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An Overview on the Marine Benthic Dinoflagellates Effects on Human and Environment

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ABSTRACT

Due to the creation of biotoxins, marine benthic dinoflagellates have caused many concerns in the ecological, economic, and health sectors. The occurrence of marine toxic microalgae blooms has increased and has caused prevalent poisoning in humans. Many dinoflagellates are benthic and epiphytic, in the sense that they usually live on the bottom of coastal areas or coral reefs and macroalgae, and during widespread blooms, because of their proximity to the coast, they can cause widespread health and economic damage. In addition, by entering the food web, dinoflagellates can spread from small organisms (such as zooplankton) to the bodies of larger aquatic organisms (such as fish), thus threatening human health. The current study was conducted to study the potential risks of dinoflagellates causing harmful algal blooms as species with the potential to produce toxins. The findings of this study showed that 80 phytoplankton species have the potential to produce poison, of which 20 benthic species cause the strongest marine biotoxins, which are deadly for aquatic animals and humans. The most dangerous of these biotoxins include gomyautoxin, brevetoxins, saxitoxin, palytoxin, yessotoxins, maitotoxins, ciguatoxins, okadaic acid, and azaspiracid, which cause widespread death of aquatic organisms in case of harmful algal blooms, and cause acute and fatal poisoning if they enter the human body. The findings of the review of previous research clearly show the notability of knowing benthic toxic dinoflagellates and the requirement to include them in monitoring programs for harmful algal blooms on beaches.

Keywords: *Biotoxins, Environment, Humans, Dinoflagellate*

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INTRODUCTION

Dinoflagellates are one of the large groups of flagellated protozoa that can live in very variable conditions so they can live in different aquatic ecosystems such as sea, saltwater, and freshwater. These microalgae have been able to settle in different environments by matching their physiology with abiotic parameters such as temperature, salinity, and depth (Wang, 2008; Deng *et al*., 2023). Some species of microalgae are the cause of red tide in many marine areas of the world, and for this reason, they can be used to check the environmental health index of aquatic ecosystems. Red tide refers to types of algal blooms in which the number of microalgae cells reaches over one million cells per liter. This event causes the color of water to change to red, orange, green, milky, and brown (Bu *et al*., 2023). The causes of this phenomenon can be attributed to human activities such as marine transportation, non-standard breeding of aquatic animals, the release of running water and sewage into aquatic environments, pollution caused by improper disposal of industrial and household waste, etc., and also Natural environmental factors such as storms, earthquakes, upwelling, climate change or ideal growth conditions due to an excessive increase in nutrients indicated that any of them can increase eutrophication or algal blooms (Hallegraeff *et al*., 2004).

Harmful Algal Blooms (HAB) is used to describe widespread algal blooms that typically cause damage to aquatic ecosystems. HAB occurs due to the interaction of many microorganisms such as bacteria, cyanobacteria, phytoplankton, and zooplankton. Changes in many biotic and abiotic parameters such as pH, salinity, and nutrients such as nitrate, phosphate, and silicate cause HABs. In some cases, the damage caused by these blooms is due to the production of toxins by microalgae. But in other cases, this damage comes from the accumulation of algal biomass, which can block light penetration by creating a shadow on the water surface and subsequently cause the decomposition of phytoplankton in the lower layers of water; Therefore, the plant biomass in the blooming area is not able to photostat and provide oxygen, and the said environment lacks the oxygen necessary for aquatic life. In this way, the ecosystem will face widespread disturbances. According to the studies of scientists, harmful algal blooms have become more widespread, with higher density, and more persistent in terms of duration and occurrence than in the past (Hallegraeff *et al*., 2021; Oh *et al*., 2023).

Most of the species that cause harmful algal blooms in the marine environment are dinoflagellates. According to the type of ecosystem and the parameters involved in the living environment, HAB species are observed as single cells, connecting in the form of long chains and some cases in the majority of large colonies (Hallegraeff, 2003). About 6% (at least

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200 species) of all known phytoplankton species cause algal blooms, and about 80 of them can produce harmful toxins. Harmful blooms can have detrimental effects; Large-scale aquatic mortality, damage to economic and natural resources, suspension of desalination operations, and damage to the regional tourism industry are examples of the effects of harmful algal blooms in aquatic ecosystems. **Figure 1** Shows the Marine invertebrate interactions with Harmful Algal Blooms.

