory microcosm study, with many living algicidal bacteria confirmed in the co-culture media of these experiments (Inaba et al., 2019). However, based on the evidence in this study, growth-inhibiting bacteria in macroalgal biofilms cannot account alone for the observed algicidal activity.

Since our results cannot be fully attributed to the effects of nutrient competition, pH elevation, or algicidal bacteria, it is reasonable to attribute much of the anti-algal activity observed in this study to allelopathic compounds produced by macroalgae, especially in the case of *Saccharina latissima*, which had anti-algal effects similar or greater in magnitude than *Ulva* but had a lesser effect on pH, nutrient reduction, and the photosynthetic activity of *Alexandrium catenella*. A wide variety of secondary metabolites extracted from macroalgal tissues have demonstrated potent anti-algal activity towards HAB-causing phytoplankton species (Sun et al., 2019). Kelps produce phlorotannins, polyphenolic compounds that have structural roles in brown algal cell walls, though there is significant evidence that phlorotannins have many secondary functions, including defense against herbivory (Arnold and Targett, 2003). Phlorotannins isolated from brown alga *Ecklonia kurome* have shown algicidal effects on multiple red tide dinoflagellates, causing both *Karenia mikimotoi* and *Margalefidinium (Cochlodinium) polykrikoides* cells exposed to high concentrations of phlorotannin isolate to become round, non-motile, and lyse within 3 h of exposure (Nagayama et al., 2003). Extracts of seagrasses *Zostera marina* and *Z. noltii* had algicidal effects on *A. catenella*, causing morphological changes and lysis very similar to those observed in this study; the phenolic content of these extracts was significantly linked to the algicidal activity, with extracts higher in phenols having lower EC50 values (Laabir et al., 2013). *Saccharina latissima* is rich in phlorotannins (Swanson and Fox, 2007), and it has been shown that many kelps induce phlorotannin production rapidly following wounding, and may continue to produce heightened levels of these compounds for 5 to 7 days after the wounding event (Hammerstrom et al., 1998). *Ulva* spp. also produce polyphenolic compounds such as flavonoids and bromophenols (Flodin et al., 1999; Wekre et al., 2019; Cotas et al., 2020) and may have higher production of these compounds in late winter and early spring (Trigui et al., 2013), the same season in which *A. catenella* blooms tend to occur. This could indicate phlorotannins, or polyphenolic compounds in general, as a major source of anti-*A. catenella* activity in this study, especially in the laboratory assays in which macroalgal thalli were cut down to size. Other potential compounds include polyunsaturated fatty acids isolated from *Ulva* spp. (Alamsjah et al., 2005, 2008; Gharbia et al., 2017; Sun et al., 2018) and sulfated polysaccharides, found in *Ulva* spp. (Mao et al., 2006; Berri et al., 2016) and also *S. latissima* (Ehrig and Alban, 2015). Furthermore, we note that in both mesocosm experiments, total chlorophyll a was not altered by either *Ulva* or *S. latissima* despite both macroalgae significantly reducing *A. catenella* population. Given that allelopathy between macroalgae and phytoplankton has been shown to be highly species-specific (Nan et al., 2004; Tang and Gobler, 2011; Tang et al., 2014; Yang et al., 2015; Gharbia et al., 2017), this supports allelopathy as the primary mechanism in these experiments, since nutrient starvation would affect the entire phytoplankton community and the pH increase by *S. latissima* in the second experiment was not large enough to be a significant factor.

Much work remains in the identification of antialgal metabolites in macroalgae, especially in species with high potential for aquaculture. The results of this study lend support to the assertion that some macroalgae – including *S. latissima* – allelopathically inhibit the growth of HAB-causing phytoplankton. (Nan et al., 2008; Tang and Gobler, 2011; Ye and Zhang, 2013; Tang et al., 2014; Gharbia et al., 2017).

Despite the attribution of anti-algal activity of seaweeds towards *Alexandrium catenella* primarily to allelopathy in this study, it is important to place the discussion of mechanisms behind the anti-algal activity in the context of the mitigation of *A. catenella* blooms in the field via macroalgal aquaculture. With the deployment of macroalgae in an ecosystem setting, none of the factors with potential anti-algal activity that were controlled in this study would be restrained. It is likely, therefore, that all four anti-algal mechanisms of macroalgae – allelopathy, pH elevation of surrounding waters, nutrient competition, and algicidal heterotrophic bacteria in macroalgae biofilms – could be active against *A. catenella* and other HAB species in an ecosystem or aquaculture setting.

