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Why are bivalves not detoxified?

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Paralytic (PSP), diarrheic (DSP), and amnesic shellfish poisonings are among the most prominent foodborne diseases threatening the food security. Because of the absence of legal methods capable of eliminating these biotoxins, the option is to rely on natural detoxification, compromising the availability of protein-based food and imposing severe socioeconomic impacts. *In vivo* detoxification methodologies have focused on the use of adsorbents (mainly applied to PSP), some of which are combined with nontoxic *algae*. Alternative methodologies for DSP have emerged, but they are based on absorption inhibition, which may be unfeasible in real situations. It is thus imperative to optimize existing proposals or develop novel, safe, and cost-effective methods so that the solution is seen as an attractive financial investment.

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Introduction

Marine biotoxins are produced by toxic microalgae and represent a major threat to food security. They are ingested by marine organisms, namely bivalves, which are natural filter feeders of the marine ecosystem. Human contamination may happen from direct consumption of the bivalves, or other organisms (e.g. crabs and fish), by propagation through the food chain.

Whether due to the increase in global warming, greater monitoring, higher sensitivity of the current techniques, and/or greater awareness of the problem, the number of harmful algae bloom (HAB) events reported has been increasing. More HAB events translate into higher contamination by marine biotoxins, threatening human health and compromising the availability of protein-based food, which is already increasingly scarce in a population growth scenario. While developed countries have implemented monitoring programs that alert society to the presence of biotoxins, largely minimizing the negative impacts on human health, in most developing countries, such monitoring programs do not exist. Furthermore, the economic viability of companies is negatively affected when prohibitions from harvesting bivalves and selling their products are decreed.

Among the main groups of marine biotoxins, three stand out [1]: paralytic shellfish poisoning (PSP) toxins, diarrheic shellfish poisoning (DSP) toxins, and amnesic shellfish poisoning (ASP) toxins. PSP and DSP were the most reported syndromes globally between 1970 and 2019, representing, respectively, 46% and 42% of total events associated with harmful algae [2]. The toxins associated with each of these syndromes have very different chemical characteristics, rendering difficult to establish a 'universal' method for removing biotoxins from bivalves. In the European Union and some other Western countries (e.g. USA), the monitoring of biotoxins in shellfish is conducted with reference to the following regulatory limits (RL): 20 mg/kg for ASP; 800 μg STX.2HCl equivalents/kg for PSP; 160 μg Okadaic Acid (OA) equivalents/kg for DSP [3,4].

The temperatures conventionally reached during the home cooking process are not sufficient for a safe reduction of toxin levels. Even when a reduction of the toxin concentration is achieved in the bivalve meat, these toxins (mainly the hydrophilic ones) are found in the cooking liquids/sauces, which are often consumed [5]. For the more hydrophobic toxins, such as those causing DSP, cooking may even concentrate them, since much of the water is lost during the cooking process [6]. As there is no legally approved method for the bivalves' detoxification from these biotoxins, a total ban on the capture and sale of bivalves is imposed in all production areas where the RL are exceeded. Capture bans may range from weeks to several months [7,8], entailing enormous losses at various levels. Several studies have pointed to annual economic losses in the order of thousands to millions of dollars/euros for entities and companies linked to shellfish [2,9]. A great budgetary impact on health was also suggested by some authors, who estimated overall costs (in 2016) ranging between $US86 and $US14 600, for mild and severe illness cases, respectively [10]. To these financial costs are added those related to food insecurity, which may result in food shortages in the developing world, together with those resulting from a negative perception of the seafood quality, especially in developed countries. Thus, it is of upmost urgency to establish optimized methods that allow the detoxification of bivalves, ensuring food security as well as greater availability of protein-based food.

We hereby present a critical view of the detoxification methods applied to bivalves, discussing their potential for implementation by different stakeholders and addressing the need to adapt or change some official regulations, aiming to guarantee greater food security while controlling economic and social impacts.

Currently proposed methods for toxin removal

Most methods proposed have been tested to remove toxins from water or from toxin-producing microalgae cultures [11–14]. Although valid as a first approach, it is very limiting, and the results cannot be blindly extrapolated to the bivalves detoxification. In tests using bivalves, the effects of natural water constituents must be considered, as they may inhibit or accelerate the adsorption and photodegradation processes [12,15,16]. The biochemical interconversions that occur in living organisms should also be considered since several studies [16–19] have evidenced differences in the toxin profiles of bivalves and the toxin-producing microalgae that they ingest. When toxins interconvert, their chemical structure is altered, with changes in molecular configuration or even net charge, inducing differences in reactivity and toxicity [1].

