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Review Article

Advanced detection methods for Okadaic acid and its derivatives in shellfish: ensuring food safety through accurate analysis

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ABSTRACT

Diarrhetic shellfish poisoning (DSP) is one of the most prevalent marine food poisonings in humans, being produced by toxins such as okadaic acid (OA) and derivatives, including dinophysistoxins (DTXs) and pectenotoxins. OA exerts its interference with cell processes through the inhibition of protein phosphatase activity capable of disrupting the cell cycle, tumor growth, and induction of cancer. These biotoxins are highly resistant to environmental conditions, such as heat and freezing, as well as most forms of processing; hence, contaminated shellfish have to be avoided to prevent human poisoning. The developed detection methods over time move from early qualitative ones, less accurate and more labor-intensive, to more modern quantitative ones, differing in their respective strengths and weaknesses. These are, in fact, continuous challenges for developing methodologies that are highly specific, sensitive, and yet easy to use and low in cost but able to analyze hundreds of samples per day to ensure food safety. The review will critically assess some such detection methods, their advantages, and their shortcomings.

Keywords: Biotoxin detection; Food safety; Immunosensor; Okadaic acid, Shellfish poisoning.

1. Introduction

Diarrhetic Shellfish Poisoning (DSP), is one of the more common types of food poisoning. Symptoms of DSP include nausea, vomiting, abdominal cramps, and diarrhea. Hundreds of people in countries such as but not limited to Japan, China, Spain, the Netherlands, France, Chile, Uruguay, Ireland, the United States, Canada, and parts of Scandinavia are poisoned every year. DSP is produced by toxic dinoflagellates of the genera *Dinophysis* and identifying and detecting these toxins (Shumway & Cucci, 1987; Rossini & Hess, 2010; Sassolas *et al.*, 2013; Roland *et al.*, 2022).

The detection of these toxins has so far been done using techniques such as the Mouse Bioassay and high-performance liquid chromatography (HPLC). These, however, are expensive and time-consuming, and since there is usually an urgent need for quick and accurate on-site identification to try and prevent the distribution of contaminated products, the development of portable sensors with improved detection capabilities has been favored. These sensors rely on a broad spectrum of methodologies, such as enzymatic assays, cell-based bioassays, biochemical assays, and electrochemical techniques, among many others. The scope of this review will be the presentation of novel methodologies developed for the detection of biotoxins, with particular attention to OA and DTXs, through the performances, advantages, and drawbacks, among others (Roland *et al.*, 2022).

2. Toxins

2.1. Okadaic acid (OA) and dinophysistoxins (DTXs)

OA was first isolated from marine sponges of the species *Halichondria okadai* and *Halichondria melanodocia* in 1981 (Schmitz *et al.*, 1981; Tachibana *et al.*, 1981). Later, it was discovered that this biotoxin, along with its derivatives collectively known as DTXs, is produced by various dinoflagellates from the *Dinophysis* and *Prorocentrum* genera. These dinoflagellates accumulate OA and other biotoxins (DTXs) in the tissues of shellfish and fish, particularly in the hepatopancreas and gonads, after consuming soft-bodied organisms such as bivalve mollusks. As a result, consuming contaminated shellfish can cause poisoning in humans (Lee *et al.*, 2016).

OA is a polyether fatty acid classified as a lipophilic toxin. It exists in 13 distinct forms (Figure 1), each with varying degrees of toxicity, including OA, DTX-1, DTX-2, DTX-3, DTX-4, DTX-5a, DTX-5b, DTX-6, acanthifolicin, OA diol esters, belzeanic acid, and the 19-epi isomer of OA (Kobayashi & Kubota, 2010). OA has a carboxylic acid at one end and an epoxide group at the other. That structural feature enables its binding to the active site in protein phosphatases, and hence it acts as an inhibitor of the enzyme (Dounay & Forsyth, 2002). Modifications in the C1 and C2 regions can substantially decrease the potency and toxicity of these toxins (Honkanan *et al.*, 1994). Initially, they target and inhibit serine/threonine protein phosphatases (PP) and PP2A, and later, they also inhibit PP1 and PP2B as secondary targets (Takai *et al.*, 1992).

