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OKADAIC ACID IN EUKARYOTIC CELLS: MECHANISMS, IMPACTS ON HUMAN HEALTH, AND CHALLENGES FOR MONITORING

ÁCIDO OKADAICO EM CÉLULAS EUCARIÓTICAS: MECANISMOS, IMPACTOS NA SAÚDE HUMANA E DESAFIOS PARA O MONITORAMENTO

ÁCIDO OKADAICO EN CÉLULAS EUCARIOTAS: MECANISMOS, IMPACTOS EN LA SALUD HUMANA Y DESAFÍOS PARA EL MONITOREO

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ABSTRACT

Harmful algal blooms (HABs) are characterized by the proliferation of microalgae capable of generating severe impacts on aquatic ecosystems and human health, especially through the consumption of contaminated filter-feeding organisms. Okadaic acid (OA) is one of the main marine toxins associated with these events, being the causative agent of Diarrhetic Shellfish Poisoning (DSP). Currently, there is growing evidence of its toxic effects across various biological models. This narrative review emphasizes the literature published between 2019 and 2025, with exceptional incorporation of previous publications, to compose the theoretical and historical foundation and elucidate the most recent evidence regarding OA toxicity. The study focuses on its mechanisms of action, clinical manifestations, chronic and ecotoxicological effects, in addition to evaluating current detection methods and risk management strategies. Finally, the review highlights knowledge gaps and recommends priorities for research and surveillance, aiming to mitigate risks to public health and aquaculture.

KEYWORDS*: Marine toxins. Genotoxicity. Phycotoxins.*

RESUMO

As florações de algas nocivas são caracterizadas pela proliferação de microalgas capazes de gerar impactos severos aos ecossistemas aquáticos e à saúde humana, especialmente por meio do consumo de organismos filtradores contaminados. O ácido okadaico é uma das principais toxinas marinhas associadas a esses eventos, sendo o agente causador da intoxicação diarreica por moluscos. Atualmente, há crescentes evidências de seus efeitos tóxicos em diversos modelos biológicos. Esta revisão narrativa enfatiza a literatura publicada entre 2019 e 2025, com a incorporação excepcional de publicações anteriores, para compor a fundamentação teórica e histórica e elucidar as evidências mais recentes sobre a toxicidade do ácido okadaico. O estudo foca em seus mecanismos de ação, manifestações clínicas, efeitos crônicos e ecotoxicológicos, além de avaliar os métodos de detecção atuais e as estratégias de gestão de risco. Por fim, a revisão destaca lacunas de conhecimento e recomenda prioridades para pesquisa e vigilância, visando mitigar os riscos à saúde pública e à aquicultura.

PALAVRAS-CHAVE: Toxinas marinhas. Genotoxicidade. Ficotoxinas.

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RESUMEN
Las floraciones de algas nocivas se caracterizan por la proliferación de microalgas capaces de generar impactos severos en los ecosistemas acuáticos y la salud humana, especialmente a través del consumo de organismos filtradores contaminados. El ácido okadaico es una de las principales toxinas marinas asociadas a estos eventos, siendo el agente causante de la intoxicación diarreica por moluscos. Actualmente, existe una creciente evidencia de sus efectos tóxicos en diversos modelos biológicos. Esta revisión narrativa enfatiza la literatura publicada entre 2019 y 2025, con la incorporación excepcional de publicaciones previas, para componer la base teórica e histórica y dilucidar la evidencia más reciente sobre la toxicidad del ácido okadaico. El estudio se centra en sus mecanismos de acción, manifestaciones clínicas, efectos crónicos y ecotoxicológicos, además de evaluar los métodos de detección actuales y las estrategias de gestión de riesgos. Finalmente, la revisión destaca las lagunas de conocimiento y recomienda prioridades para la investigación y la vigilancia, con el objetivo de mitigar los riesgos para la salud pública y la acuicultura.

PALABRAS-CLAVE*: Toxinas marinas. Genotoxicidad. Ficotoxinas.*

INTRODUCTION

The concept of One Health refers to the integration and balance between human, animal, plant, and environmental health (Pitt; Gunn, 2024). However, in light of constant climate change and the increasing anthropogenic impact on ecosystems, increasingly frequent and severe occurrences of Harmful Algal Blooms (HABs) are being observed. These events represent a transversal threat to all pillars of One Health, in addition to severe damage to local economies (Roberts *et al*., 2020).

HABs are characterized by the rapid growth and uncontrolled proliferation of photosynthetic organisms in freshwater, brackish, or marine ecosystems (Pal *et al*., 2020; Wells *et al*., 2020). The emergence and magnitude of these events have been strongly driven by anthropogenic factors, notably eutrophication, driven by excess nutrients such as phosphorus and nitrogen, in synergy with the warming of water masses resulting from global climate change (Wells *et al*., 2020).