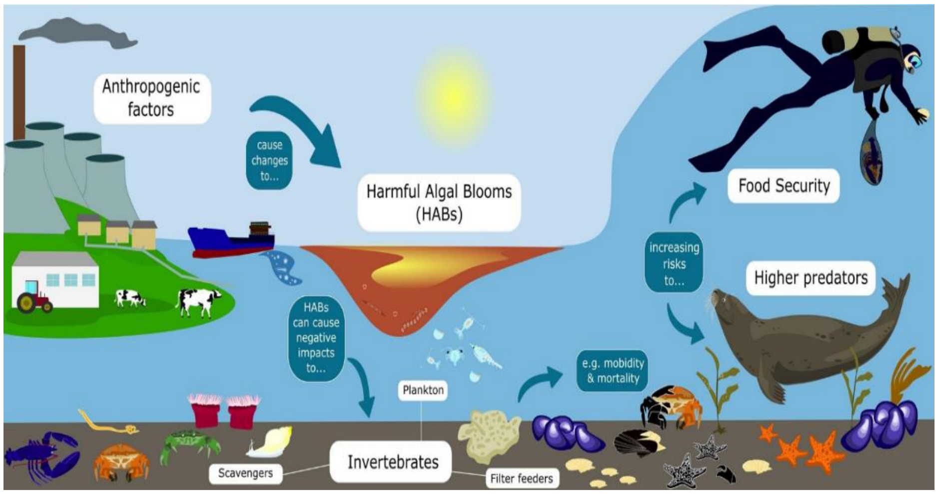

Figure 1. The marine invertebrate interactions with Harmful Algal Blooms.

Microalgae toxins even in low concentrations can be harmful to aquatic ecosystems sea and also humans are deadly (Hallegraeff, 2003). Among the species capable of producing HABs, there are about 20 marine benthic species that produce a wide range of toxins, including the most potent toxins found in nature (Rodríguez *et al*., 2018; Chomérat *et al*., 2019; Boisnoir *et al*., 2020). Biotoxin-producing benthic dinoflagellates live on macroalgae, seagrasses, coral reefs, marine sediments, and waterbeds in mangrove forests. Toxins produced by benthic dinoflagellates can be transferred to herbivorous marine organisms and filter feeder organisms through different levels of feeding, hunting, and bioaccumulation processes, and in this way reach a high concentration in the body of other organisms in the food web of the marine ecosystem. Man can be used (Boisnoir *et al*., 2020).

Because these toxins are resistant to heat and their negative effects on the health of living beings are not reduced, any of the toxic benthic microalgae can be responsible for endangering the health of aquatic animals and humans and even lead to Death will also happen. Among dinoflagellates, many species play a role in the occurrence of algal blooms, but the most important toxic dinoflagellates that cause harmful algal blooms worldwide are *Gamdierdiscus* spp., *Prorocentrum* spp., *Ostreopsis ovata*, *Amphidinium carterae*, and *Coolia monotis*. Among these, the genera *Gambierdiscus* and *Ostreopsis* are dinoflagellates that are known to synthesize strong neurotoxins and cause serious poisoning in humans in case of high-density blooms (Boisnoir *et al*., 2020). One of the products of dinoflagellates is natural metabolites called phycotoxins. These toxins, which are usually amino acids, alkaloids, and polyketides, can accumulate in the internal organs of aquatic animals after entering the food web. Although the factors affecting the production of these toxins in dinoflagellates are not well known, nevertheless, environmental parameters, along with genetic characteristics and even bacteria symbiotic with microalgae, can play a role in this to a large extent. Dinoflagellate toxins are generally classified into 5 different groups based on how they affect human health, which: ciguatera fish poisoning (CFP), azaspiracid poisoning (AZP), diarrheal shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP), and paralytic Shellfish poisoning (PSP) (Gallardo-Rodríguez *et al*., 2012).