4.3. Implications of the growth inhibition effects of macroalgae on *Alexandrium catenella*

This study demonstrated that macroalgae from three eukaryotic phyla (chlorophytes, rhodophytes, and phaeophytes) can restrict the growth of, and in some cases cause complete mortality of, the HAB-forming dinoflagellate, *Alexandrium catenella*. Culture experiments demonstrated a time-based, dose dependence in algicidal activity for most tested macroalgae, with higher concentrations of macroalgae causing significantly faster reductions in *A. catenella* density. For example, in the first assay, the highest concentration of *Ulva* (1.8 g L^{-1}) caused a significant reduction in *A. catenella* relative to the control after 48 h, while the middle concentration (1.1 g L^{-1}) did so after 72 h, and the lowest concentration (0.7 g L^{-1}) after 96 h. Despite higher doses causing significant algicidal activity in less exposure time, there was no significant difference in the ultimate magnitude of algicidal activity exhibited by different concentrations of *Ulva*, with all *Ulva* treatments reaching ~60% reduction in *A. catenella* at 96 h. Similar trends were observed in all culture studies; higher concentrations of macroalgae exhibited significant algicidal activity in less exposure time, but aside from the lowest concentrations of *Chondrus crispus*, had the same ultimate magnitude of algicidal activity as lower concentrations of the same macroalgae. Furthermore, in the second bottle incubation, in which multiple densities of *Ulva* and *S. latissima* (3 g L^{-1} and 6 g L^{-1} for both macroalgae) were tested, there were no significant differences between *A. catenella* concentrations based on dosage or macroalgae species after 96 h. Previous studies on allelopathic interactions between macroalgae and HABs have shown clearer dose-dependent effects of live macroalgae (Tang and Gobler, 2011; Tang et al., 2014), but these studies used smaller doses of macroalgae to proximate differing seafloor coverages rather than macroalgal aquaculture. It may be that our lower concentrations of macroalgae were already high enough to reach the asymptote of anti-algal activity, accounting for the less clear dose dependence in this study.

Our results indicate the potential of the aquaculture of macroalgae as a potential strategy for the prevention, mitigation, and control of *Alexandrium catenella* blooms. Among the macroalgae tested, *Saccharina latissima* and *Ulva* show more promise in this context than *C. crispus*. In the first bottle incubation, *C. crispus* reduced *A. catenella* density by 75.3% compared to a 95% reduction from identical concentrations of *Ulva* and *S. latissima*. *Ulva* and *S. latissima* outperformed *C. crispus* in culture experiments as well. In the second assay, a relatively low concentration of *Ulva* (0.9 g L^{-1}) yielded the same reduction of *A. catenella* densities as twice that concentration of *C. crispus* (1.8 g L^{-1}) at all timepoints of the study, with the low concentration of *C. crispus* (0.8 g L^{-1}) showing no significant reduction in *A. catenella* throughout the experiment. The fourth assay also showed that the low concentrations of *Ulva* (1.0 g L^{-1}) and *S. latissima* (2.5 g L^{-1}) performed equally as well or

better than the high concentration of *C. crispus* (3.2 g L^{-1}), while the low concentration of *C. crispus* (1.1 g L^{-1}) again did not reduce *A. catenella* compared to the control. The kelp species, *Saccharina japonica*, is the second most farmed seaweed in the world, with $>11.4\times10^6$ tons cultivated worldwide in 2016, primarily in East Asia (FAO, 2020; Ferdouse et al., 2018). The cultivation of *S. latissima* is an expanding endeavor in Europe and North America, particularly as an element of three-dimensional ocean farming together with bivalves (Yarish et al., 2017; Kim et al., 2019). Hence, in consideration of effectiveness and promise for aquaculture, *S. latissima* may be the ideal macroalgal species for the purposes of anti-*A. catenella* activity