These events pose a severe risk to public health and environmental stability through different mechanisms. Even in blooms dominated by non-toxic species, high biomass can lead to the depletion of dissolved oxygen in the water column (hypoxia), resulting in mortality of aquatic organisms and habitat degradation (Zohdi; Abbaspour, 2019). However, the most critical and dangerous aspect of HABs lies in the ability of certain species to synthesize potent marine toxins, which bioaccumulate in the food web (Turner *et al*., 2021).

Marine toxins are natural compounds synthesized by various phytoplanktonic microorganisms and widely disseminated on a global scale (Bian et al., 2024) The aquatic environment harbors a vast structural diversity of these biotoxins such as okadaic acid. Their insertion into the food web occurs primarily through the consumption of producer algae by filter-feeding organisms, such as bivalve mollusks, crustaceans, and fish. Due to their chemical nature, these biotoxins have a high potential for bioaccumulation, concentrating in the digestive glands and muscle tissues of these biological vectors.

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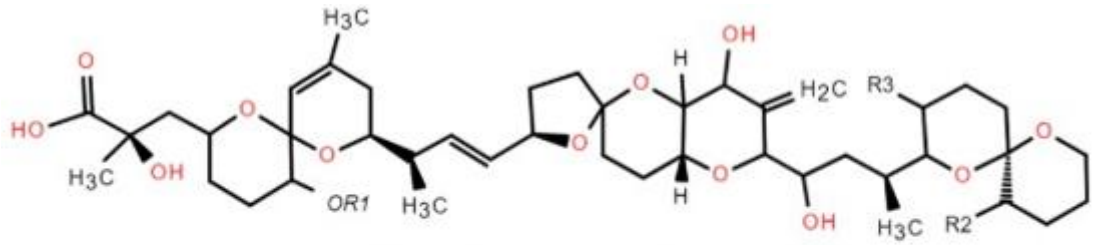
Consequently, this contamination not only triggers adverse ecological effects but also generates catastrophic economic losses for the fishing and aquaculture industries (Pradhan et al., 2022; Bian *et al.*, 2024).

The toxins responsible for DSP are primarily produced by marine microalgae of the genus Dinophysis and *Prorocentrum*. The main representatives of this group of polyether biotoxins are okadaic acid (OA), dinophysistoxins (DTXs), and their structural analogs (Figure 1) (Yuan; Li; Yang, 2024). Chemically, these molecules are characterized by their high lipophilicity, a property that gives them a high capacity for bioaccumulation in adipose tissues and significantly hinders their metabolic elimination by organisms (Yuan; Li; Yang, 2024).

In the aquatic environment, these toxins accumulate efficiently in filter-feeding organisms. An aggravating factor for public health is their notable thermostability; since they are not degraded during conventional cooking processes at high temperatures, these biotoxins maintain their toxicity and establish a direct route of contamination to human consumers (Wu *et al*., 2020). Ingestion of contaminated shellfish triggers acute gastrointestinal symptoms, including abdominal pain, diarrhea, nausea and vomiting (Louzao *et al*., 2021; Park *et al*., 2023). As a reflection of this biological dynamic of resistance and accumulation in the food chain, since the first documented incidents in the 1960s, global outbreaks of contamination by DSP-causing toxins continue to occur systematically.

Figure 1. Structure of the main DSPs, adapted from Yuan; Li; Yang, 2024



OA: R1=H; R2=H; R3=CH_3

DTX-1: R1=H; R2=CH_3; R3=CH_3

DTX2: R1=H; R2=CH_3; R3=H

The study of OA and its analogous toxins is of global importance, given its wide detection in coastal regions of Europe, Asia, and South America (Mafra *et al*., 2019). The implications of these biotoxins for public health and ecosystems are evident in recent episodes. In Brazil, for example, the state of Paraná recorded, in June 2016, an intense proliferation of Dinophysis acuminata, which generated OA concentrations in bivalves much higher than the regulatory limit and resulted in several hospitalizations (Mafra *et al*., 2019). This scenario demonstrates a serious food safety problem, showing

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that failures or the absence of environmental monitoring of these blooms can trigger severe outbreaks of human poisoning (Park *et al*., 2023).

In addition to direct biological damage, the dynamic of contamination by these biotoxins imposes serious challenges to environmental management and the coastal economy. A recent monitoring study on mussels on the coast of Italy revealed that OA and other associated lipophilic toxins, such as yessotoxins, dominate the local contamination profile, presenting marked spatial and seasonal variations (Bacchiocchi *et al*., 2025). This unpredictability causes significant disruption to the shellfish industry, requiring the constant closure of farming areas and the systematic recall of products (Bacchiocchi *et al*., 2025). Therefore, the profound losses to the fishing industry reinforce the need for investment in infrastructure, early warning systems, and continuous surveillance, aiming for strict compliance with regulatory limits (Bacchiocchi *et al*., 2025).