The present study was conducted to evaluate the potential risks of dinoflagellates causing harmful algal blooms as species with the potential to produce toxins.

MATERIALS AND METHODS

In the present study, the biotoxin of marine dinoflagellates was investigated by studying documentary and library sources using the information contained in publications, research studies, and reliable scientific databases (Scopus, Springer, Pubmed, and Science Direct) and then reviewing the studies and general results were discussed.

RESULTS AND DISCUSSION

The most dangerous marine biotoxins

Saxitoxin (STX)

Saxitoxin (STX) belongs to the group of paralytic shellfish poisoning (PSP). This poison with chemical formula $C_{10}H_{17}N_7O_4$ is non-protein, soluble in water, and very stable against heat and is known as one of the strongest natural poisons. Members of three dinoflagellate genera, including *Alexandrium* spp., *Gymnodinium Catenatum*, and *Pyrodinium bahamense*, are known as the most important saxitoxin producers (Cusick & Sayler, 2013; Silva *et al*., 2015).

Gomyautoxin (GTX)

Gomyautoxin (GTX) belongs to the group of paralytic shellfish poisoning (PSP). This toxin with the chemical formula $C_{10}H_{17}N_7O_8S$ is a part of the saxitoxin group and is naturally produced by several marine dinoflagellate species such as *Gongaular* sp., *Alexanarium* sp., and *Protogonyaulax* sp. are produced. Gomyautoxin affects the nervous system so it disrupts the function of nerve and muscle cells. It also blocks the transmission of nerve messages, which will result in temporary muscle paralysis (Wang, 2008; Meriluoto *et al*., 2017).

Brevetoxins (PbTx)

Brevetoxins (PbTx) belong to the group of neurotoxic shellfish poisoning (NSP). Brevetoxins are a group of fat-soluble cyclic polyether compounds that were first extracted from a dinoflagellate species called *Karenia brevis*. These poisons, like many marine poisons, have the properties of being tasteless, odorless, and resistant to heat (up to 300 degrees Celsius). Brotoxin has two different types A and B based on its structure. The combination of brevetoxins in the body causes the release of neurotransmitters from nerve endings. Subsequently, this action causes the release of acetylcholine and, as a result, the contraction of the smooth muscles of the trachea, as well as the degranulation of the large mast cell (Wang, 2008).

Yessotoxins (YTX)

Yessotoxins (YTX) belong to the group of neurotoxic shellfish poisoning (NSP). This toxin with chemical formula $C_{55}H_{82}O_{21}S_2$ in some dinoflagellates including *Protoceratium reticulatum*, *Gonyaulax spinifera*, and *Lingulodinium polyedrum* has it. If yessotoxins enter the organs of *bivalve molluscs*, including oysters and scallop snails, they accumulate in their tissues and thus are transferred to the higher food chain. However, there has been no report of poisoning caused by this poison in humans (Tubaro *et al*., 2010; Alfonso *et al*., 2016).

Palytoxin (PLTX)

Palytoxin (PLTX) with the chemical formula $C_{129}H_{223}N_3O_{54}$ was extracted for the first time in 1971 from a zoanthid named *Palythoa toxica* (Seemann *et al*., 2009). An analog of Palytoxin has been confirmed in the dinoflagellate *Ostreopsis siamensis* so that the monovalent positive sodium and potassium ions diffuse freely against the concentration gradient and as a result, the ion gradient of the cell is destroyed (Braz *et al*., 2012). Normally, about 100 ions pass through this channel, but with the presence of PLTX every second Millions of ions are released from the channel (Rossini & Bigiani, 2011). PLTX is one of the most toxic and chemically complex non-protein toxins observed in the marine ecosystem and can cause severe and sometimes fatal poisoning in humans. PLTX and its analogs were identified in different species of marine dinoflagellates belonging to the genus *Osteopsis* (Faimali *et al*., 2012).

