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Review

Progresses of the Influencing Factors and Detection Methods of Domoic Acid

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Abstract: Domoic acid (DA) is a neurotoxin mainly produced by *Pseudo-nitzschia* diatom, which belongs to the genera *Rhomboida*. It can combine with the receptors of glutamate of neurotransmitters, then affecting the normal nerve signal transmission of the organism and causing nervous system disorders. However, as a natural marine drug, DA can also be used for pest prevention and control. Although the distribution of DA in the world has already been reported in the previous reviews, the time and location of its first discovery and the specific information are not complete. Therefore, the review systematically summarizes the first reported situation of DA in various countries (including species, discovery time, and collection location). Furthermore, we update and analyze the factors affecting DA production, including phytoplankton species, growth stages, bacteria, nutrient availability, trace metals, and so on. These factors may indirectly affect the growth environment or directly affect the physiological activities of the cells, then affect the production of DA. Given that DA is widely distributed in the environment, we summarize the main technical methods for the determination of DA, such as bioassay, high-performance liquid chromatography (HPLC), enzyme-linked immunosorbent assay (ELISA), biosensor, and so on, as well as the advantages and disadvantages of each method used so far, which adds more new knowledge in the literature about DA until now. Finally, the DA research forecast and its industrial applications were prospected to prevent its harm and fully explore its potential value.

Keywords: domoic acid; *Pseudo-nitzschia*; neurotoxicity; toxin detection; affecting factors

Citation: Yang, A.; Zhang, H.; Yang, Y.; Jiang, Z. Progresses of the Influencing Factors and Detection Methods of Domoic Acid. *Processes* **2023**, *11*, 592. https://doi.org/10.3390/pr11020592

Academic Editor: Juan Luis Gomez Pinchetti

Received: 7 January 2023
Revised: 7 February 2023
Accepted: 13 February 2023
Published: 15 February 2023

1. Introduction

Domoic acid (DA) is a potent neurotoxin that is produced by some species of the diatom genus *Pseudo-nitzschia* (used to be called *Nitzschia multiseries*). The large-scale outbreak of harmful algal blooms will pose a serious threat to fishery production, marine ecological security, and the health of humans and marine organisms [1–3]. The first reported poisoning event caused by DA goes back to 1987 on Prince Edward Island, Canada, for people eating *Mytilus edulis* [4]. Previous studies have shown that DA exposure has toxic effects on an organism's intestine of nematodes, behavior, and lifespan. Oral exposure to a few milligrams per kilogram of DA elicits gastrointestinal effects, whereas slightly higher doses cause neurological symptoms, memory impairment, and limbic system degeneration, such as hippocampal degeneration [5–7]. DA can accumulate in shellfish and finfish, such as bivalves and some crustaceans, under certain environmental conditions, thus causing poisoning events of aquatic organisms, which seriously threaten seafood safety [8–12].

Humans and wildlife alike can easily be exposed when consuming DA-contaminated seafood, especially for coastal dwelling populations. The excitotoxicity mechanism of DA involves a complex signal regulatory network, and a large number of related genes are upregulated or suppressed [5,7]. By over-activating glutamate receptors, DA causes intracellular calcium overload, resulting in dysfunction of mitochondria and endoplasmic reticulum, loss or loss of neurons in the hippocampus or amygdala of the brain, and various degenerative diseases, such as Alzheimer's disease (Figure 1).

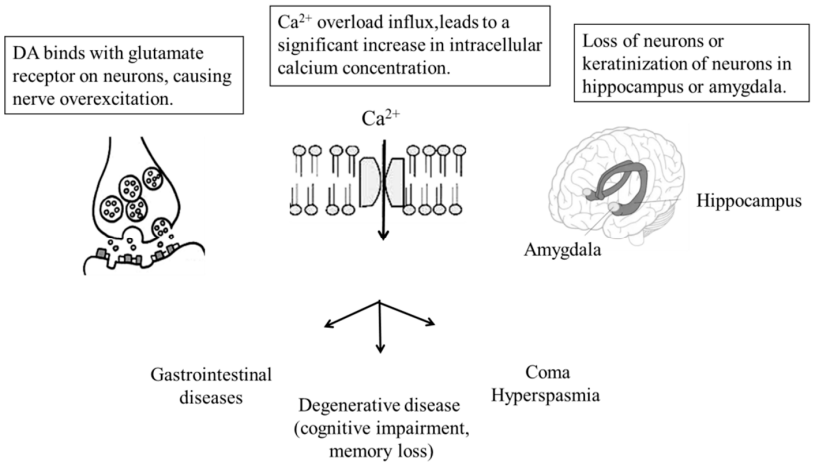

Figure 1. The mechanism of excitatory neurotoxicity of DA.

DA is an increasingly significant public health concern. Previous studies mentioned mainly summarized the structure and biological activity of DA, degradation of seawater, ecological and physiological effects, and risk of humans being exposed to DA [13], as well as species of the genera *Pseudo-nitzschia* and *Nitzschia* and their distribution [14]. In recent years, DA exposure has become more widespread due to drastic climate change, environmental pollution, and increased human activity [14]. Therefore, it is an urgent need to update the latest information on DA involving factors affecting DA production and the technical methods for DA detection. In this review, we characterize the physical and chemical properties, production mechanism, detection, and analysis of DA, which is encouraging for the research of DA and may prevent its harm and will help to make full use of its potential value.

2. The Discovery of DA and Its Physicochemical Properties

DA is a kind of neurotoxin that is mainly produced by *Pseudo-nitzschia* and can cause amnesic shellfish toxins (AST) or amnesic shellfish poisoning (ASP). It was first discovered by Takemoto and Diago from chondria armata domoi in Kagoshima Prefecture, Japan, in 1958, and then named after its Japanese name [15]. It was first isolated from *Pseudo-nitzschia* in Prince Edward Island, Canada, in 1987 [16]. As a strong neurotoxic substance, it can cause abdominal pain, diarrhea, and vomiting in mild cases and even coma and death in severe cases [17,18]. In recent years, new species (*P. brasiliana*) of *Pseudo-nitzschia* has been that can also produce DA [19]. So far, among the 54 species of *Pseudo-nitzschia*, 26 species have been confirmed to produce DA [14,20]. Table 1 shows the research history of DA from its discovery to its spread in the coastal countries of the world. Although DA poisoning cases have not been reported in some countries, such as China, DA produced by *Pseudo-nitzschia* has still been detected in some coastal areas, such as *P. uniseriata* and *P. yuensis* [20,21].

Table 1. Geographical distribution of domoic acid accord to the early reports.

Country	Sampling Date	Sampling Area	Specimen	References
Japan	1957	Tropical and sub-tropical waters	*Chrondria armata*	[15]
		Natori estuary, Ishigaki Island, Okinawa		[22]
American	1961	Capitola, California		
	1991	Monterey Bay, California Washington State beaches	*Pseudo-nitzschia australis*	[23,24]
		Florida (Gulf of Mexico)		[25]

Table 1. *Cont.*

Country	Sampling Date	Sampling Area	Specimen	References
Canada	1987	Estuaries on the eastern coast of Prince Edward Island	*Pseudo-Nitzschia pungens*	[16,26]
Mexico	1992	Gulf of Mexico	*Nitzschia pungens f. multiseries*	[27]
Portugal	1995	Not mentioned	Not mentioned	[28]
Spain	1996	Ria de Vigo, Galicia	*Pseudo-nitzschia multiseries*	[29]
New Zealand	1992/1993	Not mentioned		[30]
Vietnam	1997	Do Son	*Nitzschia navis-varingica*	[31]
France	1998	CoÃtes d'Armor (English Channel)	*P. pseudodelicatissima*	[32]
Ireland	1999	Southwest Ireland	*Pseudo-nitzschia australis*	[33]
Scotland	1999	wild and cultivated molluscs waters in Scottish	*Pseudo-nitzschia maximus* (mainly)	[34]
Italy	2000	the Gulf of Naples (Mediterranean Sea)	*Pseudo-nitzschia multiseries*	[35]
China	2001	The Bohai Sea and the lakes rivers polluted by algae in the South	*Pseudo-nitzschia simulans*	[36,37]
Greece	2002	Greek coasts along Thermaikos Gulf	genus *Pseudo-nitzschia* (*P. pungens f.pungens*, *P. pseudodelicatissima*)	[38]
Namibia	2004	Inshore and offshore stations	*P. australis* and *P. pungens*	[39]
Philippines	2004	Manila Bay, San Pedro Bay, South Sulawesi	*Pseudo-Nitzschia pungens*	[40]
Croatia	2006	the Croatian coast of the Adriatic Sea	*Pseudo-nitzschia spp.*	[41]
Morroco	2007	M'diq Bay, west Mediterranean coast of Morocco	*P. multistriata*, *P.cuspidata*, *P. galaxiae*, *P. multiseries*, *P. pseudodelicatissima*, *P. pungens var. aveirensis*, *P. Calliantha*, *P. fraudulenta.*	[42]
Tunisia	2008	Bizerte Lagoon		[43]
Thailand	2006	12°38′ N, 100°53′ E	*Pseudo-nitzschia multiseries*	[44]
Chile	2004–2006	Bahı'a Inglesa (27°7′ S, 70°52′ W) and Bahı'a Tongoy (30°15′ S, 71°20′ W)	*Pseudo-nitzschia species* (*P. Australis*, *P. calliantha*, *P. subfraudulenta*)	[45]
Turkey	2010	Sea of Marmara	*P. delicatissima*, *P. fraudulenta*, *and P. pungens*	[11]
Bulgaria	2011	North Black Sea	*Pseudo-nitzschia*	[46]
Australia	2012	Tasmania, Victoria, South Australia, Western Australia, New South Wales	*Pseudo-nitzschia delicatissima*, *P. multiseries*, *and P. australis*	[47]
Indonesia	2010	Panyula in South Sulawesi, Jakarta Bay, Lampung Bay, and Sangihe Island	*Pseudo-nitzschia* strains	[48,49]
Tunisia	2014	Bizerte Lagoon	*Nitzschia bizertensis sp. nov.*	[50]
Malaysia	2015	Johor, Negeri Sembilan, Kelantan	*Nitzschia navis-varingica*	[51]

Domoic acid is chemically expressed as [2S-[2 α, 3 β, 4 β (1Z, 3E, 5R)]-2-carboxyl-4-(5-carboxyl-1-methyl-1,3-hexadiene)-3-pyrrolidine acetic acid, with a molecular formula

of $C_{15}H_{21}NO_6$ and a molecular weight of 311.34. The pure product of DA is a solid white powder with a melting point is 223~224 °C. It is soluble in water (8 mg mL^{-1}) and slightly soluble in methanol (0.6 mg mL^{-1}). In the ultraviolet region, its maximum absorption wavelength is 242 nm. DA can remain stable for about one year [21]. To a certain extent, the structure of DA is similar to that of excitatory amino acids glutamic acid and kainic acid. It can directly activate the kainate receptor and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor to mediate excitatory neurotoxicity and cause nerve tissue damage [41,52,53]. However, its toxic effect is 2–3 times higher than that of kainic acid and more than 100 times stronger than that of glutamic acid. In recent years, isodomoic acids A, B, C, D, E, and F have been discovered, which are homologous compounds of DA [54–56].