In the ecotoxicological scope, the effects of OA on various marine organisms have aroused growing concern. Song *et al*. (2024) investigated juvenile sea urchins (Strongylocentrotus intermedius) subjected to short treatments with OA concentrations typical of harmful algal blooms (HABs). The authors observed the inhibition of vital behaviors associated with ambulacral feet, such as feeding, locomotion, and reorientation. Physiologically, although the organisms activated initial antioxidant responses, continuous exposure suppressed immunity and induced cell apoptosis. This stress scenario raises critical alerts, as the reduction in the resilience of ecosystems can alter biodiversity and compromise food webs and marine production (Song *et al*., 2024).

Concomitantly with the increase in global demand for seafood, accelerated coastal urbanization and the expansion of marine recreational activities have substantially increased the risk of human diseases associated with HABs (FAO, 2020; Lenzen; Li; Murray, 2021; Trottet *et al*., 2022). In response to this growing threat, a significant number of studies have focused on the toxicological assessment of bloom-forming species and their respective toxins. However, given the vast chemical diversity of these compounds and the intricate complexity of their mechanisms of action, the documented toxicity varies widely among different aquatic organisms (Corriere; Soliño; Costa, 2021; Devillier *et al*., 2024; Soliño; Costa, 2020; Tan *et al*., 2023). Furthermore, although drastic environmental changes and the recent expansion of monitoring networks directly influence the distribution and registration of outbreaks, the real magnitude of these intoxications remains underestimated in several regions.

Given this complexity and the need to compile dispersed data in the literature, this review aims to gather and analyze recent scientific advances on OA. The present work focuses its emphasis on elucidating the molecular mechanisms of toxicity of the substance, evaluating its adverse effects on various biological systems, and discussing emerging strategies for the detection and control of this biotoxin.

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METHODOLOGY

The present study was designed as a narrative review of the literature. The bibliographic survey was conducted through structured searches in the following electronic databases: ScienceDirect; *Portal de Periódicos da CAPES*; SciELO, and Google Scholar. The main time window stipulated for data collection comprised the period from January 1, 2019, to September 2025, aiming to capture the most recent scientific advances on the subject.

To retrieve the documents, a combination of standardized descriptors and free terms (in English) was used. The keywords selected to compose the search keys were: “okadaic acid”, “marine toxin”, “diarrhetic shellfish poisoning”, “toxicity”, “PP2A inhibition”, “oxidative stress”, “genotoxicity”, “toxic effect”, and “the assessment of toxic effects”. All 189 studies obtained from electronic databases were deposited and managed on the Rayyan platform (https://rayyan.ai), where all duplicate studies were identified and removed by the reviewers.

The selection of works followed rigorous inclusion and exclusion criteria. Original articles, reviews, technical reports, theses, and dissertations that directly addressed toxicological, molecular, ecological, or monitoring aspects of OA, and were published in English, Portuguese, or Spanish, were included. Studies whose main focus was not toxicity were excluded. However, publications prior to 2019 that presented high relevance and a direct focus on the toxicity of the compound were exceptionally included to compose the theoretical and historical foundation. Finally, the analysis of the selected studies followed a narrative approach, with emphasis on the critical interpretation of the findings and the identification of gaps in the current literature.

RESULTS AND DISCUSSION

Molecular mechanisms of toxicity

DSP group toxins induce a wide range of adverse cellular effects, including cytotoxicity, genotoxicity, immunotoxicity, and histopathological changes (Neves et al., 2019). The main mechanism of action of DSP group biotoxins is the inhibition of serine/threonine protein phosphatases 1 and 2A (PP1 and PP2A), which results in the profound deregulation of numerous intracellular processes (Suganuma *et al*., 1992). Since PP2A is involved in the regulation of a vast network of essential signaling pathways (Verbinnen *et al*., 2021), the systematic blockage of this enzyme is identified as the main factor responsible for the pathogenicity characteristic of DSP toxins (Fujiki *et al*., 2023).

As a direct consequence of this enzymatic inhibition, exposed cells trigger oxidative stress conditions, activate response pathways to DNA damage, and initiate severe inflammatory responses. It is precisely these cellular mechanisms that sustain reports of genotoxicity and the possible role of OA as a tumor promoter (Jiménez-Cárcamo; García; Contreras, 2020). Such evidence suggests that

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the impact of OA transcends the acute conditions of the diarrhetic syndrome, representing a much broader public health risk and consolidating the toxin as a critical agent in marine ecotoxicology.

To understand this toxicity at a structural level, OA stands out as one of the most studied phosphatase inhibitors, binding specifically to PP2A and strongly suppressing its activity (Chen *et al*., 2006). The effectiveness of this binding occurs because the methyl group, located at the hydrophobic end of OA, fits perfectly into the hydrophobic cavity of the catalytic subunit of the enzyme (PP2Ac) (Huhn *et al*., 2009). Based on this fitting dynamic, the varying inhibitory potency of OA and its analogs on PP2A can be attributed to differences in the number and position of the methyl groups in the main structure of the toxin (Huhn *et al*., 2009). Molecular modeling studies corroborate this structure-activity relationship by indicating, for example, that the presence of the 35-axial methyl group in the DTX-2 molecule causes unfavorable interactions at the enzyme binding site, thus explaining its lower toxicity compared to OA (Huhn *et al*., 2009).