Most studies using bivalves focus on PSP and DSP, in line with the higher prevalence of these poisoning syndromes globally [2]. However, few methodologies have been proposed for the detoxification of bivalves in the last five years, which suggests an investment by the scientific community below what would be desirable to solve a problem with such severe impacts. Some works refer to methods that involve the death of shellfish [5,20], sometimes resorting to more aggressive and expensive procedures and/or involving extensive sample processing. Even so, the effectiveness of such procedures depends on several factors (e.g. the species of bivalve, the group of toxins) and could imply a considerable investment from the food industry, including specific training for professionals.

Attention has been devoted to the development of *in vivo* detoxification methodologies. Some of the proposals proved inefficient in reducing toxicity [21,22], while others showed a global or partial decrease in toxicity, but their implementation in a real system is unfeasible due to temporal, technical, and/or logistical issues. Table 1 summarizes the characteristics of recent studies that evaluate the detoxification of bivalves in a 'natural' way and others that use specific treatments ('non-natural' methodologies). The classification of 'natural' detoxification encompasses studies whose main objective is not to develop a specific methodology to accelerate the detoxification of bivalves, but rather to evaluate its behavior and impact on other physical/chemical/biological parameters [18,19,23–27]. The data in the table corroborate that the natural detoxification of bivalves takes many days. In turn, the classification of 'non-natural' methodologies includes those that are specifically developed to accelerate the detoxification of bivalves through the addition of an external factor or the intentional change of some parameter [16,17,21,22,28–30]. It is worth noting that, in the studies presented in Table 1, bivalves were previously contaminated with toxin-producing microalgae, and the detoxification phase began after the food supply stopped. This means that there are two distinct periods (ingestion and detoxification). This does not happen in natural ecosystems, where these periods may overlap in time, leading to different results from those obtained in the laboratory [31]. Concerning 'non-natural' methodologies, the analysis of this table reveals the prevalence of studies on the detoxification of live bivalves from PSP toxins. In our view, this could be justified for two main reasons: the severity of the associated symptoms (they may cause death) and the physical-chemical properties of these toxins. PSP toxins assume a more hydrophilic character than DSP toxins, which means that they are preferentially soluble in aqueous medium. On the contrary, DSP toxins are more hydrophobic, having a greater affinity for lipid environments. As such, it is expected that PSP toxins will have a lower affinity for retention in the bivalve's tissues, which affects both their distribution between different organs and their excretion by the bivalve. In contrast, the lipophilicity associated with DSP toxins may hinder the removal/extraction of these toxins from bivalve tissues, which further complicates the development of effective methods of detoxifying live bivalves from these toxins.

Two recent studies [32,33] by Wei-Dong Yang's team report a different approach. Instead of removing toxins, the authors tested the inhibitory effect of several phytochemicals on the accumulation of DSP toxins in the digestive gland and gill of mussels *Perna viridis* (an *a priori* strategy). However, despite the positive results obtained in the digestive glands with 60 μM of

Table 1

Methods of detoxifying live bivalves.

Toxins[Reference]	$Conc._{initial}$	Bivalve	Treatment	Speed up detoxification? Detoxification rate, %	Below RL?
PSP [23]	5208.1 ± 1302.4 μg STX.2HCl eqv/kg (1), 5346.2 ± 414.0 μg STX.2HCl eqv/kg (2)	Oysters *Ostrea chilensis*, from estuary (1) and bay (2)	Feeding with a toxin-free diet (100% *Isochrysis galbana*) for 30 days.	—[a] ~86% (1) ~97% (2)	Yes
PSP [24]	516 μg STX. eqv/kg (average value, N = 13)	Mussels *M. edulis*	Starvation for 6 weeks.	—[a] ~61% (based on average values[b])	—
PSP [19]	590 μg STX. eqv/kg (1), 603 μg STX. eqv/kg (2)[c]	Mussels *Mytilus* sp.	Feeding with the non-toxic alga, *Diacronema lutheri*, for 14 days.	—[a] ~69% ~83%	—
DSP [18]	[OA] = 1674 μg/kg; [DTX1] = 6506 μg/kg (in digestive gland)	Mussels *M. galloprovincialis*	Starvation for 10 days.	—[a] OA: 33% DTX1: 18%	No
DSP [25]	[OA] = 2819.2 ± 522.2 μg/kg; [DTX1] = 1107.1 ± 267.9 μg/kg (values in digestive gland)	Mussels *M. galloprovincialis*	Feeding with the mixture of *Isochrysis* sp. and *Tetraselmis* sp. for 15 days.	—[a] 84% 53%	No
PSP [17]	4194 μg STX.2HCl eqv/kg 7794 μg STX.2HCl eqv/kg	Mussels *M. galloprovincialis* Scallops *Chlamys farreri*	Wood-based activated carbon (0.05 g/L, 37–48 μm), without food, for 72 h.	Yes 68% in mussels 25% in scallops (Both in the digestive gland)	No
PSP [21]	10 505.6 ± 4281.4 μg STX eqv/kg	Mussels *M. chilensis*	Chitosan (medium MW), without food, for 20 days.	No (comparatively to controls)	No
PSP [28]	45.6 ± 4.7 MU/g, in the viscera (79% of the total toxicity)	Oysters *Ostrea rivularis*	i) starving, ii) feeding with *Platymonas subcordiformis* (PS), iii) PS mixed with carboxymethyl chitosan (50 mg/L), for 13 days.	Yes ~90% (for treatments ii and iii, which do not differ significantly)	[d]
PSP [16]	973–981 μg STX.2HCl eqv/kg	Mussels *M. edulis*	Cation-exchange resin (1 g/L, *Na*-form), without food, for 24 h.	Yes 16% (vs. 8% in control)	No
PSP [29]	385.52 and 6381.18 μg STX eqv/kg in hepatopancreas and kidneys, respectively	Bay scallops	Silica-malic acid chitosan hydrogel, SiO_2-MA-CS (1 g to 15 L of seawater every day), without food, for 5 days.	Yes 17.60% and 56.50% in hepatopancreas and kidney, respectively (compared with the control group)	No
ASP (DA) [22]	—	King scallop, *Pecten maximus*	*N*-Acetylcysteine, NAC (250 mg/L), for 6 days (also fed with *Tisochrysis lutea*).	No (comparatively to controls, also fed)	No
DSP (OA) [30]	596 ± 25 ng/g	Wedge shell *Donax trunculus*	Nontoxic diets (*Isochrysis* aff. *Galbana*, T-iso, or commercial paste of *Tetraselmis suecica* '*Phytobloom Ice Tetraselmis*', PIT) vs. starvation, and temperature (16°C or 20°C), for 14 days.	Yes Between 67.1% (starvation at 16°C) and 84.7% (PIT at 20°C)	[e]