3. Factors Affecting DA Production

At present, preliminary results of the DA biosynthesis pathway have been obtained based on the functional annotation of genes in the DA transcriptome library [57]. The first step of DA biosynthesis may be that geranyl pyrophosphate (GPP) reacts with L-glutamic acid (Glu) to form N-geranyl-l-glutamic acid (l-NGG) under the catalysis of terpene cyclase. Then, the subsequent reaction takes place under the catalysis of a-ketoglutarate-dependent dioxygenase and cytochrome P450 [57]. However, the biological, physiological, and biochemical molecular mechanism of DA production is still unclear. It is worth mentioning that *Pseudo-nitzschia* of different or the same algal species with different strains have different interspecific and intraspecific toxin production capacities [58]. Based on the findings of existing research, the toxicity production and level of *Pseudo-nitzschia* species are closely related to the species/strains, physiological status, and related ecological and environmental factors (Figure 2; Table 2) [59–61].

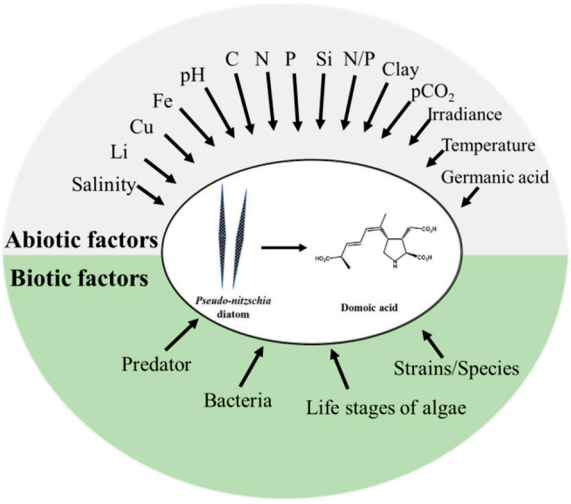

Figure 2. Factors affecting the production of DA.

3.1. Species and Life Stages of Algae

Different species or strains of *Pseudo-nitzschia* have varying abilities to produce DA at different life stages. Early studies found that *P. multilocularis* almost did not produce DA in the exponential growth phase, but in the stationary phase, it produced a significant quantity of DA [62]. Some species, on the contrary, such as *P. vulgaris* and *P. australis*, gradually increase cellular DA concentrations from the exponential growth period to the stationary period and finally discharge them into the water [33,63]. Moreover, compared with the nutrient limitation, the exponential growth period enables algae to produce the maximum net DA yield [63]. In the process of culturing four strains of *Pseudo-nitzschia* isolated from the field, it was found that DA was detected in all strains on the 25th day of culture (stationary period), and the amount of DA produced by *P. australis* strain PLY1St.52B

was significantly higher than that of the other three strains [64]. It can be seen that under the same cultural environments, different species or strains of *Pseudo-nitzschia* have different abilities to produce DA. Even for the same species, DA production will also change with growth rate and cell morphology due to different growth environments [13,14,65].

3.2. Nutrients Supply

Many studies have shown that DA production of *Pseudo-nitzschia* significantly increases under a limited supply of nutrients [66,67]. Among the nutrients, silicon (Si), nitrogen (N), and phosphorus (P) had the most obvious effect on DA production by *Pseudo-nitzschia*.

Some studies have shown that *P. seriata* produced DA under limited P and Si availability, and DA production further increased when the algae were in the stationary period. Silicon deficiency was comparatively more prominent than P for enhancing DA production [68]. Through the analysis of transcriptome data, the gene expression activity of DA synthesis significantly upgraded under phosphorus deficiency [58]. This could be attributed to the fact that cells can preferentially promote the gene expression of toxin synthesis by reducing their own basic metabolic activity, thus promoting the production of DA [65]. DA production also increased when the N:P ratio was high (that is, the content of phosphorus was low) and silicon was not limited. Moreover, its production also increased when other basic metabolisms, such as carbon, nitrogen, phosphorus, silicon, and other absorption levels, were decreased [69].

The content and type of nitrogen source also affected DA production. Studies have shown that when nitrogen existed as a macroelement, the DA content of *P. cuspidata* in the exponential growth period was significantly higher than that in the stationary period [70]. When the content of the nitrogen source was the same, organic nitrogen promoted algae to increase DA production more than inorganic nitrogen. For example, compared with inorganic nitrogen sources, when urea was used as a nitrogen source, the amount of DA in the exponential growth period was significantly increased [71]. Martin-Jézéquel found that for *P. multilocularis*, under urea application as a nitrogen source, the DA production was the highest, but for *P. australis*, DA production reached the maximum when glutamate was added as a nitrogen source, confirming that the DA production was also dependent on the type of nitrogen source and algae species [72].

3.3. Trace Metals

DA may be a kind of chelate of some trace metals such as iron (Fe) and copper (Cu). *Pseudo-nitzschia* can selectively combine with trace elements to produce DA. Thus, the concentration of trace elements is closely related to the production of DA in seawater [73].

Maldonado et al. studied the relationship between DA production and the iron and copper content of *P. multilocularis* and *P. australis*. They found that its production in intracellular and extracellular increased due to iron deficiency or copper toxicity during the exponential growth period [74]. However, its intracellular production was increased, accompanied by the increase in iron in *P. multilocularis* [14]. In addition to iron content, extracellular production of DA also varied with life stages, showing that there is a maximum DA production under iron deficiency in the exponential growth stage and decline stage, while the result is the opposite in the stationary stage [14]. This may happen due to the regulation of electron transfer reactions (such as photosynthesis and respiration) by Fe, which indirectly affects the production of DA [75]. Early studies have also found that a high concentration of lithium could significantly promote DA production by *Pseudo-nitzschia* [76]. This could be due to the smaller radius and higher polarity of lithium, which is easier to replace cations such as sodium and potassium ion, thus affecting the normal operation of the ion pump in the plasma membrane; moreover, lithium can combine with various ligands to form aggregates and play a role in cells [75,76].

3.4. Temperature and Irradiance

Temperature and irradiance are very important environmental and ecological factors. Their effects on DA may be worked by directly affecting the physiological activity of a single cell (such as enzyme activity) or indirectly affecting the algal's density (such as growth rate). Therefore, the interaction of temperature and light can significantly affect the yield of DA during the cultivation of *P. australis* [77].

Under the same culture conditions, the effect of temperature on the toxicity of *Pseudo-nitzschia* varied with species. Generally, high temperature promotes DA production. DA production by the *P. australis* S7 strain was below the detection limit at temperatures <20 °C but increased exponentially from 23 to 30 °C [78]. It should be noted that this is not the case for all algae, as in the *P. multilocularis* strain PM4, the intracellular DA production at 27 °C was much lower than that at 18 °C in a specific temperature range [79]. This may be caused by different physiological and ecological reaction mechanisms in algae.

Irradiance can affect DA content by the change of photoperiod and light intensity. Early studies found that under a long photoperiod (18 h light: 6 h dark), DA production of *P. tenuifolia* significantly increased [80]. Although DA can be produced under weak irradiance, the yield of DA under strong light is much higher compared to weak light. Moreover, under strong light, DA production further increases with increasing light intensity [64,77]. The reason for the irradiance effect on DA production may be photosynthesis provides the energy required for DA production.

3.5. Bacteria

Single bacteria or bacterial communities can also affect the DA production process of *Pseudo-nitzschia*. In the study of *P. multilocularis*, it was found that the production of DA was closely related to the presence of bacteria [81,82]. Early studies showed that although algae treated with antibiotics grew well, their toxin production capacity would be 8–10 times lower than that of bacteria, and their DA production would be 2–95 times higher than a single strain of the added original bacteria. In other words, the presence of extracellular bacteria can effectively promote the production of DA [81]. Later research also confirmed this view; that is, in the presence of living bacteria, the production of DA by algae was significantly higher than that in a sterile environment [82].

However, there is not a single corresponding relationship between DA production and bacteria, and their toxigenicity differs with species of the diatom *Pseudo-nitzschia*. For example, the physiological activity of *P. pseudodelicatissima* is not toxic and does not affect the absence of original bacteria or the presence of foreign bacteria, and it never produces DA, while *P. multiseries* is toxic, growing rapidly under sterile conditions while growing slowly when co-cultured with foreign bacteria and producing a small amount of DA [83]. Research showed that the existence of DA affected the composition and structure of the bacterial community to a certain extent, and there is a mutual association between DA and bacteria [84]. Further studies are needed to find out the relationship between the genus of *Pseudo-nitzschia* and bacteria.