At the cellular and molecular level, the impacts of OA extend beyond the digestive system, raising critical alerts about its hepatotoxicity and long-term effects. Research using hepatoma models demonstrated that, even at non-cytotoxic concentrations, the toxin is capable of causing profound transcriptomic, proteomic, and phosphoproteomic changes (Wuerger *et al*., 2024). This ability to modify the expression of pathways related to metabolism, phosphorylation, and response to xenobiotics indicates that OA can actively interfere with drug metabolism. Consequently, the risk of dangerous drug interactions becomes an essential factor to be considered in long-term human toxicological evaluations (Wuerger *et al*., 2024).

Acting as a vigorous phosphatase inhibitor, OA causes profound changes in the phosphorylation of HepaRG liver cells (human hepatocarcinoma lineage). Treatment with the biotoxin results in a global increase in cellular phosphorylation status, critically impacting signaling, cell cycle control, and regulation of apoptosis (Wuerger *et al*., 2024). In the scope of protein translation, the inhibition of the PP2A enzyme directly affects key targets, such as S6 kinase (RSK). Normally dephosphorylated and inactivated by PP2A, RSK was hyperphosphorylated under the effect of OA; consequently, its primary target, ribosomal protein S6 (RPS6), also exhibited high levels of phosphorylation (up-regulation) in the proteomic dataset (DigiWest), with a signaling peak detected after 12 and 24 hours of treatment at 100 nM (Wuerger *et al*., 2024).

In addition to post-translational changes, cell cycle regulation emerges as one of the pathways most severely affected by the toxin, manifesting predominantly at the transcriptomic level (Wuerger *et al*., 2024). Gene Ontology (GO) enrichment analyses applied to RNA sequencing (RNAseq) data revealed that exposure to lower concentrations of OA (33 nM) induces strong positive gene regulation (up-regulation). These overexpressed genes were intrinsically associated with cell cycle control processes and DNA replication, evidencing the profound genomic imbalance generated by the biotoxin (Wuerger *et al*., 2024). These transcriptomic findings are corroborated by the changes observed in the

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cellular protein profile. Fundamental proteins associated with cell cycle progression, such as Retinoblastoma protein (RB), were found in DigiWest analysis clusters with strong accumulation (up-regulation) after 12 and 24 hours of exposure to 100 nM OA (Wuerger *et al*., 2024).

Since PP2A acts as a master regulator of cell cycle machinery, its blockage alters the signaling hierarchy. In this context, cyclin-dependent kinases CDK1 and CDK2 were identified as potential key regulators in the aberrant signaling network modulated by the toxin (Wuerger *et al*., 2024). As the outcome of this complex cascade of deregulation, which encompasses hyperphosphorylation, transcriptional stress, and replicative loss of control, OA demonstrates a significant capacity to deregulate apoptotic pathways. Notably, the effect of induction or suppression of programmed cell death by this biotoxin is strictly dependent on its concentration in the cellular microenvironment (Wuerger *et al*., 2024).

Regarding oxidative stress, OA has demonstrated strong potential to induce cellular damage in different biological models. In studies involving mammals and cell lines, exposure to the toxin resulted in significant oxidative damage (Vieira *et al*., 2013). This toxicity pattern is repeated in aquatic organisms; laboratory experiments confirm that OA acts as a potent oxidative stressor in bivalves, such as oysters (*Crassostrea gigas*) and mussels (*Mytilus galloprovincialis*) (Prego-Faraldo *et al*., 2017). Changes in environmental conditions often act as stressors, stimulating the excessive production of Reactive Oxygen Species (ROS), a process that culminates in cellular oxidative stress (Lushchak, 2011). To neutralize this threat, the systemic defense of organisms depends on a network of antioxidant enzymes that interact to restore the balance between ROS production and elimination (Lushchak, 2011).

The dynamics of this immune response were evidenced in studies with the scallop *Chlamys farreri* (*C. farreri*), in which exposure to OA promptly activated the defense system, culminating in a general stimulation of antioxidant enzymes in the branchial tissue of the animals (Lushchak, 2011; Wang *et al*., 2021a). Detailed evaluation of *C. farreri* gills exposed to OA revealed the mobilization of three crucial enzymatic pathways. Superoxide dismutase (SOD) and catalase (CAT) activity suffered a significant stimulus after 96 hours of exposure, rising by 1.55 and 1.3 times, respectively, compared to the control group. At the same time, glutathione S-transferase (GST) activity was already increased by 1.13 times after 48 hours of treatment (Wang *et al*., 2021a).