MW, molecular weight.

[a] In each of these works, a comparative study of different detoxification treatments, after contamination with the same toxic microalgae, was not carried out. As such, we do not have data to confirm whether there was an acceleration of the process. This treatment is classified as 'natural' detoxification.

[b] A high inter-individual variability of PST concentration was reported by the authors.

[c] Each concentration was achieved after exposure to *Alexandrium minutum* and *A. catenella*, respectively.

[d] Note: In the viscera, mantle + gill and muscle, individually, the authors report that toxicity is below the RL. However, considering the sum of toxicity in all tissues, after 13 days, it is likely that toxicity is above the RL (based on the results presented by the authors).

[e] Apparently, yes. The authors refer "A reduction of OA toxins from approximately 500 to 160 mg OA equivalents kg^{-1} was achieved after 6 days of depuration (.)".

cinnamaldehyde [32] or 20 μM of curcumin [33], this approach has limitations because it implies that phytochemicals are present during the ingestion of toxins by bivalves. Indeed, it is difficult to know when bivalves will start ingesting microalgae, and the addition of 'foreign' compounds to the natural aquatic environment is not feasible. Thus, to the best of our knowledge, there is no methodology for the detoxification of live bivalves that is properly and widely validated for *in situ* tests.

Technical and economic considerations, and legislative implications

In countries with monitoring systems, the legislation applied to shellfish production defines four health statutes (A, B, C, 'prohibited') based on the risk of contamination of bivalves by pathogenic bacterial and viral microorganisms [34]. This classification does not consider the presence of biotoxins in bivalves, but their harvesting is prohibited whenever the amounts of biotoxins exceed the RL.

The excessive amount of marine biotoxins and their accumulation by aquatic organisms (and, consequently, by humans) compromise food security, causing enormous damage to human health and the economy. So, what strategies and measures may be applied to minimize or solve this problem? As exposed above, strategies *a priori* [11,32,33] are difficult to implement and control. Therefore, treatments *a posteriori*, in a controlled environment, should be considered. Then, how may they be developed and implemented? Based on the current health classification, most bivalves must be submitted to the purification, transposition, or transformation processes (those included in statutes B and C). The costs associated with detoxifying bivalves will be amplified the longer they are processed. Additionally, some studies reveal that consumers primarily purchase fresh or preserved seafood to frozen seafood [35,36]. Therefore, taking into account the already described limitations of *a priori* treatments and consumer preferences, combined with the greater possibility of controlling treatment conditions in closed or semiclosed systems (without direct interference with the natural ecosystem) and the possibility of selling live bivalves (e.g. highly valued in species such as oysters [36]), the principle of detoxification of live bivalves seems to gain prominence compared with other approaches. To achieve this, a set of legal barriers would have to be overcome to allow the harvesting of bivalves with high levels of biotoxins and their subsequent detoxification in a system similar to the purification environment.