3.6. Other Factors

The production of DA is not only affected by nutrients, light, and temperature but also by other substances and factors such as:

(1) Clay and Germanic acid: In early studies, Yu et al. found that both clay minerals and Germanic acid could inhibit the production of DA by *P. multilocularis*. Germanic acid completely inhibited the production of DA when the Ge/Si ratio was 35 [85,86]. The reason may be that the high concentration of clay affects the photosynthesis and nutritional environment of cells and thus affects the production of DA, while Germanic acid may destroy or even interrupt the normal silicification in cells, destroying the respiration, nucleic acid synthesis, and protein compounds of algae, thus inhibiting DA production.

(2) pH: Lundholm et al. found that DA produced by *P. multilocularis* in the late exponential period significantly increased with the increase in pH (9.3~9.8) in the laboratory [87]. In the field observation, the water body of *P. multilocularis* usually had higher pH (about 9 or even 10), which suggested that this water body might be polluted with lots of DA. The effect of pH on DA production may be realized by affecting enzyme process, carbon content, metal toxicity, or bacterial structure. pH in natural water is not easy to regulate and mainly depends on the water's ecosystem self-healing. If it is a specific area, such as fish ponds, there are relevant methods of equilibrium pH. Therefore, pH can affect the production of DA, but whether DA will affect pH, in turn, needs further research.

(3) pCO_2: Increasing of pCO_2 can promote the production of DA in two different *Pseudo-nitzschia*, especially under phosphorus [88] or silicon deficieny [89]. Even if the nutrients are enough, the intracellular DA production of some algae, such as *P. multilocularis*, increased due to the increased pCO_2 [90]. The expression of intracellular DA synthesis gene upregulated with the increased pCO_2 [57]. With global warming and ocean acidification, it is of great practical significance to study the impact of pCO_2 on algae.

(4) Predator: Several studies have shown that the toxicity of toxic diatoms such as *P. seriata* increased under the direct or indirect existence of calanoid copepods, indicating that toxic diatoms may resist predation by producing poison [91]. For zooplankton, there was no obvious selection tendency in the predation of toxic and nontoxic diatoms, and the predation of toxic diatoms had no obvious effect on itself. Therefore, zooplankton is more likely to act as a carrier to realize the transfer or transformation of DA indirectly in the marine food web by predating toxic diatoms [92,93].

Table 2. Factors affecting the production of domoic acid (DA) by *Pseudo-nitzschia* spp.

Factors	Effects on DA Production	Related Species	Reference
Biotic factors			
Strains/Species	DA production varies in different strains	*P. australis*	[64]
Life stages	Produce lots of DA in stationary phase while noting on exponential growth phase	*P. multilocularis*	[62]
	Intracellular DA production increased from the exponential growth period to stationary period	*P. vulgaris and P. australis*	[33,63]
Bacteria	Effectively promote the production of DA	*P. multiseries*	[80,82]
Predator	DA production increased up to 3300% when exposed to grazing copepodites	*P. seriata*	[94]
	DA production induced in nontoxic species	*P. obtusa*	[94]
Abiotic factors			
Irradiance	DA production increases with increasing irradiance	*P. australis*	[77]
Temperature	DA production was below the detection limit at temperatures <20 °C, but increased exponentially from 23 to 30 °C	*P. australis*	[78]
	The intracellular DA production at 27 °C was much lower than that at 18 °C	*P. multilocularis*	[79]
pH	Elevated pH induced production of domoic acid DA production in the late exponential growth period increased significantly with pH (9.3–9.8) in the laboratory	*P. multilocularis*	[87]
pCO_2	Increase due to the increased pCO_2	*P. multilocularis*	[89]

Table 2. *Cont.*

Factors	Effects on DA Production	Related Species	Reference
Nitrogen	Higher DA production when grown on NO^{3-} or NH^{4+} than on urea during exponential growth	*P. cuspidata*	[95]
	Highest DA production on urea and NO3^{-}	*P. multiseries*	[72]
	DA production on urea >than on NO^{3-}, NH^{4+}	*P. multiseries*	[96]
	Highest DA production on glutamate and NH^{4+}	*P. australis*	[72]
Silicon (Si)	DA production increased when stressed by Si limitation during the stationary phase	*P. seriata*	[64]
Copper (Cu)	increased due to the excessive copper during exponential growth period	*P. multilocularis* and *P. australis*	[74]
Phosphorus (P)	DA synthesis was significantly upregulated under phosphorus restriction	*P.multiseries*	[57,65]
Iron (Fe)	Increased due to the lack of iron or excessive copper during exponential growth period	*P. multiseries* and *P. australis*	[74]
	Intracellular DA production increased, accompanied by increase in iron	*P. multilocularis*	[14]
Lithium (Li)	Significantly promote DA production	*P.multiseries*	[76]
Salinity	DA production rates varied significantly with salinity; they were low and similar at salinities of 5–15 (2.56–3.12 ng mL^{-1} day^{-1}) and increased with increasing salinity, highest in 35	*P. pungens*	[97]
Clay (halloysite)	Inhibit the production of DA	*Psuedonitzschia pungens f. multiseries*	[85]
Germanic acid	Completely inhibit the production of DA when the Ge/Si ratio was 35	*P. pungens*	[86]

4. Detection Methods of DA

Detection methods can be divided into algae DA concentration, water DA concentration, and shellfish DA concentration determination according to the detecting subject. Each detection method, biological, chemical, and physical, has its own advantages and limitations. In this paper, the main detection and analysis methods are introduced. Table 3 summarizes the current main methods for DA detection.

Table 3. Characteristics of main DA detection methods.

Methods	Detection Limitation	Merits	Limitations	Reference
Bioassay				
Mouse bioassay	>20 $\mu g \cdot g^{-1}$	Universal detection, easy to perform, cheap	Ethical pressure; poor repeatability; interference of extracts and salts; long operation time and inability to distinguish toxins types; high detection limit; error % high	[98]
Receptor bioassay	0.001 $ng \cdot g^{-1}$	Sensitive	Difficult to obtain the receptor	[99]
HPLC			Needs standards, needs toxicology information for each toxin	

Table 3. *Cont.*

Methods	Detection Limitation	Merits	Limitations	Reference
HPLC-UV	20 ng·mL^{-1}	High versatility, high sensitivity, easy to use, simple maintenance, low equipment cost, can detect a large number of samples	Low sensitivity to compounds with poor UV absorption	[9]
HPLC-UV&SPE	0.04 ng·mL^{-1}	High sensitivity, automatic analysis, suitable precision (<5%)	Special instrument, professional operation	[100]
HPLC-FLD	0.2 ng·mL^{-1} (1.5 pg·mL^{-1} for seawater)	High sensitivity, automatic analysis, less clutter interference	Most of the derivatization reagents are expensive and unstable, and the reagent's deterioration may lead to toxin's incomplete derivatization	[11]
HPLC-MS/MS	0.02 ng·mL^{-1}	No need for derivative reagent and toxin standard, wide detection range, high sensitivity, fast speed, and the operation is simple	The equipment requirements are high, and can not be used for a large number of grass-roots day-to-day monitoring	[9]
HPLC/ESI-IT-MS	0.02 ng·mL^{-1}	High sensitivity, high selectivity, can carry on the mass examination. Can provide chemical structure information	High requirements for sample pretreatment	[101]
LC-MS	<1 pg·mL^{-1}	Allows quantification sensitive	Slow, complex, expensive, needs standards	[102]
LAESI-HRMS	0.24 µg·g^{-1}	Realized high-throughput screening or quantitation of DA in a variety of shellfish matrices	Low accuracy, suit to screening than direct quantitation	[103]
LC-HRMS	0.12 ng·mL^{-1}	Less solvent consumption, low cost, the absence of the evaporation step, and short time requirement.	High requirements for pH, the number of aspirating/dispensing cycles, and the type and volume of eluent	[104]
ELISA				
ELISA	0.02 ng·mL^{-1}	High sensitivity, easy to use	Unable to detect all individuals. Expensive DA standards, professional microplate instruments, small molecular weight of DA, difficulties in preparation of immune antigen	[105]
CEEIA	0.02 ng·mL^{-1}	Rapid detection and high sensitivity		[106]
ICS	5 ng·mL^{-1}	Fast, sensitive, quantitative, easy to use	Need enough toxin to obtain antibody Expensive	[107]
Other methods				
cITP-CZE	1.5 ng·mL^{-1}	Simple to use, low cost, and portability. High sensitivity	High requirement for pH value, poor repeatability	[108]
SERS	0.1 µg·mL^{-1} (in pure water) 0.01µg·mL^{-1} (in seawater)	Lower limit of detection, rapid detection of DA in different situations	Sensitivity and accuracy are far less than those of HPLC and ELISA	[109]

4.1. Bioassay Methods

Mouse bioassay (MBA) is a classical method for most marine toxins, except for domoic acid. It mainly uses mice of a certain age, size, and weight to detect the toxicity of algal toxins and finally uses half-lethal doses to evaluate the toxicity. This method was first used for DA detection in 1987 [4]. However, subsequently, it was found that there were many uncertain factors (such as the size of experimental animals, physiological state, operation technology, and experimental time) in using this method, and the detection limit was high (suitable for DA concentration >20 $\mu g \cdot g^{-1}$). This method has been gradually replaced by new detection methods due to some other defects such as poor repeatability, long operation time, and inability to distinguish toxins types, but it still plays an irreplaceable role in toxicology research [98]. Besides the mouse model, zebrafish (Danio rerio) as a translational model is also used extensively for toxicological studies. The contemporary Bibliography is replete with studies of "fish embryo toxicity tests" for the study of environmental contaminants (pollutants, drugs, and toxins) in which zebrafish larvae are used as indicators of toxicity. For example, dexamethasone sodium phosphate (DEX) exposure could affect the survival and hatching rate, morphology score, and body length in zebrafish larvae, especially disturbing the antioxidant defense system [110]. Several mycotoxins, such as Aflatoxin B1 (AFB1) and Fumonisin B1 (FB1), both exerted negative effects on zebrafish (Danio rerio) embryos [111].