Despite the strong activation of the antioxidant machinery (SOD, CAT, GST), the defense system was not able to maintain the redox balance in the face of ROS overproduction (Prego-Faraldo *et al*., 2017). As a direct consequence, a significant increase in malondialdehyde (MDA) content was observed in scallops after 48 and 96 hours of exposure (Wang et al., 2021a). MDA is the final product of lipid peroxidation (LPO) and acts as an indirect marker of the extent of this process, being a crucial indicator of oxidative stress and a determining factor for loss of cellular function (Almeida et al., 2007). Therefore, the expressive accumulation of MDA proves that defenses were breached, resulting in severe cell damage mediated by LPO (Prego-Faraldo *et al*., 2017).

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The induction of inflammatory responses is one of the most documented systemic effects of OA exposure in various organisms. In the invertebrate immune system, phagocytosis acts as a primary defense mechanism, essential for the removal of invading microorganisms and cellular debris (Wang et al., 2021a). Research suggests that alteration in phagocytic activity is a crucial pathway through which scallops respond to OA toxicity; the intensification of this process allows for the clearance of damaged proteins and apoptotic cells, thus mitigating inflammation and the progression of tissue damage (Wang *et al*., 2021a).

In contrast, evaluations in cell lines elucidate the molecular mechanisms underlying this inflammatory response. OA acts as a direct activator of nuclear factor kappa B (NF-κB), which functions as a master transcription factor for several pro-inflammatory cytokines (Wuerger *et al*., 2023b). Once activated, NF-κB triggers the massive release of these cytokines, which subsequently activate the JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling pathway, perpetuating and amplifying the inflammatory cascade in the cell (Wuerger *et al*., 2023b). This severe inflammatory induction has direct consequences on cellular detoxification capacity, being identified as one of the main causes of changes in xenobiotic metabolism, specifically, the suppression of cytochrome P450 (CYP) enzymes by OA was strictly dependent on this previous activation of NF-κB (Wuerger *et al*., 2023a, 2023b). Corroborating this dynamic, recent analyzes using human liver cells (HepaRG) confirmed that the inflammation induced by the biotoxin results in an expressive negative regulation (down-regulation) of CYP enzymes, which significantly compromises the metabolism of other substances (Wuerger *et al*., 2024).

OA acts as a potent tumor promoter, demonstrating in mouse skin models initiated with 7,12-dimethylbenz(a)anthracene (DMBA) a potency comparable to that of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) (Suganuma *et al*., 1988). However, the mechanism of action of OA differs fundamentally from TPA, as the biotoxin acts as a direct chemical inhibitor of protein phosphatases 1 and 2A (PP1 and PP2A) (Suganuma *et al*., 1988). Systematic inhibition of these enzymatic activities has established itself as a general mechanism of tumor promotion in various organs of rodents (Fujiki; Suganuma, 1993). The cellular consequences of this enzymatic inhibition are broad. Suppression of protein phosphatase activity not only induces autonomous cell proliferation but also triggers a strong non-autonomous effect associated with endogenous inflammation, which is mediated by the production of pro-inflammatory cytokines; both factors act synergistically in tumor development (Fujiki *et al*., 2023).

In fact, the signaling cascade triggered by the OA class can be mimicked by the effects of cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) (Fujiki; Suganuma, 1993). Corroborating this dynamic, studies show that after topical application of OA or TPA to mouse skin, TNF-α gene expression is commonly induced in a dose-dependent manner within an interval of only 4 hours (Fujiki *et al*., 2000). The understanding of this chemical model in rodents provided the biological basis for elucidating cancer progression in humans. The current concept establishes that pathological

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inhibition of PP2A activity represents a common and crucial mechanism in oncological progression (Fujiki *et al*., 2023). In human carcinomas, the role that OA plays in the experimental model is assumed by endogenous inhibitors of PP2A, notably SET and CIP2A proteins (Fujiki *et al*., 2023). Overexpression of SET and CIP2A in human cancer cells induces strong inhibition of PP2A activity, replicating exactly the mechanism of action of OA (Fujiki *et al*., 2018). This inactivation of PP2A is, for example, a widely documented event in the pathogenesis of colorectal cancer (Cristóbal *et al*., 2014).

Based on the bibliographic survey carried out, the main studies investigating genotoxic damage in eukaryotic cells are summarized in Table 1.

Tabela 1. Summary of the main studies investigating genotoxic and oxidative damage induced by okadaic acid in eukaryotic models

Study	Model / System	Exposure	Genotoxic endpoint / assay
Cavion *et a*l. (2025)	*Artemia franciscana* (microcrustacean)	Experimental concentrations (HAB-relevant levels)	Oxidative stress markers, survival, sublethal endpoints; suggestions of indirect genomic damage
Huang *et a*l. (2025)	In vitro cellular models (intestinal/epithelial cells)	Co-exposure OA + polystyrene micro/nanoplastics (experimental)	Oxidative stress markers, DNA damage markers (comet/γH2AX indicated)
Wuerger *et al*. (2024)	Human HepaRG cells (differentiated hepatocarcinoma)	In vitro experimental concentrations (reported in the article; varied)	Transcriptomics, proteomics, phosphoproteomics; DNA repair markers and stress pathways
Yang *et al*. (2023)	Fish larvae (*Oryzias latipes* / medaka)	Experimental concentrations in water (varied)	Transcriptomics; signs of DNA repair and stress pathways