Ciguatoxins (CTX)

Ciguatoxins (CTX) belong to the ciguatera fish poisoning (CFP) group. Ciguatera fish poisoning, which is the most common disease caused by marine toxins worldwide, can poison more than 50,000 people every year. Ciguatera syndrome is caused by toxins produced by different dinoflagellates and causes different effects on humans. Ciguatoxins are usually produced by the epiphytic dinoflagellate *Gambierdiscus toxicus* and are a lipid-soluble polyether polycyclic toxic compound. This dinoflagellate is usually observed in symbiosis with macroalgae and corals (Lehane & Lewis, 2000; Nicholson & Lewis, 2006). Studies show that the amount of Ciguatoxins produced by *Gambierdiscus* can change under the influence of environmental factors such as light, salinity, temperature, the number of nutrients, and microcell cell growth stages. Ciguatoxin has 3 different types based on its chemical structure, type 1 includes CTX1-3 and CTX-4 (A, B), type 2 includes CTX-2 (A1) and CTX-3C, and type 3 includes C-CTX1 (Wang, 2008). This poison and its metabolites accumulate in the organs of more than 400 species of fish, such as carp, grouper, and redfish, and every year more than 25 thousand people suffer from neurological diseases such as numbness of the limbs, mouth, and lips, by consuming these fish. Muscle and joint pain, cardiovascular and digestive problems (diarrhea and vomiting). Of course, these symptoms vary from person to person and depend on the amount of poisons introduced into the body as well as the geographical origin of the consumed fish (Chinain *et al*., 2019).

Maitotoxins (MTX)

Maitotoxins (MTX) are also in the ciguatera fish poisoning (CFP) group. Maitotoxins with the chemical formula $C_{164}H_{256}O_{68}S_2Na_2$ are another very strong and water-soluble toxic compound produced by the dinoflagellate *Gambierdiscus toxicus*. Three forms of Maitotoxins including MTX-1, MTX-2, and MTX-3 have been identified in this dinoflagellate species. Maitotoxins with a molecular weight of 3424 are one of the largest and most potent non-synthetic marine toxins known so far. So this toxin is at least 5 times more toxic than Tetrodotoxin. Studies have shown that intraperitoneal injection of 0.17 μg/ml of this toxin can be lethal in mice (Wang, 2008).

Azaspiracids (AZAs)

Azaspiracids (AZAs) with the chemical formula $C_{47}H_{71}NO_{12}$ are polyether toxins that are produced by the toxin-producing species of *Azadinium* and the dinoflagellate *Protoperidinium crassipes*. AZA toxins accumulate in edible oysters and the consumption of these oysters by humans will lead to gastrointestinal diseases (Wang, 2008).

Okadaic acid (OA)

Okadaic acid (OA) is in the diarrheal shellfish poisoning (DSP) group. Okadaic acid (OA) with the chemical formula $C_{44}H_{68}O_{13}$ is one of the lipophilic marine toxins produced by dinoflagellates *Prorocentrum lima*, *Prorocentrum concavum*, *Dynopigisis acuta*, and *Dynophysis Fortii*. At first, it was thought that Okadaic acid (OA) and its analogs specifically target only protein phosphatases A1 (PP1) and A2 (PP2). But today, the effect of these toxins on other protein phosphatases (PP2B, PP4, and PP5) has also been proven. Overall, there is little information about the molecular mechanisms and implementation involved in the cellular responses caused by Okadaic acid (OA). The most extensive if the cytotoxicity of OA is related to the induction of apoptosis, this toxin inhibits the growth or apoptosis in many types of cells, such as intestinal cells, nerve cells, liver cells, lung cells, blood cells, etc. (Valdiglesias *et al*., 2013). Since Okadaic acid (OA) is a PP2A inhibitor, today it is known as a useful tool in the screening of drugs involved in the prevention and treatment of Alzheimer's disease, the study of Alzheimer's pathology, and the recognition of the mechanism of neuronal degeneration (Ferrer *et al*., 2005; Kamat & Nath, 2015).