The permissible limits for these toxins, when administered intraperitoneally in mice, are established as 1 for OA, 1 for DTX-1, and 0.6 for DTX-2. The Toxic equivalency factors (TEFs) for oral exposure are established at 1, 1.5, and 0.3, respectively.

Several studies have estimated the lethal dose of these toxins to be different in value, but an approximate lethal dose can be considered in one study at 760 μg kg^{-1} body weight for OA and 487 μg kg^{-1} for DTX-1 (Abal *et al.*, 2018). Its inhibition of protein phosphatases is reversible: peak toxicity occurs within 20 minutes, symptoms last two to three days with resolution gradually occurring (Fish, 2011; Twiner *et al.*, 2016). For OA, it is reported that in a laboratory, 360 liters of cultured algae can yield about 1.1 mg of pure OA. In the case of DTX-1 and DTX-2, yields reported are 0.5 mg in 80% yield and 0.42 mg in 95% yield, respectively (Suárez-Gómez *et al.*, 2001; Larsen *et al.*, 2007; Pang *et al.*, 2011). Their detection is based on one analytical method involving the inhibition of PP2A. OA is one among several well-studied inhibitors of protein phosphatases and a few related research applications (Twiner *et al.*, 2016; Abal *et al.*, 2018).

2. 2. Pectenotoxins (PTXs)

In 2002, researchers discovered that PTXs not only cause DSP but can also trigger additional conditions, such as liver necrosis and cardiac muscle damage, even though they remain classified under DSP (Dominguez *et al.*, 2010).

PTXs were first extracted from scallops and mussels, but it was later confirmed that their production is linked to species of *Dinophysis* (Yasumoto *et al.*, 1985; Draisci *et al.*, 1996). These toxins include nine compounds, specifically PTX-1, PTX-2, PTX-3, PTX-6, PTX-*Prorocentrum*, which produce potent polyether compounds such as okadaic acid (OA) and its ester derivatives, including dinophysistoxins (DTX-1, DTX-2, etc.), along with polyether lactones, popularly known as PTXs. Notably, contamination by these toxin-producing microalgae may pose a serious threat to shellfish harvested from coastal waters even in the absence of visible algal blooms (Liu *et al.*, 2014; Corriere *et al.*, 2021).

OA works by inhibiting the protein phosphatases activity present in the mammalian cytosol. OA blocks the dephosphorylation process of proteins which, as a result, leads to gastrointestinal inflammation, intestinal distress, and diarrhea. These biotoxins have been reported to induce apoptosis and disrupt normal cell cycle function; they may also facilitate tumor growth (Lembeye, 1993; Li *et al.*, 2020).

In contrast, PTXs act through interference with sodium channels, causing cell impairment. Fish populations are also affected by DSP toxicity, whose symptoms include altered behavior and physical deformities and have even resulted in death. In the case of shellfish, PTXs lead to losses characterized by death among eggs, embryos, and adults. However, some shellfish respond by shell closure and/or mucus production. However, chronic exposure to these toxins does not seem to affect the populations of fish and shellfish as a result (Mendez, 1993; Lu *et al.*, 2012; Martino *et al.*, 2020).

The permissible legal limits for OA and PTXs are set at 0.16 and 0.12 μg g^{-1} of shellfish meat, respectively. Fishing bans are established in the case of values exceeding limits set by regulatory bodies, which seriously affects economic and social implications for fishermen and coastal communities. A minimal increase of one percent in the production of biotoxins can lead to a drop of 0.66% in the production of shellfish. Without these fishing bans, the supply of nontoxic seafood becomes more limited and thereby hurts the very livelihood of the fishermen themselves. Protecting communities from these diseases and intoxications is a sure way to tell just how imperative it is to develop better ways of 11, PTX-12, and PTX-2 seco acid (Figure 2), with PTX-1, PTX-3, and PTX-6 being oxidation products of PTX-2 (Kobayashi & Kubota, 2010).