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Study	Model / System	Exposure	Genotoxic endpoint / assay
Fu *et al*. (2019)	Review	N/A (review)	Synthesis of genotoxicity evidence and mechanisms (PP2A/PP1 inhibition, oxidative stress)
Valdiglesias *et al*. (2013)	Review (compilation of in vitro/in vivo studies)	N/A (review)	Synthesis of reported endpoints (comet, micronucleus, γH2AX, gene expression)
Valdiglesias *et al*. (2011b)	Human cells (various cell lines)	In vitro experimental concentrations (varied)	Micronucleus test, γH2AX, cytotoxicity, cell cycle alterations
Valdiglesias *et al*. (2011a)	Human cells	In vitro experimental concentrations	Markers of oxidative DNA damage (8-oxo-dG etc.)
Valdiglesias *et al*. (2010)	Human cells (various cell lines)	In vitro experimental concentrations (varied; nM–μM)	Comet assay, DNA repair analyses

Legend: HAB: Harmful Algal Blooms; OA: Okadaic Acid; PP1: Protein Phosphatase 1; PP2A: Protein Phosphatase 2A; 8-oxo-dG: 8-oxo-2'-deoxyguanosine (a biomarker of oxidative DNA damage); nM: Nanomolar; N/A: Not Applicable.

Cavion *et al*. (2025) point out that although numerous studies have investigated the effects of DSP toxins in mammals, the assessment of their toxicity in other animals is still limited. Regarding bivalves, *in vitro* assays conducted with hemocytes from the clam *Ruditapes decussatus* demonstrated a rapid genotoxic effect induced by OA. In contrast, *in vivo* exposure of the whole organism revealed that damage to the genetic material was concentrated exclusively in the branchial tissue, even at low concentrations of the toxin (Flórez-Barrós *et al*., 2011). Another genotoxic effect classically recorded in these organisms is the induction of micronuclei, resulting from the loss of chromosomal fragments or entire chromosomes (Pinto-Silva *et al*., 2003). Interestingly, in exposures to very high concentrations of

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OA, a decrease in the frequency of these micronuclei was observed in some bivalves, a phenomenon that probably reflects the extreme activation of repair or cell death mechanisms (Pinto-Silva; Creppy; Matias, 2005).

Although some classic studies do not use direct genotoxicity assays (such as the micronucleus test or the comet assay), the evaluation of oxidative stress biomarkers provides crucial evidence, as this is a fundamental molecular mechanism that precedes DNA damage. Corroborating this pathway, Huang *et al*. (2025) demonstrated that co-exposure to microplastics and OA significantly increased oxidative stress, epithelial barrier permeability, and DNA damage markers in *in vitro* intestinal cell models, compared to isolated exposure to the biotoxin. In parallel, analyzes using differentiated human liver cells (HepaRG) revealed significant changes in DNA repair pathways, oxidative stress, and intracellular signaling. Such omic evidence of cellular dysfunction strongly supports the hypothesis of systemic induction of genotoxicity (Wuerger *et al*., 2024).

Expanding the scope of analysis to aquatic vertebrates, Yang *et al*. (2023) evaluated Medaka fish larvae (*Oryzias latipes*) subjected to experimental concentrations of OA in the water. Through transcriptomic approaches, the study detected genetic changes closely compatible with DNA damage, also affecting pathways related to development and carcinogenesis. These findings are extremely relevant, as they provide robust evidence that OA activates complex response networks for genomic maintenance in aquatic eukaryotes, analogously to what is observed in mammals.

The synthesis of these genotoxic evidences and their correlated mechanisms, such as the inhibition of PP1/PP2A enzymes and oxidative stress, had already been addressed by Fu *et al*. (2019). In their review, the authors compiled data on DNA damage and highlighted gaps in knowledge, emphasizing the urgency of chronic studies and the validation of biomarkers for these biotoxins. Considering this history, although this review defined the systematic search period between 2019 and 2025 to identify the most recent molecular mechanisms, it was decided to structure Table 1 including selected studies since 2010. This methodological choice was intended to generate a more robust and contextualized bibliographic starting point.

Despite the current literature reporting toxic mechanisms in various biological models, it is evident that expanding the number of research studies is essential for the definitive understanding of the molecular networks affected by OA.

Toxicological effects

Regarding the acute effects caused by DSPs, OA is the responsible agent and its acute clinical manifestation includes diarrhea, nausea, vomiting, and abdominal pain, usually with rapid onset after consumption of contaminated shellfish; surveillance episodes and studies confirm that monitoring failures can lead to foodborne outbreaks (Wang *et al*., 2024).

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Regarding subchronic/chronic effects, some studies report repeated administration in animal models, along with omics investigations in cell lines indicate that repeated or prolonged exposure to OA can induce liver changes, repair pathway dysfunctions, and potential tumor-promoting effects via inhibition of PP2A/PP1. This draws attention to a possible focus on assessing the impact of chronic low-dose exposure in human populations exposed through food consumption (Park *et al*., 2023).