Effect of dinoflagellate biotoxin on aquatic life cycle

In general, organisms in the early stages of development are more sensitive to toxins, because they lack effective enzyme systems for detoxification and are more exposed to toxins due to the speed of metabolic growth. Also, biotoxins may reduce the amount or quality of gametes or affect the development of the embryo. In general, there is not much information about the effects of toxins produced by dinoflagellates on marine invertebrates, especially in the early stages of embryonic development (Ramos & Vasconcelos, 2010). However, the results of studies show that marine toxic microalgae can have a destructive effect on the early life stages of invertebrate species, disrupt the ability of gametes to reproduce in animals, and cause problems by causing disease and disrupting the existing organs throughout the life of these aquatic animals. These factors can affect their survival disturb the balance of the ecosystem where they live and lead to significant population changes (Neves *et al*., 2017).

Figure 2 shows the effects of climate change stressors (e.g., temperature, nutrients, pH, salinity, hypoxia, anthropogenic, and turbidity) on HABs (Harmful Algal Blooms) and fish and shellfish species.

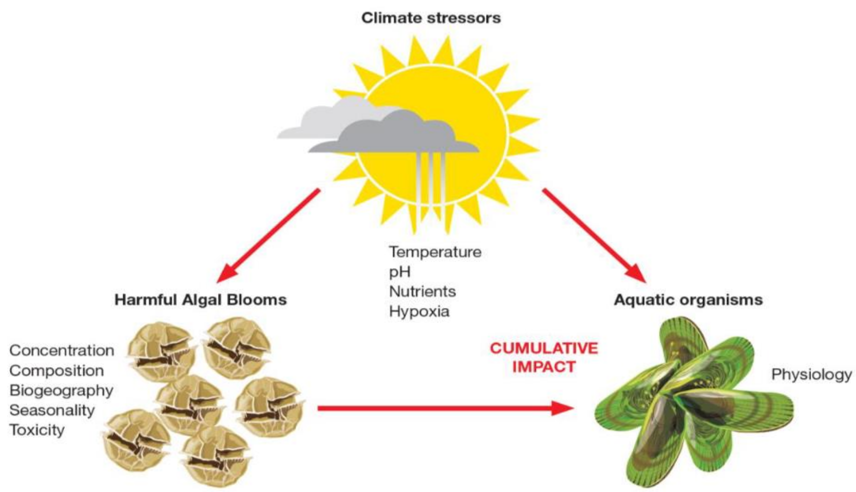

Figure 2. The effects of climate change stressors on HABs (Harmful Algal Blooms) and fish and shellfish species.

It is important to consider that survival rates in organisms exposed to a microalga toxin may indicate a degree of resistance to the toxin that will have a long-term effect on the population of that organism. This issue is important because ecologically, zooplankton resistant to toxins that feed on harmful algae have a greater potential for the accumulation of toxins and can be the cause of the transfer of toxins to higher consumers and the dispersion of toxins through becoming a marine food chain. For this reason, the organisms that are resistant to the poison are more dangerous than the organisms that are sensitive to the poison (Neves *et al*., 2017). The interactions between harmful microalgae and their predators need to be better investigated to assess the potential ecological effects of phycotoxins on their predators and the distribution of toxins through marine food webs. Since many harmful dinoflagellates are benthic, it is possible that with the change of environmental parameters due to climate change and its effect on coral reefs, we will see a high density of these species in these ecosystems, in which case we can expect an increase in mortality. Various marine invertebrates and larval species had ecological and economic importance due to the release of poison in these areas.

Mechanism of action of biotoxin

The chemical structures and mechanism of action of marine dinoflagellate biotoxins can be very different from each other so that these toxins are functionally divided into two groups of neurotoxins and hepatotoxins, where the contribution of neurotoxins is much higher (Wang, 2008). These polycyclic ether or polyketide biotoxins through mechanisms such as changes in channels or ion pumps of cell membranes, effects on the normal function of nerve tissues, inhibition of serine/threonine phosphoprotein phosphatases, disruption of cell control mechanisms, and changes in the cytoskeleton plays its functional role. For example, the importance of palytoxin is due to the powerful effect mechanism of its analogs in changing the function of homeostasis in the living organism, which disrupts the function of the cell membrane and loss of ion regulation, and this factor may lead to the failure of the body's osmotic regulator which is one of the most obvious examples of adaptation to the living environment in some aquatic animals (Faimali *et al*., 2012).