The co-culture of *Saccharina latissima* and bivalves could have significant ecological and economic benefits. Blooms of *Alexandrium catenella* are a significant economic burden for the bivalve industry due to closures and contamination of products with toxins (Hoagland et al., 2002). In the current study, modest aquaculture concentrations (1 g L^{-1}) of *S. latissima* significantly reduced saxitoxin levels in the blue mussel, *Mytilus edilus*, after 4-day exposure to dense concentrations of *A. catenella* ($\sim10^3$ cells mL^{-1}). In fact, the presence of sugar kelp reduced the levels of saxitoxin in the mussels from above (93.47±8.11 μg STX 100 g^{-1}) the US FDA standard for saxitoxin in shellfish (80 μg STX 100 g^{-1}) to below (71.80±1.98 μg STX 100 g^{-1}). It is possible that a lower exposure density of *A. catenella*, a higher density of *S. latissima,* and/or a shorter exposure period would have led to even lower saxitoxin accumulation in the mussels. Beyond HABs, other benefits of the inclusion of seaweeds in the aquaculture of bivalves include the bioextraction of nutrients produced by aquacultured animals (Ahn et al., 1998; Kim et al., 2015; Marinho et al., 2015) and the potential buffering of ocean pH by photosynthesis protecting bivalves from the effects of ocean acidification (Fernández et al., 2019; Jiang et al., 2020; Young and Gobler, 2018). While Jiang et al. (2020) showed increases in total chlorophyll *a* in open-water *Saccharina japonica* farms in Xiangshan Bay, phytoplankton species diversity was also significantly higher at kelp farms during the kelp growing season. In our mesocosm experiments, *S. latissima* significantly reduced *A. catenella* levels in the mesocosms while chlorophyll *a* levels were unchanged, indicating the total food available for bivalves was unchanged. Given that the response of phytoplankton to macroalgal allelopathy is highly species-specific (Nan et al., 2004; Tang and Gobler, 2011; Tang et al., 2014; Yang et al., 2015; Gharbia et al., 2017), and that our data show that *A. catenella* is particularly vulnerable to the anti-algal activity of *S. latissima*, it is possible that aquaculture of *S. latissima* may simultaneously inhibit *A. catenella* blooms and increase phytoplankton diversity while maintaining phytoplankton biomass on kelp farms. Regardless, our results provide strong rationale for the integration of *S. latissima* into shellfish aquaculture for the purpose of mitigating *A. catenella* blooms, particularly for small, independently owned shellfish farms that may not be able to withstand the downturns in shellfish harvesting due to shellfish toxicity.

While *Ulva* is not currently a marketable food product to the extent of many kelps, it has many applications in aquaculture and as a product itself, for bioremediation of nutrient-polluted waters (Lawton et al., 2013; Ben-Ari et al., 2014; Al-Hafedh et al., 2015), usage as an alternative, more sustainable food source for fed aquaculture than pelleted fishmeal (Bolton et al., 2009; Cruz-Suárez et al., 2010), an energy source for bio-refineries (Bruhn et al., 2011), and use as fertilizer for land crops. Given that the anti-algal activity of *Ulva* against *A. catenella* was uniquely potent in its consistent reduction of photosynthetic efficiency alongside algicidal activity and in its reduction of nutrient levels, it may have potential in macroalgae aquaculture operations carried out specifically to target HABs and reduce nutrients rather than as a crop. In a study by Inaba et al. (2020), artificial *Ulva* beds were successfully created for the purpose of harboring growth-limiting bacteria which could inhibit HABs; our results suggest that such installments would also have significant allelopathic effects on *A. catenella* as well. In contrast to *S. latissima* aquaculture, artificial *Ulva* beds could be mobile, cultured at one facility and deployed when needed to areas afflicted by HABs.

Our results suggest that the aquaculture of macroalgae should be considered as an effective strategy for the control of *A. catenella* blooms that may be more ecologically safe than other HAB mitigation approaches. The integration of macroalgal aquaculture with shellfish aquaculture, in addition to its established economic benefits, may increase the resilience of shellfish farms to damage caused by *A. catenella* blooms. Further research is required to understand the effectiveness of the implementation of this strategy in open-water environments, in the contexts of (1) integration of commercial macroalgae aquaculture with existing aquaculture farms in a polyculture fashion, and (2) targeted deployment of mobile, cultivated artificial macroalgae beds to HAB-infested estuaries.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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