In addition to acute conditions, the assessment of the risk of chronic exposure to OA is essential to guide safety regulations aimed at habitual consumers of seafood. In vivo studies show the aggressiveness of the toxin in the gastrointestinal tract; in mice, exposure to sublethal doses of OA proved to be as toxic as that of DTX-1, causing weight loss, ascites, and increased depth of intestinal crypts (Park *et al*., 2023). Aggravating this situation, research indicates that OA severely alters the colonic microenvironment. In murine models, the biotoxin damages the epithelial barrier, modifies the mucosa, decreases populations of mutualistic bacteria, and favors the growth of pathogenic strains (Liu *et al*., 2023). This dynamic suggests that the toxin's action transcends classical intoxication, potentially inducing dysbiosis, chronic inflammation, and even aggravating pre-existing intestinal or metabolic diseases (Liu *et al*., 2023).

Toxic effects in experimental models exposed to OA have been more studied in *in vitro* models (human hepatic, epithelial, neuronal lineages), for their advantages such as speed, accessibility, the ability to isolate variables, and ethical data collection. Moreover, *in vivo* models (rodents, fish and invertebrates) have been employed using techniques such as comet, micronucleus, γH2AX, transcriptomic/proteomic analyzes and oxidative stress markers (Vieira *et al*., 2013; Wuerger *et al*., 2024). These complementary approaches allow mapping from molecular effects to ecotoxicological responses (Vieira *et al*., 2013; Wuerger *et al*., 2024).

Some human lineages exposed to OA exhibit DNA damage, genomic instability, cell cycle changes, and apoptosis; in marine organisms, this polyether causes oxidative stress, behavioral changes, and sublethal effects that can affect populations and trophic chains, especially when environmental factors or co-occurring contaminants such as microplastics exist (Cavion *et al*., 2025). Bibliographic searches demonstrate that the subject is still little studied in Brazil, mainly on the coast of Rio de Janeiro, since the state is in the group of those that have mariculture as one of its economically weighted activities.

Detection and monitoring

Regarding the detection of marine biotoxins, LC–MS/MS (liquid chromatography coupled with tandem mass spectrometry), an analytical technique that separates compounds from liquid chromatography with sensitive and specific mass spectrometry detection, remains the reference method for detection and quantification of OA and analogs (DTX1/DTX2/esters) in bivalves, sediments, and water, because it allows quantifying multiple lipophilic toxins simultaneously and distinguishing

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esters/analogs after hydrolysis/alkaline treatment (Hao; Zhang; Lian, 2024; Panda *et al*., 2022). There were advances regarding automated extraction and preparation (on-line SPE), increased sensitivity and standardization of protocols for surveillance routines (Hao; Zhang; Lian, 2024; Panda *et al*., 2022).

ELISA immunoassays (Enzyme-linked immuno Sorbent Assay) remain the most used rapid screening method, with new developments such as TRFIA (time-resolved fluoroimmunoassay) and AlphaLISA that increase sensitivity and response time, allowing faster routine screenings before confirmation by LC–MS/MS (Qin *et al*., 2022, 2023). Some assays based on PP2A inhibition (protein phosphatase inhibition assays) are used as functional bioassays that detect toxicological activity of OA groups (Ikehara; Oshiro, 2024). Recent reviews and studies discuss the application and limitations of the PP2A assay as a screening method before analytical confirmation (Ikehara; Oshiro, 2024).

Currently, biosensors based on aptamers, electrochemical platforms, microcantilevers, and Surface Plasmon Resonance (SPR) biosensors have emerged with very low detection limits (pg–ng·mL^{-1}), high selectivity, and real-time capability (Song *et al*., 2022; Tian *et al*., 2022; Wang et al., 2021b). DNA aptamers for OA were selected and employed in electrochemical aptasensors and microcantilevers (Song *et al*., 2022; Tian *et al*., 2022; Wang *et al*., 2021b). Recent research combines aptamers with nanotechnology for signal amplification. These sensors promise rapid, portable screening and integration with *in situ* monitoring systems (Song *et al*., 2022; Tian *et al*., 2022; Wang *et al*., 2021b).

To protect consumers from OA group toxins, the governments of the European Union, the USA, Canada, and Japan have established maximum limits of 160 µg of OA equivalent (eq.)/kg in the edible parts of live bivalves; this includes a combination of free OA, DTX1 and DTX2 and their acyl-esters (DTX3) (European food safety authority, 2021; Ministry of health, Labour and Welfare, 2015; Food and drug administration, 2019).

In Brazil, monitoring programs are organized through ordinances and normative instructions that adopt sampling and analysis procedures; however, harmonization with specific limits and confirmation methods usually follows international standards (EU/FAO). It is modernizing with the establishment of the National Program for Safe Bivalve Mollusks (MoluBiS), approved by MAPA Ordinance No. 884 of September 2023, consolidating previous guidelines and harmonizing national parameters with international standards under a One Health approach (Brazil, 2023).