In addition to the legislative issue, the economic issue also arises: how much would bivalves' detoxification cost? The price per kilogram of bivalves varies widely among species, and this may render it difficult, in some cases, to implement an economically profitable methodology. For example, considering three of the main bivalve species produced and consumed in Europe, the treatments applied to oysters and clams could be much more profitable than those applied to mussels. In 2020, the first sale prices for live oysters and clams varied, respectively, in the range of 1.80–5.50 €/Kg [36] and 5.50–11.72 €/Kg [37]. In turn, the first sale prices for fresh mussels ranged between 0.70 €/Kg and 1.70 €/Kg [35]. It is therefore important to consider the production costs associated with the implementation of the methodology. While the efficiency of bivalve detoxification is undoubtedly a great asset from the viewpoint of food availability and food security, the interest of producers, purification centers, and consumers may be diminished if the methodology entails costs that imply an excessive increase in the final sale price. So, the whole process must be carefully considered. The ideal detoxification method will be the one capable of removing toxins to safety levels for human consumption in the shortest time and at the lowest possible cost, ensuring consumer food safety and the competitiveness of producers and stakeholders involved in the process.

It appears that providing nontoxic food to bivalves contributes positively to accelerating detoxification in the medium and long term [18,28]. Additionally, feeding the bivalves could be advantageous, in the case of longer treatments, to preserve the quality and quantity of the meat. However, before proceeding in this direction, it is crucial to select the best diets for shellfish during the detoxification process, since algal species may be decisive for the efficiency of detoxification [28,30]. Moreover, the addition of nontoxic food during the detoxification would imply some adaptations to current systems, as a sterile aqueous environment must be ensured. For example, the addition of food could imply the inclusion of a treatment step or greater renewal of the water to ensure the elimination of excreted by-products. However, if other treatments are sufficiently effective on their own within a short period of time (e.g. up to 48–72 h), investment in added feed may be unjustified. In parallel, some methodologies could be optimized for implementation in the detoxification process. If an approach involving the addition of a compound that acts at a metabolic level is considered, additional studies are necessary to ensure that the process does not alter the nutritional properties, texture, and quality of the meat. Furthermore, the possible formation of by-products, their excretion time, and treatment must be considered to guarantee the safety of the method. On the other hand, an approach that does not directly interfere with the metabolism (e.g. adsorbents) may seem simpler, but it also depends on factors that may impact the efficiency of the method and its cost. Firstly, it is important to define the solubility/stability of the adsorbents in water, since this property will have an impact on their removal from the aqueous medium, as well as their possible reuse. Another pertinent issue is related to the size of the particles, which may have to be adjusted to the species and size of bivalve. This is relevant because if the adsorbent particles are small enough to be metabolized by bivalves, further studies will have to be carried out, as mentioned previously. If the adsorbent particles are not retained or metabolized, then their action will be exerted through intermolecular interactions, with the toxins being attracted to the suitably functionalized adsorbent surface. In practical terms, this last approach could be more advantageous due to the greater simplicity of removing adsorbents from the aqueous system, and because it should not imply major adaptations to current purification systems. However, the assessment of its efficiency must be done on a case-by-case basis.

Conclusion and future trends

Three main factors should be considered when deciding about the detoxification method to be implemented: food security, quality of the bivalves, and costs. The balance between them may vary depending on the species and its commercial value, which may also dictate the interest of producers and interested parties in lobbying the competent authorities for a change in legislation. The focus of the scientific community and interested parties should be on developing a safe, viable, and competitive method that allows mitigating the huge problem of toxin poisoning and its impacts. For this purpose, more appropriate experimental designs are necessary, as well as the standardization of toxicity units (according to standard methods in force), for a better evaluation and comparison of methodologies. Furthermore, the use of procedural controls and conditions as similar as possible to the final conditions for implementation of the methodology will be an added value. Another finding is related to ‘compartmentalized’ studies. From a scientific viewpoint, the importance of these studies is indisputable. However, a large part of bivalves (e.g. oysters, clams, and mussels) are consumed as a whole and not in separate parts. Therefore, it could be more useful for competent authorities and stakeholders if reliable conclusions were available on the impact of the proposed methodologies on the overall toxicity of bivalves. Each strategy should be designed so that, even if it cannot be applied equally to all syndromes (PSP, ASP, and DSP), it can at least be efficient for the majority of species, among those affected by the same syndrome. Currently, bivalves are not detoxified because the law does not allow it, nor are there effective methods for this task, under the existing technical conditions. But we will be closer to achieving these conditions, and investing in the detoxification of bivalves, if the issues raised here are rethought and considered in future approaches.

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Data Availability

Data will be made available on request.

Declaration of Competing Interest

We declare that there are no conflicts of interest or misconduct behavior.

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- • of special interest
- •• of outstanding interest.

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