4.2. High-Performance Liquid Chromatography (HPLC)

Although the use of HPLC requires special instruments and the cost is relatively high, HPLC is recognized as the most effective method among detection methods such as liquid chromatography, thin layer chromatography, capillary electrophoresis, amino acid analysis, receptor analysis, and many other methods, due to its rapid detection, suitable repeatability, high accuracy [112]. Among shellfish toxins analyzed by HPLC, DA analysis is the most successful one, which has been listed as the national standard method in many countries. According to Chinese national standards, the content of DA in marine bivalves and their products (excluding salted products) should be detected by reverse-phase high-performance liquid chromatography (RP-HPLC) with a detection limit of 1.0 μg.

Combined with HPLC, a series of new detection methods have been developed, such as high-performance liquid chromatography ultraviolet detection (HPLC-UV), high-performance liquid chromatography fluorescence detection (HPLC-FLD), high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) and high-performance liquid chromatography electrospray ion trap mass spectrometry (HPLC/ESI-IT-MS) and so on (see Table 3), to determine residues of residues in shellfish in the past 20 years [9–12,112]. Subsequently, some optimized LC-MS techniques were applied to DA detection. For example, solid solvent extraction combined with LC-MS technology can be used to detect DA at a trace level (<1 $pg \cdot mL^{-1}$) [102]. DA of 5 $\mu g \cdot g^{-1}$ can be detected in fresh scallops tissue samples by laser ablation electrospray ionization high-resolution mass spectrometry (LAESI-HRMS), which is a quarter of the detection limit [103]. In contrast, the detection limit of DA in urine can reach 0.12 $ng \cdot mL^{-1}$ by liquid chromatography high-resolution mass spectrometry (LC-HRMS) [104].

As the most mature technology for DA detection, HPLC is generally stable and sensitive for the determination of samples. It is less affected by operational and environmental factors. HPLC technology has the advantages of stable sample determination, high sensitivity, and less affected by the operation and environmental factors, but it has weaknesses in efficiency, quantity, and cost of determination.

4.3. Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is a kind of analytical method that uses the principle of specific binding between enzyme-linked antigens and antibodies. Now, it has become the most widely used immunological detection technology because of its convenience, high specificity, low detection limit, easy qualitative and quantitative, and no need for special equipment.

DA was detected and quantitatively analyzed by specific antibodies against shellfish toxin when using ELISA. The detection limits of DA could reach 0.02 [105], 0.15 [113], and 0.15 [114] ng·mL^{-1} when using direct competition of polyclonal antibody, indirect competition of polyclonal antibody, and indirect competition of monoclonal antibody, respectively.

ELISA has high sensitivity and can be used for rapid DA detection. At present, a variety of ELISA methods and kits for DA detection have been developed [105,115–118]. Among them, the development of colloidal gold technology has grown rapidly. This technique is to develop a colloidal gold immunochromatographic strip by using competitive immune reaction and labeled monoclonal antibodies to detect DA. Tsao et al. used monoclonal antibodies from hybridoma cell line 9F1F11 to prepare a colloidal gold immunochromatographic strip (ICS). The detection time of DA was reduced to less than 10 min, and the sensitivity was increased to 5 ng·mL^{-1}. The rapid and batch detection of DA was realized [107].

Some improved ELISA techniques have emerged and highlighted their own advantages, such as capillary electrophoresis-based enzyme immunoassay (CEEIA), which can detect DA in shellfish samples within 5 min by electrochemical method, and the sensitivity is 16 times higher than that of traditional ELISA [106]. In addition, a multi-functional detection technology-flow cytometry microsphere array, which combines three immunological methods (solid-phase microsphere method, flow cytometry, and Luminex xMAP Technology), has also been applied to the detection of DA, and the half inhibitory concentration (IC_{50}) can reach (1.9 ± 0.1) ng·mL^{-1} [119].

Although the ELISA method has many advantages in use, the expensive DA standards, professional microplate instruments, small molecular weight of DA, difficulties in the preparation of immune antigen, and field operation all limited its application in DA analysis to a certain extent.

4.4. Other Detection Methods

In addition to the commonly used methods such as HPLC and ELISA, other detection methods, such as biosensors, capillary electrophoresis, and neural receptor binding detection, have also been applied to detect DA.

Biosensor is a kind of easy and cheap DA detection and quantification technology. This technology can transform biological reaction information into electrical signals, then output those quantitatively processed electrical signals so as to determine substances' concentration. In the past 20 years, various biosensor has been widely used in the detection of chemical pollutants or pathogens [120,121]. For example, when using surface plasmon resonance (SPR) technology to detect DA in food, the semi-inhibitory concentration can reach 4.8–6.9 ng·L^{-1} and 2.3–6.0 ng·L^{-1}, respectively, when using monoclonal antibody and polyclonal antibody [122].

Capillary electrophoresis (CE) is one of the earlier methods applied to separate and detect marine biotoxins because of its simplicity to use, low cost, and portability. CE is based on the principle that differently charged particles have different migration rates in the electric field, then separate the objects [123]. The detection limit can reach 1.5 μg/L by a coupled capillary isotachophoresis–capillary zone electrophoresis (cITP-CZE) method for the determination of domoic acid in shellfish [109].

With the development of technology, other new DA detection methods, such as pure or amino-functionalized Ag nanoparticles and surface-enhanced Raman scattering (SERS), are emerging, which gradually realized the rapid and accurate detection of DA in different situations [108]. However, the sensitivity and accuracy of the above methods are far less than those of chromatography and immunology, so the application scope is still limited.

The detection methods of DA production shall be improved. With the development of research, more toxic algae and their toxins are expected to be discovered and studied. At present, there are many methods to detect DA, but there are still some limitations in their use. HPLC has the advantages of rapid detection, suitable repeatability, and high accuracy, which is recognized as the most effective method. However, in recent years, ELISA kits have attracted more and more attention for the merits of being easy to carry

and can be used for on-site monitoring, and some rapid detection strips are also becoming a new research direction. We can grasp the geographical distribution of DA through the detection of DA and establish appropriate models to predict the generation and migration of DA in the ecosystem so as to prevent potential DA disasters.

5. Conclusions

As a neurotoxin, on the one hand, DA pose a potential threat to aquatic organisms and human, while, on the other hand, it has a significant insecticidal and bactericidal role. Therefore, the research on DA has very important practical significance. At present, globally, a new *Pseudo-nitzschia* has been found, but the research on DA and *Pseudo-nitzschia* is still very limited. In addition to summarizing the distribution, species composition, and toxin production of *Pseudo-nitzschia* in various sea areas, the authors think the following three aspects need further scientific research.

The research on the DA production mechanism must be strengthened to understand the effects of specific environmental and biological factors on its production and distribution. At present, the up and down-regulated related to DA production, enzymes involved in DA synthesis, and possible mechanisms have been found by using advanced molecular biology and genetic methods [57,124,125]. On this basis, the use of enzyme inhibitors, gene knockout, or gene silencing techniques may increase or inhibit the production of DA in algae. In addition, the research can be carried out in the genus *Pseudo-nitzschia* rather than just for a certain species so as to ensure the universality of the previous findings.

Although there are many DA detection methods and corresponding products, the detection methods need further improvement. Through the update of technology or the combination of multiple methods, DA detection will be much simpler, faster, and more efficient. The application prospect of DA needs to be further explored. As a natural marine drug, DA has obvious advantages over organic synthetic chemicals; for example, it can be used as a useful reagent for neurophysiological research. People could make full use of its biological activity, such as the insecticidal ability of DA, and develop and utilize insecticides [126]. Autism spectrum disorder (ASD) features deficits in social interaction and communication and includes repetitive behaviors and circumscribed interests. Research has shown that the behaviors and neuropathology resulting from prenatal exposure to DA are strikingly similar to those in ASD. In addition, the geographic distribution of ASD suggests the possibility that exposure to toxic chemicals in seafood might contribute to the prevalence of some forms of autism. Infant rats exposed to DA express long-term social withdrawal in adults [127]. Therefore, more fully monitor of DA is needed for coastal human and non-human mammalian populations. Product development based on the characteristics of DA is an effective way to develop a green industry. In view of this, we can use gene recombination and other means to screen and cultivate high DA-producing strains so as to carry out the scientific and controllable production and application of DA.

Author Contributions: A.Y., H.Z. and Z.J. contributed to the planning of the main ideas and visualization; A.Y. and Y.Y. were responsible first draft manuscript; A.Y., H.Z. and Z.J. were responsible for the revision and final version. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Shandong Provincial Natural Science Foundation of China (ZR2018PC003) and Linyi University Ph.D. Fund for Scientific Start-up (LYDX2018BS036, LYDX2018BS031, and LYDX2019BS028) and College Students' Innovative Training Program (X202010452124, X202210452475, and X202210452103).