Co-exposure effects and information GAPS

The concurrence of OA with other lipophilic toxins (DTX, YTX, PTX, AZA) in bivalves is documented in surveillance studies (Alarcan *et al*., 2019). *In vitro* and *in vivo* investigations show that interactions between these toxins can be antagonistic, additive, or synergistic depending on concentrations and endpoints (cytotoxicity, inflammation, and DNA damage), which imposes uncertainties on current risk assessment schemes (Alarcan *et al*., 2019; Weng *et al*., 2024).

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Aggravating the scenario of environmental degradation, recent research has focused on the interaction of OA with other emerging pollutants. Investigating the joint exposure of microplastics (bioplastics) and OA, Lin *et al*. (2021) demonstrated a significant increase in toxicity in enteric cells. This co-exposure resulted in the exacerbation of oxidative stress, severe structural damage to the epithelial barrier, and the activation of inflammation signaling pathways (Lin *et al*., 2021). Such findings draw attention to a complex ecological reality: the simultaneous presence of multiple toxic agents in aquatic environments can trigger unpredictable synergistic or additive effects. This phenomenon suggests that isolated toxicological assessments may be underestimating the real danger. Therefore, continuous investigation of these interactions becomes an indispensable scientific requirement for the formulation of environmental risk assessments and truly integrated public health strategies (Lin *et al*., 2021).

There are still gaps in chronic data for humans (Huang *et al*., 2022; Park *et al*., 2023). Despite experimental evidence in animal and cellular models of subchronic effects and possible tumor promotion, there is a lack of robust epidemiological or clinical data on chronic effects of dietary exposure to low levels of okadaic acids in humans (Huang *et al*., 2022; Park *et al*., 2023). This deficiency is concerning because extrapolation to chronic human risk remains contestable and is frequently highlighted in current reviews and articles, and it is necessary to define long-term risks, considering habitual consumers of shellfish (Huang *et al*., 2022; Park *et al*., 2023).

Some recent studies have been advocating the use of integrative approaches: toxicokinetics, multi-omics, mixture models and environment × toxin integration (Rodríguez-Santos *et al*., 2024; Wuerger *et al*., 2024). The use of integrative toxicological models is essential to translate molecular signals observed *in vitro* into meaningful endpoints for public health and ecosystems; recent studies demonstrate the power of these strategies to prioritize mechanisms and reduce uncertainties in risk assessment (Rodríguez-Santos *et al*., 2024; Wuerger *et al*., 2024).

CONCLUSIONS

OA, a marine toxin belonging to the group that causes DSP, has emerged as one of the most relevant phycotoxins from toxicological and ecotoxicological perspectives. This importance stems from its wide global incidence and the complexity of the molecular mechanisms it triggers in eukaryotic cells. Its strong ability to inhibit phosphatases 1 and 2A (PP1 and PP2A) causes profound dysregulation in vital signaling pathways, affecting the cell cycle, apoptosis, inflammatory response, and genomic integrity. This profile gives OA a prominent role in understanding tumor promotion processes. In line with this, the recent studies (2019–2025) reviewed in this work emphasize the occurrence of secondary genotoxic effects and persistent oxidative stress in human cell lines and marine organisms, underscoring the vast ecosystem impact of environmental exposure to this biotoxin.

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Despite considerable advances in detection and monitoring methodologies, the literature still presents critical gaps, especially regarding chronic toxicity in humans and the effects of co-exposure with other lipophilic toxins. The scarcity of robust epidemiological data makes it difficult to draw accurate predictions about the risk of long-term exposure. Furthermore, the patterns of co-accumulation in mollusks and the combined synergistic effects of OA with other toxic agents show that classic toxicological models, focused on isolated exposures, are not sufficient to reproduce and predict complex biological outcomes observed in the natural environment. Given this scenario, the development of integrative models, combining toxicogenomics, ecotoxicology, toxicokinetic modeling, and monitoring of environmental data, emerges as an urgent scientific necessity to ensure risk assessments based on real scenarios.

Moreover, the current regulatory framework for OA, which relies predominantly on limits designed to prevent acute gastrointestinal outbreaks, must be critically reassessed. Given the mounting evidence of subchronic genotoxicity, tumor promotion, and the unpredictable synergistic effects of OA with emerging pollutants like microplastics, safety thresholds based solely on acute exposure may underestimate the true risk to habitual seafood consumers. Addressing these multifaceted threats requires a paradigm shift in environmental management. Surveillance programs must evolve from reactive closures of aquaculture areas to proactive, predictive modeling. Integrating *in situ* biosensor networks with climatic and oceanographic data will be crucial to forecast HABs and mitigate their impacts before they compromise the marine food web. Ultimately, tackling the OA crisis demands a genuine One Health approach, recognizing that safeguarding ecosystem resilience is the prerequisite for mitigating economic losses in aquaculture, ensuring global food security, and protecting human health.

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