Ciguatoxins are also neurotoxins that bind to voltage-sensitive sodium channels in the cell membrane (Neves *et al*., 2017). In all HAB species, toxin production is a constitutive property of the cell, meaning that if the toxin is produced it will be present at all stages of the life cycle and cell growth. However, the amount of toxin in a cell can vary dramatically with growth conditions, so that some species, such as *Dinophyisis,* or the ability to produce acid during active cell division (exponential growth phase) than when limited by some nutrients (stationary phase) they produce less amount of poison. The exact opposite occurs in the case of *Alexandrium* species that produce saxitoxin. Thus, in these species, the highest level of toxin production occurs during the growth cycle causing the cells to multiply exponentially (growth phase).

In addition, the amount of toxin produced in dinoflagellates can vary with different types of nutrient limitation. For example, cells that run out of phosphorus produce much more saxitoxin than other cells. Also, as nitrogen sources decrease, cells become more toxic. Therefore, the biotic and abiotic parameters that affect the food consumed by the species causing HAB can be up to 10 times more effective on their toxicity, so that the strains of a particular species that are isolated in two different places or at two different times can be significantly different in terms of the presence of poison and its effect on living organisms, even when these species grow under the same conditions (Hess *et al*., 2017). Therefore, it is possible that some species of microalgae, which did not show toxicity in the early stages of their life, may be dangerous to the health of other organisms when their cellular content is released in the form of bioactive compounds in the marine environment. Knowledge of the structure and mechanism of action of these biotoxins can be a useful method in combating their poisoning or a tool for designing new drugs. Because some microalgae, contrary to toxic effects, may have beneficial functions such as antifungal, antimicrobial, and anticancer activities with potential therapeutic properties (Echigoya *et al*., 2005; Kobayashi & Kubota, 2007; Meng *et al*., 2010). Inhibit the malignant tumor of the lung (SKU) (Mejía-Camacho *et al*., 2021). For this reason, the biotechnological potential of these types of dinoflagellates should be studied more to know more precisely the effects of their bioactive molecules. Further studies are necessary to identify the different modes of action of the diverse toxic compounds produced by benthic dinoflagellates in the ecosystems where they are actively present. This aspect of research requires a more precise and targeted approach, and part of the research should be focused on the cellular aspects of such studies with the aim of better understanding the toxic mechanisms of these compounds.

Analytical methods of biotoxins

Today, different analytical methods are used to analyze lipophilic biotoxins. In this context, liquid chromatography-mass spectrometry (LC-MS/MS) has been designated as a reference method in the European Union since 2011. Another method of measuring biotoxins is the use of bioassays by experimenting on mice, which investigates the effect of the animal's behavior when exposed to microalgae toxins, and is considered an alternative method in this field (Visciano *et al*., 2016). Several other alternative or complementary techniques are allowed individually or in combination according to European Commission Regulation No. 2011/15 provided that it does not violate public health guidelines. These methods include biotoxin assays by chromatography, including high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), gas chromatography-mass spectrometry (GC-MS), and gas chromatography-mass spectrometry (GC-IV) (Fujii *et al*., 2004). However, these methods have drawbacks, for example, their use is expensive, and in addition, they require specialized labor (in the case of liquid and gas chromatography). However, there is a need to conduct toxicological effects tests to estimate thresholds for marine organism mortality during harmful algal blooms. Thus, ecotoxicological assays such as poison tests on aquatic animals are commonly used in monitoring polluted environments as well as in evaluating bioactive substances and biotoxins. In the meantime, investigating the effects of phycotoxins on Artemia species is one of the main tests and experiments in many countries (Pavaux *et al*., 2020).

Providing solutions to prevent Harmful algal bloom and environmental monitoring

In general, the increase in the abundance of harmful dinoflagellates in coastal environments can have negative economic effects on aquaculture fisheries and tourism activities, which are important sources of local income in coastal areas. According to these cases, toxic benthic dinoflagellates that have a high reproduction rate and benefit from the important ability to produce cysts in unfavorable conditions may increase with the increase of food resources that have entered the sea through humans or occur in connection with climate change, spread to other areas and become a potential threat to marine organisms and human health by flourishing to a large extent. **Figure 3** shows the algal bloom environmental factors.