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Berdalet, E.; Fleming, L.E.; Gowen, R.; Davidson, K.; Hess, P.; Backer, L.C.; Moore, S.K.; Hoagland, P.; Enevoldsen, H. Marine harmful algal blooms, human health and wellbeing: Challenges and opportunities in the 21st century. *J. Mar. Biol. Assoc. UK* **2016**, *96*, 61–91. [CrossRef] [PubMed]
2. Brown, A.R.; Lilley, M.; Shutler, J.; Lowe, C.; Artioli, Y.; Torres, R.; Berdalet, E.; Tyler, C.R. Assessing risks and mitigating impacts of harmful algal blooms on mariculture and marine fisheries. *Rev. Aquacult.* **2020**, *12*, 1663–1688. [CrossRef]
3. Sellner, K.G.; Doucette, G.J.; Kirkpatrick, G.J. Harmful algal blooms: Causes; impacts and detection. *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 383–406. [CrossRef] [PubMed]
4. Hynie, I.; Hockin, J.; Wright, J.; Iverson, F. Panel discussion: Evidence that domoic acid was the cause of the 1987 outbreak. *Can. Dis. Wkly. Rep.* **1990**, *16*, 37–40.
5. Tian, D.; Zhang, G. Toxic effects of domoic acid on *Caenorhabditis elegans* and the underlying mechanism. *Int. J. Biol.* **2019**, *11*, v11n3p1. [CrossRef]
6. Miller, M.A.; Moriarty, M.E.; Duignan, P.J.; Zabka, T.S.; Dodd, E.; Batac, F.I.; Young, C.; Reed, A.; Harris, M.D.; Greenwald, K.; et al. Clinical signs and pathology associated with domoic acid toxicosis in southern sea otters (*Enhydra lutris nereis*). *Front. Mar. Sci.* **2021**, *8*, 585501. [CrossRef]
7. Radad, K.; Moldzio, R.; Al-Shraim, M.; Al-Emam, A.; Rausch, W.D. Long-term neurotoxic effects of domoic acid on primary dopaminergic neurons. *Toxicol. Vitr.* **2018**, *52*, 279–285. [CrossRef]
8. Brodie, E.C.; Gulland, F.M.D.; Greig, D.J.; Hunter, M.; Jaakola, J.; Leger, J.S.; Leighfield, T.A.; Dolah, F.M.V. Domoic acid causes reproductive failure in california sea lions (*Zalophus californianus*). *Mar. Mammal. Sci.* **2006**, *22*, 700–707. [CrossRef]
9. Lefebvre, K.A.; Robertson, A.; Frame, E.R.; Colegrove, K.M.; Nance, S.; Baugh, K.A.; Wiedenhoft, H.; Gulland, F.M.D. Clinical signs and histopathology associated with domoic acid poisoning in northern fur seals (*Callorhinus ursinus*) and comparison of toxin detection methods. *Harmful Algae* **2010**, *9*, 374–383. [CrossRef]
10. Zheng, G.; Wu, H.; Guo, M.; Peng, J.; Zhai, Y.; Tan, Z. First observation of domoic acid and its isomers in shellfish samples from Shandong Province, China. *J. Oceanol. Limnol.* **2022**, *40*, 2231–2241. [CrossRef]
11. Dursun, F.; Yurdun, T.; Ünlü, S. The First Observation of Domoic Acid in Plankton Net Samples from the Sea of Marmara, Turkey. *Bull. Environ. Contam. Toxicol.* **2016**, *96*, 70–75. [CrossRef] [PubMed]
12. Hassoun, A.E.R.; Ujević, I.; Mahfouz, C.; Fakhri, M.; Roje-Busatto, R.; Jemaa, S.; Nazlić, N. Occurrence of domoic acid and cyclic imines in marine biota from Lebanon-Eastern Mediterranean Sea. *Sci. Total Environ.* **2021**, *755*, 142542. [CrossRef] [PubMed]
13. Zabaglo, K.; Chrapusta, E.; Bober, B.; Kaminski, A.; Adamski, M.; Bialczyk, J. Environmental roles and biological activity of domoic acid: A review. *Algal Res.* **2016**, *13*, 94–101. [CrossRef]
14. Bates, S.S.; Hubbard, K.A.; Lundholm, N.; Montresor, M.; Leaw, C.P. *Pseudo-nitzschia*, *Nitzschia*, and domoic acid: New research since 2011. *Harmful Algae* **2018**, *79*, 3–43. [CrossRef]
15. Takemoto, T.; Daigo, K. Constituents of *Chondria armata* and their pharmacological effect. *Chem. Pharm. Bull.* **1958**, *6*, 578–580. [CrossRef]
16. Bates, S.S.; Bird, C.J.; Freitas, A.S.W.d.; Foxall, R.; Gilgan, M.; Hanic, L.A.; Johnson, G.R.; McCulloch, A.W.; Odense, P.; Pocklington, R.; et al. Pennate diatom *Nitzschia pungens* as the primary source of domoic acid, a toxin in shellfish from Eastern Prince Edward Island, Canada. Can. *J. Fish Aquat. Sci.* **1989**, *46*, 1203–1215. [CrossRef]
17. Grattan, L.M.; Boushey, C.J.; Liang, Y.; Lefebvre, K.A.; Castellon, L.J.; Roberts, K.A.; Toben, A.C.; Morris, J.G. Repeated dietary exposure to low levels of domoic acid and problems with everyday memory: Research to public health outreach. *Toxins* **2018**, *10*, 103. [CrossRef]
18. Lefebvre, K.A.; Robertson, A. Domoic acid and human exposure risks: A review. *Toxicon* **2010**, *56*, 218–230. [CrossRef]
19. Sahraoui, I.; Bates, S.S.; Bouchouicha, D.; Mabrouk, H.H.; Hlaili, A.S. Toxicity of Pseudo-nitzschia populations from Bizerte Lagoon; Tunisia; southwest Mediterranean; and first report of domoic acid production by *P. brasiliana*. *Diatom Res.* **2011**, *26*, 293–303. [CrossRef]
20. Li, A. Occurrence of *Pseudo-nitzschia* species and associated domoic acid production along the Guangdong coast, South China Sea. *Harmful Algae* **2020**, *98*, 101899–101916.
21. Yang, Y. The Comparative Proteomic Study of Potential Toxic *Pseudonitzschia* (Bacillariophyta)-Inverstigation of Toxin-Related Proteins. Master's Thesis, Xiamen University, Fujian, China, 2011. (In Chinese).
22. Kotaki, Y.; Lundholm, N.; Onodera, H.; Kobayashi, K.; Bajarias, F.F.A.; Furio, E.F.; Iwataki, M.; Fukuyo, Y.; Kodama, M. Wide distribution of *Nitzschia navisvaringica*; A new domoic acid-producing benthic diatom found in Vietnam. *Fish Sci.* **2004**, *70*, 28–32. [CrossRef]
23. Buck, K. Autecology of the diatom *Pseudonitzschia australis*, a domoic acid producer, from Monterey Bay, California. *Mar. Ecol. Prog. Ser.* **1992**, *84*, 293–302. [CrossRef]
24. Wekell, J.C.; Gauglitz, E.J., Jr.; Bamett, H.J.; Hatfield, C.L.; Simons, D.; Ayres, D. Occurrence of domoic acid in Washington state razor clams (*Siliqua patula*) during 1991–1993. *Nat. Toxins* **1994**, *2*, 197–205. [CrossRef] [PubMed]
25. O'Dea, S.N.; Flewelling, L.J.; Wolny, J.; Brame, J.; Henschen, K.; Scott, P.; Hubbard, K.A.; Wren, J.; Jones, C.; Knight, C.; et al. Florida's first shellfish closure due to domoic acid. In *Seventh Symposium on Harmful Algae in the U.S.*; Sarasota, FL, USA, 2013; p. 103.
26. Wright, J.L.; Boyd, R.K.; Freitas, A.D.; Falk, M.; Foxall, R.A.; Jamieson, W.D.; Laycock, M.V.; McCulloch, A.W.; McInnes, A.G.; Odense, P.; et al. Identification of domoic acid, a neuroexcitatory amino acid, in toxic mussels from eastern Prince Edward Island. *Can. J. Chem.* **1989**, *67*, 481–490. [CrossRef]