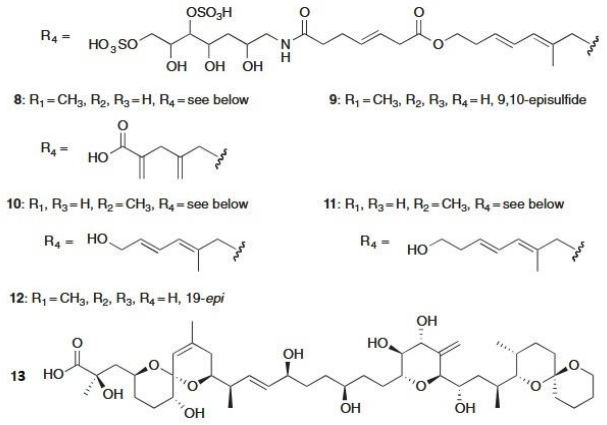

Figure 1.
Chemical structures of OA and its 13 distinct derivatives.

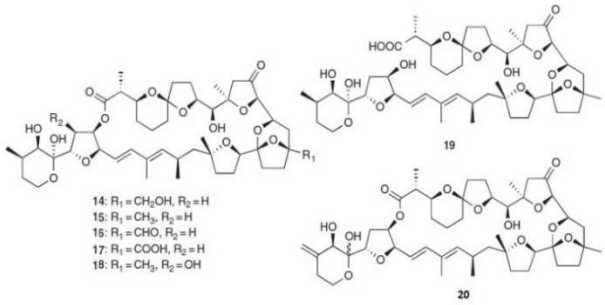

Figure 2.
Chemical structures of PTXs and their oxidation products.

3. Identification Methods

Generally, identification may be approached by two categories, which are biological and non-biological assays. The former comprises both in

vivo and in vitro techniques. On the other hand, the latter involves chemical and bioanalytical approaches. Each category includes several types of techniques Figure 3.

3. 1. Biological assays

In vivo bioassays represent the traditional methods of toxin detection; the most widely applied is called a mouse bioassay, MBA. In the course of an MBA, the type of toxin is determined based on the characteristic pattern of its action on the animals, whereas quantity and concentration are inferred solely from the absence or presence (Aase & Rogstad, 1997). The method is very time-consuming and has several associated ethical issues. Another key disadvantage of the MBA involves the fact that stronger toxins may well mask weaker one's detection; this eventually can cause the death of the test animals. Interestingly, the identification of toxins using this method substantially depends on the efficiency of the applied extraction method.

Another type of biological assay is the in vitro methods, which is conducted in the laboratory under controlled conditions and involve the evaluation of the toxins' effects on selected components of an organism such as cells and tissues. The techniques typically yield faster results, are viewed as ethically acceptable, and are less cumbersome to conduct compared to the in vivo techniques. However, the findings of the in vitro studies may be less scientifically valid and credible compared to those obtained from the in vivo methods.

3. 2. Non-biological assays

Another category that can be depicted is the non-biological assay, which includes chemical and bioanalytical methods, where the highlighting will be based on chemical and biochemical analysis of toxins. Such techniques become important during detection and measurement due to their chemical nature. Among the many chemical techniques employed for the identification and measurement of toxins, HPLC and mass spectrometry (MS) are included. In contrast, bioanalytical techniques used for the detection and quantification of toxins in biological components make use of enzymes or cells as sensing agents, ensuring toxin identification with a high degree of sensitivity and specificity.

Also, technological development and research allowed the establishment of more sophisticated and sensitive identification techniques, including molecular methods and biosensors (Aghajani *et al.*, 2024). Newer techniques ensure an increase in accuracy, sensitivity, and speed in toxin identifications.