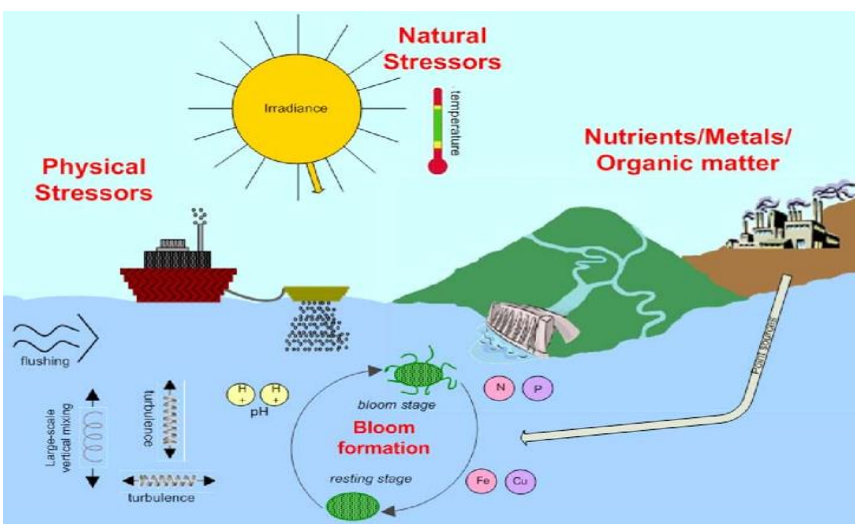

Figure 3. The algal bloom environmental factors.

Manipulation of coastal watersheds for agriculture, industry, housing, and recreation has greatly increased nutrient loads in coastal waters. Just as applying fertilizer to lawns can increase grass growth, seaweeds also grow in response to nutrients entering coastal waters. Agricultural fertilizers enter lakes and oceans through farm runoff. Other nutrients also enter aquatic ecosystems through streams, soil erosion from aquaculture farms, and urban and industrial wastewater. It seems that shallow waters and coastal areas are more involved in the problems of algal blooms related to the increase of nutrients. Enrichment of nutrients in these areas often leads to excessive production of organic matter, accelerates the process of eutrophication, and subsequently increases the density and bloom period of microalgae including HABs (Hallegraeff *et al*., 2004). Meanwhile, ships can also transport hundreds of millions of live HAB species in the balance water, for example, HABs were first introduced into the waters of Australia and New Zealand in this way.

Species identification and cell counts are very important during harmful algal blooms, but estimating the threat of a bloom without accurate knowledge of the toxicity of the species in that area does not provide reliable information. In general, investigating the possibility of toxicity of harmful algal species and their toxin effects, along with the precise identification of the blooming location of these species, will provide a useful tool for extensive studies on the control and monitoring of areas where there is a possibility of blooming and environmental hazards.

CONCLUSION

Marine biotoxins produced by toxic microalgae are one of the most important causes of widespread mortality of aquatic organisms during harmful algal blooms, especially in coastal areas. In most cases, these biotoxins cause poison-related syndromes, such as ciguatera fish poisoning (CFP), azaspiracid poisoning (AZP), diarrheal shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP), and paralytic Shellfish poisoning (PSP) causes acute neurological, digestive and respiratory symptoms in a person and can lead to death due to serious damage to sensitive organs such as the liver. Therefore, if humans feed on aquatic animals carrying these toxins, severe and even fatal poisoning can be expected. Several unique cases of these toxins include ciguatoxin, palytoxin, okadaic acid, and saxitoxin are among the main toxins that threaten life in marine ecosystems. Therefore, the methods of measuring these toxins and defining a standard to check the presence of the minimum level of safe toxins in aquatic products are important. In the past, different methods have been used to measure marine biotoxins, however, the use of bioassay methods with marine invertebrates, especially *Artemia*, along with the use of methods to measure the contents of toxins using devices such as ICH PLC is recommended for best results. A better understanding of biotoxin-producing species and the mechanism of action of these toxins can help to control this dangerous agent as effectively as possible and provide a useful tool for monitoring areas where there is a possibility of flourishing and environmental hazards.

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