27. Dickey, R.W.; Fryxell, G.A.; Granade, H.R.; Roelke, D. Detection of the marine toxins okadaic acid and domoic acid in shellfish and phytoplankton in the Gulf of Mexico. *Toxicon* **1992**, *30*, 355–359. [CrossRef]
28. Vale, P.; Sampayo, M.A.; Quilliam, M. DSP complex toxin profiles relation with *Dinophysis spp.* occurrence and domoic acid confirmation by LC-MS in Portuguese bivalves. In *Harmful Algae*; Reguera, B., Blanco, J., Fernández, M.L., Wyatt, T., Eds.; Xunta de Galicia and Intergovernmental Oceanographic Commission of UNESCO: Vigo, Espagne, 1998; pp. 503–506.
29. Míguez, A.; Fernandez, M.L.; Fraga, S. *First Detection of Domoic Acid in Galicia (NW Spain) Harmful and Toxic Algal Blooms*; Yasumoto, T., Oshima, Y., Fukuro, Y., Eds.; Intergovernmental Oceanographic Commission of UNESCO: Paris, France, 1996; pp. 143–145.
30. Rhodes, L.; White, D.; Syhre, M.; Atkinson, M. *Pseudonitzschia Species Isolated from New Zealand Coastal Waters: Domoic Acid Production In Vitro and Links with Shellfish Toxicity Seventh International Conference on Toxic Phytoplankton*; Yasumoto, T., Oshima, Y., Fukuyo, Y., Eds.; UNESCO: Sendai, Japan, 1995; pp. 155–158.
31. Kotaki, Y.; Koike, K.; Yoshida, M.; Chu, V.T.; Huyen, N.T.M.; Hoi, N.C.; Fukuyo, Y.; Kodama, M. Domoic acid production in *Nitzschia* sp. (Bacillariophyceae) isolated from a shrimp-culture pond in Do Son, Vietnam. *J. Phycol.* **2000**, *36*, 1057–1060. [CrossRef]
32. Amzil, Z.; Fresnel, J.; Gal, D.L.; Billard, C. Domoic acid accumulation in French shellfish in relation to toxic species of *Pseudo-nitzschia multiseries* and *P. pseudodelicatissima*. *Toxicon* **2001**, *39*, 1245–1251. [CrossRef]
33. Cusack, C.K.; Bates, S.S.; Quilliam, M.A.; Patching, J.W.; Raine, R. Confirmation of domoic acid production by *Pseudo-nitzschia australis* (Bacillariophyceae) isolated from Irish waters. *J. Phycol.* **2002**, *38*, 1106–1112. [CrossRef]
34. Gallacher, S.; Howard, G.; Hess, P.; Mac Donald, E.; Kelly, M.C.; Bates, L.A.; Brown, N.; MacKenzie, M.; Gillibrand, P.; Turrell, W.L. *The Occurrence of Amnesic Shellfish Poisons in Shellfish from Scottish Waters Harmful Algal Blooms 2000*; Hallegraff, G.M., Blackburn, S.I., Bolch, J.C., Lewis, R.J., Eds.; IOC of UNESCO: Paris, France, 2001; pp. 30–33.
35. Sarno, D.; Dahlmann, J. Production of domoic acid in another species of *Pseudo-nitzschia*: *P. multistriata* in the Gulf of Naples (Mediterranean Sea). *Harmful Algae News* **2000**, *21*, 5.
36. Chen, X.; Wang, C.; Hu, J.; Lu, B. Determination of domoic acid in water and aquatic animals by high performance liquid chromatography. *J. Hyg. Res.* **2001**, *30*, 247–248.
37. Li, D.Z.; Zhu, W.J.; Song, W.B.; Lin, B.C. Capillary electrophoretic analysis of amnesic shellfish toxin-domoic acid. *Chin. J. Chromatogr.* **2002**, *20*, 125–128.
38. Kaniou-Grigoriadou, I.; Mouratidou, T.; Katikou, P. Investigation on the presence of domoic acid in Greek shellfish. *Harmful Algae* **2005**, *4*, 717–723. [CrossRef]
39. Louw, D.; Doucette, G.; Lundholm, N. Morphology and toxicity of *Pseudo-nitzschia* species in the northern Benguela Upwelling System. *Harmful Algae* **2018**, *75*, 118–128. [CrossRef]
40. Bajarias, F.F.A.; Kotaki, Y.; Relox, J.R., Jr.; Romero, M.; Kodama, M. Screening of diatoms producing domoic acid and its derivatives in the Philippines. *Coast. Mar. Sci.* **2006**, *30*, 121–129.
41. Iverson, F.; Truelove, J. Toxicology and seafood toxins: Domoic acid. *Neurogastroenterol. Motil.* **2010**, *2*, 334–339. [CrossRef]
42. Benlahcen, R.l.; Lundholm, N.; Goux, D.; Véron, B.; Sagou, R.; Taleb, H.; Nhhala, H.; Er-Raioui, H. *Pseudo-nitzschia Peragallo* (Bacillariophyceae) diversity and domoic acid accumulation in tuberculate cockles and sweet clams in M'diq Bay, Morocco. *Acta Bot. Croat.* **2013**, *72*, 35–47.
43. Bouchouicha-Smida, D.; Lundholm, N.; Sahraoui, I.; Lambert, C.; Mabrouk, H.H.; Hlaili, A.S. Detection of domoic acid in *Mytilus galloprovincialis* and *Ostrea edulis* linked to the presence of *Nitzschia bizertensis* in Bizerte Lagoon (SW Mediterranean). *Estuar. Coast. Shelf Sci.* **2015**, *165*, 270–278. [CrossRef]
44. Takata, Y.; Sato, S.; Dao, V.; Montojo, U.; Kamolsiripichaiporn, S.; Kotaki, Y.; Fukuyo, Y.; Kodama, M. Occurrence of domoic acid in tropical bivalves. *Fish Sci.* **2009**, *75*, 473–480. [CrossRef]
45. Alvarez, G.; Uribe, E.; Quijano-Scheggia, S.; López-Rivera, A.; Mariño, C.; Blanco, J. Domoic acid production by *Pseudo-nitzschia australis* and *Pseudo-nitzschia calliantha* isolated from North Chile. *Harmful Algae* **2009**, *8*, 938–945. [CrossRef]
46. Peteva, Z.V.; Georgieva, S.; Stancheva, M.; Makedonski, L. Recreational angler exposure to domoic acid via consumption of contaminated shellfish from the Black Sea, Bulgaria: A preliminary study. *Arch. Balk. Med. Union* **2017**, *52*, 291–297.
47. Malhi, N.; Turnbull, A.; Tan, J.; Kiermeier, A.; Nimmagadda, R.; McLeod, C. A national survey of marine biotoxins in wild-caught abalone in Australia. *J. Food Prot.* **2014**, *77*, 1960–1967. [CrossRef] [PubMed]
48. Romero, M.L.; Kotaki, Y.; Lundholm, N.; Thoha, H.; Ogawa, H.; Relox, J.; Terada, R.; Takeda, S.; Takata, Y.; Haraguchi, K.; et al. Unique amnesic shellfish toxin composition found in the South East Asian diatom *Nitzschia navis-varingica*. *Harmful Algae* **2011**, *10*, 456–462. [CrossRef]
49. Thoha, H.; Kotaki, Y.; Panggabean, L.; Lundholm, N.; Ogawa, H.; Lim, P.T.; Takata, Y.; Kodama, M.; Fukuyo, Y. Screening of diatoms that produce ASP toxins in Southernmost Asian waters. *Coast. Mar. Sci.* **2012**, *35*, 34–38.
50. Smida, D.B.; Lundholm, N.; Kooistra, W.H.C.F.; Sahraoui, I.; Ruggiero, M.V.; Kotaki, Y.; Ellegaard, M.; Lambert, C.; Mabrouk, H.H.; Hlaili, A.S. Morphology and molecular phylogeny of *Nitzschia bizertensis* sp. nov.-A new domoic acid-producer. *Harmful Algae* **2014**, *32*, 49–63. [CrossRef]
51. Tan, S.N.; Teng, S.T.; Lim, H.C.; Kotaki, Y.; Bates, S.S.; Leaw, C.P.; Lim, P.T. Diatom *Nitzschia navis-varingica* (Bacillariophyceae) and its domoic acid production from the mangrove environments of Malaysia. *Harmful Algae* **2016**, *60*, 139–149. [CrossRef]
52. Pulido, O.M. Domoic acid toxicologic pathology: A review. *Mar. Drugs* **2008**, *6*, 180–219. [CrossRef]