The final identification methodology would depend on many variables: types, resources, accuracy desired, and regulatory requirements mix of a few. Most researchers and analysts use a combination of several methodologies in order to reach reliable comprehensive toxin identification.

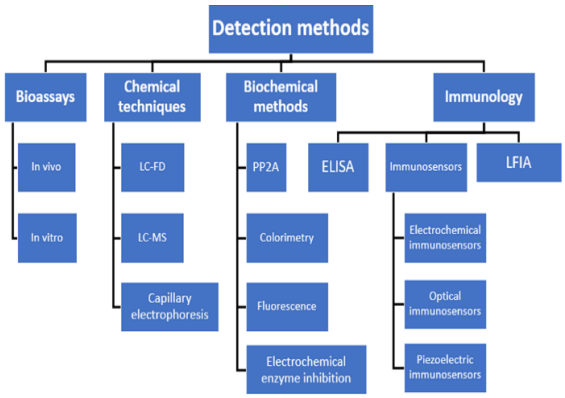

Figure 3.
Categorization of toxin identification methods: biological *vs.* non-biological assays.

4. Chemical analysis

Chemical analysis methods make use of High-Performance Liquid chromatography-HPLC combined with various detection techniques such as mass spectrometry-MS, fluorescence-FL, ultraviolet-UV, and others (Lee *et al.*, 1987). LC coupled with fluorescence or mass spectrometry detectors has become one of the recognized standard methods for the quantitative analysis of OA in many countries. The technique of LC-MS is highly valued for its high selectivity, accuracy, sensitivity, and large working range, besides

being easy to operate; for this reason, it remains an outstanding choice for carrying out the detection and quantification of OA and its derivatives, among other marine toxins (Suzuki & Yasumoto, 2000). However, this technique requires very expensive equipment; thus, the availability of this technique in routine laboratory settings is limited. Besides that, this technique also needs skilled personnel and great care in the ways of sample preparation techniques in order for it to work efficiently (Hu *et al.*, 1992).

Since this separation and labeling of toxins are required for the method of LC-FLD, the overall cost of the assays may increase and is not applicable to all toxic compounds; thus, considerable false-positive results may appear.

5. Biochemical analysis

Since OA induces its toxic effects by inhibiting serine/threonine protein phosphatases, this mechanism can be leveraged for the identification and quantification of OA (Dounay & Forsyth, 2002). In the enzyme inhibition method that employs colorimetry, the color change of the enzyme-substrate PP2A is assessed. It is based on the purity of the sample and the efficiency and quality of the substrate. It is an inexpensive, sensitive method that is very accurate; also, it is easy quick, and highly reproducible (Lee *et al.*, 1987).

The lower sensitivity of fluorescence to toxic compounds in the enzyme inhibition method coupled with fluorescence detection can be used to lower the number of false-positive results. This technique also contains fewer errors and testing of seawater can be done directly in order to find out the toxins under study (Mountfort *et al.*, 2001). In relation to this, one of the main advantages of the latter assay identified by Mountfort et al. (2001) is that it requires only 1.5 nanomolar of the PP2A enzyme, which tends to save costs. Generally speaking, fluorometry tends to be more accurate and sensitive than colorimetry (Mountfort *et al.*, 2001).

6. Immunosensors

Among the techniques discussed, the enzyme-linked immunosorbent assay (ELISA) utilizing colloidal gold monoclonal antibodies has shown the greatest affinity for OA (Rossi *et al.*, 2012). This method features an impressive detection limit for OA at 12 picograms per milliliter and a recovery rate of up to 84% when using colloidal gold (Rossi *et al.*, 2012). The sensitivity of this method has been reported to be as low as 12 nanograms per milliliter, making it a promising option for practical applications.

Biosensors that use cells, enzymes, and aptamers, which have a high affinity for specific antigens, are commonly employed for toxin detection. However, a study found that rapid diagnostic kits produced unsatisfactory results for pre-determined samples regarding the concentration and quantity of OA toxin (Ajani *et al.*, 2021). Nonetheless, these kits may be a viable option for toxin identification due to their cost-effectiveness, quick preparation time, and user-friendly nature, provided that their performance is enhanced and technology continues to advance (Viviani, 1992; Zhang & Zhang, 2012; Wang *et al.*, 2017).