53. Wu, D.; Zhang, Y.; Cheng, W.; Lu, J.; Zheng, Y. Research Advance in neurotoxic mechanism of domoic acid. *Asian J. Ecotoxicol.* **2013**, *8*, 1–6.
54. Saeed, A.F.; Awan, S.A.; Ling, S.; Wang, R.; Wang, S. Domoic acid: Attributes, exposure risks, innovative detection techniques and therapeutics. *Algal Res.* **2017**, *24*, 97–110. [CrossRef]
55. Munday, R.; Holland, P.T.; McNabb, P.; Selwood, A.I.; Rhodes, L.L. Comparative toxicity to mice of domoic acid and isodomoic acids A, B and C. *Toxicon* **2008**, *52*, 954–956. [CrossRef]
56. Sawant, P.M.; Tyndall, J.D.; Holland, P.T.; Peake, B.M.; Mountfort, D.O.; Kerr, D.S. In vivo seizure induction and affinity studies of domoic acid and isodomoic acids-D, -E and -F. *Neuropharmacology* **2010**, *59*, 129–138. [CrossRef]
57. Brunson, J.K.; McKinnie, S.M.K.; Chekan, J.R.; McCrow, J.P.; Miles, Z.D.; Bertrand, E.M.; Bielinski, V.A.; Luhavaya, H.; Obornik, M.; Smith, G.J.; et al. Biosynthesis of the neurotoxin domoic acid in a bloom-forming diatom. *Science* **2018**, *361*, 1356–1358. [CrossRef]
58. Chen, J.F.; Huang, W.J.; Xu, N.; Xie, L.C.; Qi, Y.Z. Domoic acid producing diatom genus *Pseudo-nitzschia peragallo*: A review. *Mar. Sci.* **2003**, *27*, 13–17. (In Chinese)
59. Turk Dermastia, T.; Dall'Ara, S.; Dolenc, J.; Mozetič, P. Toxicity of the diatom genus *Pseudo-nitzschia* (Bacillariophyceae): Insights from toxicity tests and genetic screening in the Northern Adriatic Sea. *Toxins* **2022**, *14*, 60. [CrossRef] [PubMed]
60. Rowland-Pilgrim, S.; Swan, S.C.; O'Neill, A.; Johnson, S.; Coates, L.; Stubbs, P.; Dean, K.; Parks, R.; Harrison, K.; Alves, M.T.; et al. Variability of Amnesic Shellfish Toxin and *Pseudo-nitzschia* occurrence in bivalve molluscs and water samples-Analysis of ten years of the official control monitoring programme. *Harmful Algae* **2019**, *87*, 101623. [CrossRef] [PubMed]
61. Nishimura, T.; Murray, J.S.; Boundy, M.J.; Balci, M.; Bowers, H.A.; Smith, K.F.; Wood, D.T.H.; Rhodes, L.L. Update of the planktonic diatom genus *Pseudo-nitzschia* in Aotearoa New Zealand coastal waters: Genetic diversity and toxin production. *Toxins* **2021**, *13*, 637. [CrossRef] [PubMed]
62. Bates, S.S. Ecophysiology and metabolism of ASP toxin production. In *Physiological Ecology of Harmful Algal Blooms*; Anderson, D.M., Cembella, A.D., Hallegraeff, G.M., Eds.; Springer-Verlag: Berlin, Germany, 1998; pp. 405–426.
63. Pan, Y.L.; Parsons, M.; Busman, M.B.; Moeller, P.; Doucette, G. *Pseudo-nitzschia* sp. cf. *pseudodelicatissima*-a confirmed producer of domoic acid from the northern Gulf of Mexico. *Mar. Ecol. Prog. Ser.* **2001**, *220*, 83–92. [CrossRef]
64. Fehling, J.; Green, D.H.; Davidson, K.; Bolch, C.J.; Bates, S.S. Domoic acid production by *Pseudo-nitzschia seriata* (Bacillariophyceae) in scottish waters. *J. Phycol.* **2004**, *40*, 622–630. [CrossRef]
65. Pan, Y.; Bates, S.S.; Cembella, A.D. Environmental stress and domoic acid production by *Pseudo-nitzschia*: A physiological perspective. *Neurogastroenterol. Motil.* **2010**, *6*, 127–135.
66. Lelong, A.; Hégaret, H.; Soudant, P.; Bates, S.S. *Pseudo-nitzschia* (Bacillariophyceae) species; domoic acid and amnesic shellfish poisoning: Revisiting previous paradigms. *Phycologia* **2012**, *51*, 168–216. [CrossRef]
67. Trainer, V.L.; Bates, S.S.; Lundholm, N.; Thessen, A.E.; Cochlan, W.P.; Adams, N.G.; Trick, C.G. *Pseudo-nitzschia* physiological ecology, phylogeny, toxicity, monitoring and impacts on ecosystem health. *Harmful Algae* **2012**, *14*, 271–300. [CrossRef]
68. Fehling, J.; Davidson, K.; Bolch, C.J.; Bates, S.S. Growth and domoic acid production by *Pseudo-nitzschia seriata* (Bacillariophyceae) under phosphate and silicate limitation. *J. Phycol.* **2004**, *40*, 674–683. [CrossRef]
69. Pan, Y.; Subba Rao, D.V.; Mann, K.H. Changes in domoic acid production and cellular chemical composition of the toxigenic diatom *Pseudo-nitzschia multiseries* under phosphate limitation. *J. Phycol.* **1996**, *32*, 371–381. [CrossRef]
70. Auro, M.E. *Nitrogen Dynamics and Toxicity of the Pennate Diatom Pseudo-Nitzschia Cuspidata: A Field and Laboratory Study*; San Francisco State University: San Francisco, CA, USA, 2007; p. 91.
71. Howard, M.; Cochlan, W.P.; Ladizinsky, N.; Kudela, R.M. Nitrogenous preference of toxigenic *Pseudo-nitzschia australis* (Bacillariophyceae) from field and laboratory experiments. *Harmful Algae* **2007**, *6*, 206–217. [CrossRef]
72. Martin-Jézéquel, V.; Calu, G.; Candela, L.; Amzil, Z.; Jauffrais, T.; Séchet, V.; Weigel, P. Effects of Organic and Inorganic Nitrogen on the Growth and Production of Domoic Acid by *Pseudo-nitzschia multiseries* and *P. australis* (Bacillariophyceae) in Culture. *Mar. Drugs* **2015**, *13*, 7067–7086. [CrossRef]
73. Rue, E.; Bruland, K. Domoic acid binds iron and copper: A possible role for the toxin produced by the marine diatom *Pseudo-nitzschia*. *Mar. Chem.* **2001**, *76*, 127–134. [CrossRef]
74. Maldonado, M.T.; Hughes, M.P.; Rue, E.L.; Wells, M.L. The effect of Fe and Cu on growth and domoic acid production by *Pseudo-nitzschia multiseries* and *Pseudo-nitzschia australis*. *Limnol. Oceanogr.* **2002**, *47*, 515–526. [CrossRef]
75. Shahzad, B.; Mughal, M.N.; Tanveer, M.; Gupta, D.; Abbas, G. Is lithium biologically an important or toxic element to living organisms? An overview. *Environ. Sci. Pollut. R.* **2017**, *24*, 103–115. [CrossRef]
76. Rao, D.V.S.; Pan, Y.; Mukhida, K. Production of domoic acid by *Pseudo-nitzschia multiseries* Hasle, affected by lithium. *Mar. Ecol.* **1998**, *19*, 31–36. [CrossRef]
77. Thorel, M.; Fauchot, J.; Morelle, J.; Raimbault, V.; Le Roy, B.; Miossec, C.; Kientz-Bouchart, V.; Claquin, P. Interactive effects of irradiance and temperature on growth and domoic acid production of the toxic diatom *Pseudo-nitzschia australis* (Bacillariophyceae). *Harmful Algae* **2014**, *39*, 232–241. [CrossRef]
78. Zhu, Z.; Qu, P.; Fu, F.; Tennenbaum, N.; Tatters, A.O.; Hutchins, D.A. Understanding the blob bloom: Warming increases toxicity and abundance of the harmful bloom diatom *Pseudo-nitzschia* in California coastal waters. *Harmful Algae* **2017**, *67*, 36–43. [CrossRef]

79. Amato, A.; Lüdeking, A.; Kooistra, W.H.C.F. Intracellular domoic acid production in *Pseudo-nitzschia multistriata* isolated from the Gulf of Naples (Tyrrhenian Sea, Italy). *Toxicon* **2010**, *55*, 157–161. [CrossRef] [PubMed]
80. Fehling, J.; Davidson, K.; Bates, S.S. Growth dynamics of non-toxic *Pseudo-nitzschia delicatissima* and toxic *P. seriata* (Bacillariophyceae) under simulated spring and summer photoperiods. *Harmful Algae* **2005**, *4*, 763–769. [CrossRef]
81. Bates, S.S.; Douglas, D.J.; Doucette, G.J.; Léger, C. Enhancement of domoic acid production by reintroducing bacteria to axenic cultures of the diatom *Pseudo-nitzschia multiseries*. *Nat. Toxins* **1995**, *3*, 428–435. [CrossRef] [PubMed]
82. Kobayashi, K.; Takata, Y.; Kodama, M. Direct contact between *Pseudo-nitzschia multiseries* and bacteria is necessary for the diatom to produce a high level of domoic acid. *Fish Sci.* **2009**, *75*, 771–776. [CrossRef]
83. Guannel, M.L.; Horner-Devine, M.C.; Rocap, G. Bacterial community composition differs with species and toxigenicity of the diatom *Pseudo-nitzschia*. *Aquat. Microb. Ecol.* **2011**, *64*, 117–133. [CrossRef]
84. Lelong, A.; Hégaret, H.; Soudant, P. Link between domoic acid production and cell physiology after exchange of bacterial communities between toxic *Pseudo-nitzschia multiseries* and non-toxic *Pseudo-nitzschia delicatissima*. *Mar. Drugs* **2014**, *12*, 3587–3607. [CrossRef] [PubMed]
85. Yu, Z.M.; Rao, D.V.S. Impact of halloysite on growth of *Psuedonitzschia pungens f. multiseries* and production of algal toxin. *Oceanol. Limnol. Sin.* **1998**, *29*, 47–52.
86. Yu, Z.M.; Rao, D.V.S. Effects of Germanium on the growth and the production of microcystins in *Pseudo-nitzschia multiseries*. *Chin. Sci. Bull.* **1998**, *43*, 2311–2315. (In Chinese)
87. Lundholm, N.; Hansen, P.J.; Kotaki, Y. Effect of pH on growth and domoic acid production by potentially toxic diatoms of the genera *Pseudo-nitzschia* and *Nitzschia*. *Mar. Ecol. Prog. Ser.* **2004**, *273*, 1–15. [CrossRef]
88. Sun, J.; Hutchins, D.A.; Feng, Y.; Seubert, E.L.; Caron, D.A.; Fu, F.-X. Effects of changing pCO_2 and phosphate availability on domoic acid production and physiology of the marine harmful bloom diatom *Pseudo-nitzschia multiseries*. *Limnol. Oceanogr.* **2011**, *56*, 829–840. [CrossRef]
89. Tatters, A.O.; Fu, F.X.; Hutchins, D.A.; Brett, N. High CO_2 and Silicate Limitation Synergistically Increase the Toxicity of *Pseudo-nitzschia fraudulenta*. *PLoS ONE* **2012**, *7*, e32116. [CrossRef] [PubMed]
90. Tatters, A.; Schnetzer, A.; Xu, K.; Walworth, N.; Fu, F.; Spackeen, J.; Sipler, R.; Bertrand, E.; McQuaid, J.; Allen, A.; et al. Interactive effects of temperature, CO_2 and nitrogen source on a coastal California diatom assemblage. *J. Plankton Res.* **2018**, *40*, 151–164. [CrossRef]
91. Tammilehto, A.; Nielsen, T.; Krock, B.; Møller, E.; Lundholm, N. Induction of domoic acid production in the toxic diatom *Pseudo-nitzschia seriata* by calanoid copepods. *Aquat. Toxicol.* **2015**, *159*, 52–61. [CrossRef]
92. Leandro, L.; Teegarden, G.; Roth, P.; Wang, Z.; Doucette, G. The copepod *Calanus finmarchicus*: A potential vector for trophic transfer of the marine algal biotoxin; domoic acid. *J. Exp. Mar. Biol. Ecol.* **2010**, *382*, 88–95. [CrossRef]
93. Maneiro, I.; Iglesias González, P.; Guisande, C.; Riveiro, I.; Barreiro Felpeto, A.; Zervoudaki, S.; Granéli, E. Fate of domoic acid ingested by the copepod *Acartia clausi*. *Mar. Biol.* **2005**, *148*, 123–130. [CrossRef]
94. Harðardóttir, S.; Pančić, M.; Tammilehto, A.; Krock, B.; Møller, E.F.; Nielsen, T.G.; Lundholm, N. Dangerous Relations in the Arctic Marine Food Web: Interactions between Toxin Producing *Pseudo-nitzschia* Diatoms and Calanus Copepodites. *Mar. Drugs* **2015**, *13*, 3809–3835. [CrossRef]
95. Auro, M.; Cochlan, W. Nitrogen Utilization and Toxin Production by Two Diatoms of the *Pseudo-nitzschia pseudodelicatissima* Complex: *P. cuspidata* and *P. fryxelliana*. *J. Phycol.* **2013**, *49*, 156–169. [CrossRef]
96. Radan, R.L.; Cochlan, W.P. Differential toxin response of *Pseudo-nitzschia multiseries* as a function of nitrogen speciation in batch and continuous cultures, and during a natural assemblage experiment. *Harmful Algae* **2018**, *73*, 12–29. [CrossRef]
97. Pednekar, S.M.; Bates, S.S.; Kerkar, V.; Matondkar, S.G.P. Environmental Factors Affecting the Distribution of *Pseudo-nitzschia* in two monsoonal estuaries of Western India and effects of salinity on growth and domoic acid production by *P. pungens*. *Estuar. Coast.* **2018**, *41*, 1448–1462. [CrossRef]
98. Botana, L. The Mouse Bioassay as a Universal Detector. In *Seafood and Freshwater Toxins*; CRC Press: Boca Raton, FL, USA, 2008.
99. Dolah, F.M.; Finley, E.L.; Haynes, B.; Doucette, G.J.; Moeller, P.; Ramsdell, J. Development of rapid and sensitive high throughput pharmacologic assays for marine phycotoxins. *Nat. Toxins* **1994**, *2*, 189–196. [CrossRef]
100. Vera-Avila, L.; Marín-Pérez, D.; Covarrubias-Herrera, R. Trace level determination of domoic acid in seawater by Off-line/on-line Solid-phase extraction coupled to HPLC-UV. *J. Mex. Chem. Soc.* **2011**, *55*, 65–71.
101. Furey, A.; Lehane, M.; Gillman, M.; Fernandez-Puente, P.; James, K.J. Determination of domoic acid in shellfish by liquid chromatography with electrospray ionization and multiple tandem mass spectrometry. *J. Chromatogr. A* **2001**, *938*, 167–174. [CrossRef] [PubMed]
102. Wang, Z.; Maucher-Fuquay, J.; Fire, S.E.; Mikulski, C.M.; Haynes, B.; Doucette, G.J.; Ramsdell, J.S. Optimization of solid-phase extraction and liquid chromatography-tandem mass spectrometry for the determination of domoic acid in seawater, phytoplankton, and mammalian fluids and tissues. *Anal. Chim. Acta.* **2012**, *715*, 71–79. [CrossRef] [PubMed]
103. Beach, D.G.; Walsh, C.M.; Cantrell, P.; Rourke, W.; O'Brien, S.; Reeves, K.; McCarron, P. Laser ablation electrospray ionization high resolution mass spectrometry for regulatory screening of domoic acid in shellfish. *Rapid Commun. Mass Spectrom.* **2016**, *30*, 2379–2387. [CrossRef] [PubMed]
104. Zhang, Y.; Chen, D.; Hong, Z. A rapid LC-HRMS method for the determination of domoic acid in urine using a Self-Assembly Pipette Tip Solid-Phase extraction. *Toxins* **2016**, *8*, 10. [CrossRef] [PubMed]

105. Yu, F.; Liu, B.; Wu, T.; Chi, T.; Su, M. Development of a sensitive Enzyme-Linked Immunosorbent Assay for the determination of domoic acid in shellfish. *J. Agric. Food Chem.* **2004**, *52*, 5334–5339. [CrossRef]
106. Zhang, X.W.; Zhang, Z.X. Quantification of domoic acid in shellfish samples by capillary electrophoresis-based enzyme immunoassay with electrochemical detection. *Toxicon* **2012**, *59*, 626–632. [CrossRef]
107. Tsao, Z.J.; Liao, Y.C.; Liu, B.H.; Su, C.C.; Yu, F.Y. Development of a monoclonal antibody against domoic acid and its application in Enzyme-Linked Immunosorbent Assay and colloidal gold immunostrip. *J. Agric. Food Chem.* **2007**, *55*, 4921–4927. [CrossRef]
108. Kvasnicka, F.; Sevcik, R.; Voldrich, M. Determination of domoic acid by on-line coupled capillary isotachophoresis with capillary zone electrophoresis. *J. Chromatogr. A* **2006**, *1113*, 255–258. [CrossRef]
109. Müller, C.; Glamuzina, B.; Pozniak, I.; Weber, K.; Cialla, D.; Popp, J.; Cîntă Pînzaru, S. Amnesic shellfish poisoning biotoxin detection in seawater using pure or amino-functionalized Ag nanoparticles and SERS. *Talanta* **2014**, *130*, 108–115. [CrossRef]
110. Di Paola, D.; Abbate, J.M.; Iaria, C.; Cordaro, M.; Crupi, R.; Siracusa, R.; D'Amico, R.; Fusco, R.; Impellizzeri, D.; Cuzzocrea, S.; et al. Environmental Risk Assessment of Dexamethasone Sodium Phosphate and Tocilizumab Mixture in Zebrafish Early Life Stage (*Danio rerio*). *Toxics* **2022**, *10*, 279. [CrossRef] [PubMed]
111. Di Paola, D.; Iaria, C.; Capparucci, F.; Arangia, A.; Crupi, R.; Cuzzocrea, S.; Spanò, N.; Gugliandolo, E.; Peritore, A.F. Impact of Mycotoxin Contaminations on Aquatic Organisms: Toxic Effect of Aflatoxin B1 and Fumonisin B1 Mixture. *Toxins* **2022**, *14*, 518. [CrossRef] [PubMed]
112. Hess, P.; McGovern, E.; McMahon, T.; Morris, S.; Stobo, L.A.; Brown, N.A.; Gallacher, S.; McEvoy, J.D.G.; Kennedy, G.; Young, P.B.; et al. LC-UV and LC-MS methods for the determination of domoic acid. *Trends Anal. Chem.* **2005**, *24*, 358–367. [CrossRef]
113. Garthwaite, I.; Ross, K.M.; Miles, C.O.; Hansen, R.P.; Towers, N.R. Polyclonal antibodies to domoic acid; and their use in immunoassays for domoic acid in sea water and shellfish. *Nat. Toxins* **2015**, *6*, 93–104. [CrossRef]
114. Kawatsu, K.; Hamano, Y.; Noguchi, T. Production and characterization of a monoclonal antibody against domoic acid and its application to enzyme immunoassay. *Toxicon* **1999**, *37*, 1579–1589. [CrossRef] [PubMed]
115. Kleivdal, H.; Kristiansen, S.-I.; Nilsen, M.; Goksøyr, A.; Briggs, L.; Holland, P.; McNabb, P. Determination of domoic acid toxins in shellfish by Biosense ASP ELISA-A direct competitive enzyme-linked immunosorbent assay: Collaborative study. *J. AOAC Int.* **2007**, *90*, 1011–1027. [CrossRef] [PubMed]
116. Litaker, R.; Stewart, T.; Eberhart, B.-T.; Wekell, J.; Trainer, V.; Kudela, R.; Miller, P.; Roberts, A.; Hertz, C.; Johnson, T.; et al. Rapid Enzyme-linked Immunosorbent Assay for Detection of the Algal Toxin Domoic Acid. *J. Shellfish. Res.* **2008**, *27*, 1301–1310. [CrossRef]
117. Liu, S.; Zhao, X.; Cheng, J.; Wang, Q.; Wang, W. Establishment of indirect ELISA to detect domoic acid. *Acta Sci. Circumstantiae* **2014**, *34*, 404–408. (In Chinese)
118. Wang, Q.; Chen, J.; Gao, L.; Dong, Y.; Lei, X. Development of Direct Competitive Enzyme-Linked Immunosorbent Assay for the Determination of Domoic Acid. *Environ. Sci.* **2012**, *33*, 647–651. (In Chinese)
119. Fraga, M.; Vilarino, N.; Louzao, M.C.; Rodriguez, P.; Campbell, K.; Elliott, C.T.; Botana, L.M. Multidetection of paralytic, diarrheic, and amnesic shellfish toxins by an inhibition immunoassay using a microsphere-flow cytometry system. *Anal. Chem.* **2013**, *85*, 7794–7802. [CrossRef]
120. Abdul Rahman, M.S.; Jayasundera, K.; Mukhopadhyay, S.C. A low cost novel sensing system for detection of dangerous marine biotoxins in seafood. Sensor. *Actuat. B Chem.* **2009**, *137*, 67–75.
121. McGrath, T.F.; Andersson, K.; Campbell, K.; Fodey, T.L.; Elliott, C.T. Development of a rapid low cost fluorescent biosensor for the detection of food contaminants. *Biosens. Bioelectron.* **2013**, *41*, 96–102. [CrossRef] [PubMed]
122. Yakes, B.; Buijs, J.; Elliott, C.; Campbell, K. Surface plasmon resonance biosensing: Approaches for screening and characterising antibodies for food diagnostics. *Talanta* **2016**, *156–157*, 55–63. [CrossRef] [PubMed]
123. Abdul Keyon, A.; Guijt, R.; Gaspar, A.; Kazarian, A.; Nesterenko, P.; Bolch, C.; Breadmore, M. Capillary electrophoresis for the analysis of paralytic shellfish poisoning toxins in shellfish: Comparison of detection methods. *Electrophoresis* **2014**, *35*, 1496–1503. [CrossRef]
124. Boissonneault, K.R.; Henningsen, B.M.; Bates, S.S.; Robertson, D.L.; Milton, S.; Pelletier, J.; Hogan, D.A.; Housman, D.E. Gene expression studies for the analysis of domoic acid production in the marine diatom *Pseudo-nitzschia multiseries*. *BMC Mol. Biol.* **2013**, *14*, 25–43. [CrossRef]
125. Di Dato, V.; Musacchia, F.; Petrosino, G.; Patil, S.; Montresor, M.; Sanges, R.; Ferrante, M.I. Transcriptome sequencing of three *Pseudo-nitzschia* species reveals comparable gene sets and the presence of Nitric Oxide Synthase genes in diatoms. *Sci. Rep.* **2015**, *5*, 12329. [CrossRef]
126. Lewis, N.I.; Bates, S.S.; Quilliam, M.A. Production of domoic acid from large-scale cultures of *Pseudo-nitzschia multiseries*: A feasibility study. *Harmful Algae* **2018**, *79*, 58–63. [CrossRef]
127. Lahvis, G.P. What California sea lions exposed to domoic acid might teach us about autism: Lessons for predictive and preventive medicine. *EPMA J.* **2017**, *8*, 229–235. [CrossRef]