Aptamers have been utilized as identification molecules in conjunction with various signaling techniques, including colorimetry, fluorescence, and chemiluminescence, for detecting and monitoring food safety. A competitive aptamer-based assay employing rolling circle amplification (RCA) was introduced for the first time to detect OA in shellfish (Gu *et al.*, 2017). Numerous types of fluorescent aptasensors are widely used, with detection limits ranging from millimolar to femtomolar levels. In the referenced study, a fluorescent aptasensor was developed specifically for the detection of OA (Wang *et al.*, 2011).

Various signal enhancement techniques utilizing nucleic acids have been developed in these highly sensitive aptasensors, allowing for the quantitative measurement of low concentrations (Yang *et al.*, 2016). The RCA technique has been employed to improve detection and analysis performance, including detection range, sensitivity, and selectivity, due to its single-stranded DNA or RNA properties. Nucleic acid-based signal amplification is generally more convenient and effective than antibody-based amplification. With the aid of RCA, aptamers have demonstrated high

sensitivity and a broad detection range. This aptamer-based approach could serve as an alternative to antibodies in the development of commercial kits, exhibiting highly specific performance, good repeatability, and effectiveness for detecting OA in seafood (Gu *et al.*, 2017).

Another study introduced a sensitive lateral flow immunoassay (LFIA) method for detecting OA (Hendrickson *et al.*, 2022). In this approach, OA indirectly interacts with labeled anti-OA antibodies through gold nanoparticles (AuNPs), facilitating cascade signal amplification (Figure 4). The method involves a mixture of anti-OA antibodies and test samples (controls) that flow along the LFIA strip, undergoing multiple cycles of interaction with the antibody-conjugated AuNPs.

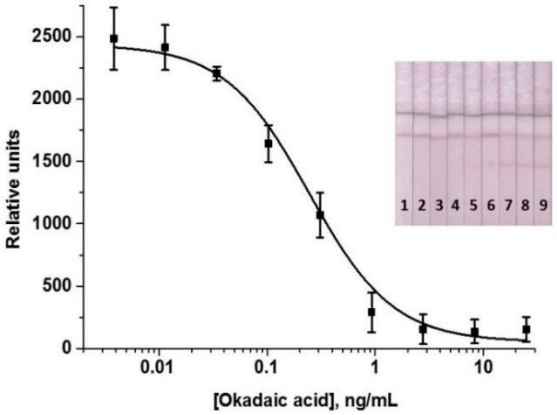

Figure 4.
Calibration curve of OA in the enhanced LFIA (n = 3) and the corresponding test strips. Concentrations of OA were 25 ng/mL (1); 8.3 ng/mL (2); 2.8 ng/mL (3); 0.93 ng/mL (4); 0.31 ng/mL (5); 0.10 ng/mL (6); 34 pg/mL (7); 1.2 pg/mL (8); 0.04 pg/mL (9); (OA (Hendrickson *et al.*, 2022).

7. Conclusions and perspectives

While the detection and quantification of marine toxins are paramount in ensuring the safety of shellfish products, OA, especially, and its derivatives remain an issue. Methods have evolved, for instance, during these years from conventional bioassays to modern chemical and bioanalytical techniques. Although some of those techniques, such as HPLC and MS, provide high levels of sensitivity and accuracy, their operational costs and inherent technical difficulties make them unsuitable for routine testing on a large scale. Aptamer-based biosensors and assays are emerging technologies offering improved detection, reduced cost, and increased convenience. However, research into further refinement of these methodologies will continue to be necessary so that they meet the increasing demands from regulatory agencies and the food industry. Fundamentally, a combination of all such superior techniques will likely result in the more effective and robust detection of toxins, for the sake of public health and stability in regions where this is an issue.

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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