Sostanze Organiche Naturali di origine marina

Tra le specie animali viventi (circa 1.000.000), almeno 500.000 vivono in ambienti acquatici: numero, questo, destinato ad aumentare con l'esplorazione dei fondali marini. Degli animali marini alcune migliaia di specie sono ritenute tossiche, ma di queste solo una piccola percentuale è stata studiata; **nel 2005 non erano più di un centinaio le tossine marine** di cui erano conosciute con esattezza la struttura chimica e la loro azione farmacologica sugli organismi viventi.

Si definisce tossina una sostanza capace di indurre manifestazioni fisiologiche dannose negli organismi viventi, anche se ingerita in quantità esigue.
Una tossina, per risultare tale, deve possedere i seguenti requisiti, secondo quanto stabilito da Vogt (Toxicon, 1970, 8, p. 2511):

a) presenza in animali, piante, batteri etc.
b) estraneità nei confronti dell'organismo vittima
c) effetto tossico riconosciuto sul benessere o sulla vita dell'organismo vittima

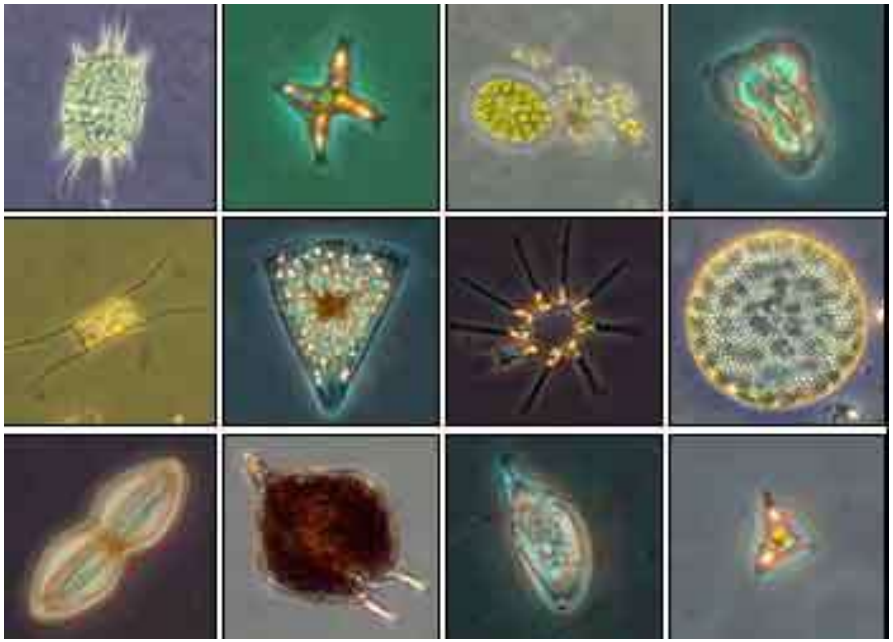
Spesso a tossine di origine marina sono stati attribuiti dei nomi di fantasia: in effetti, il principio generale nella scelta del nome di una sostanza tossica prevede che il nome dell'organismo in cui è stata rilevata preceda il suffisso tossina (saxitossina, tetrodotossina).

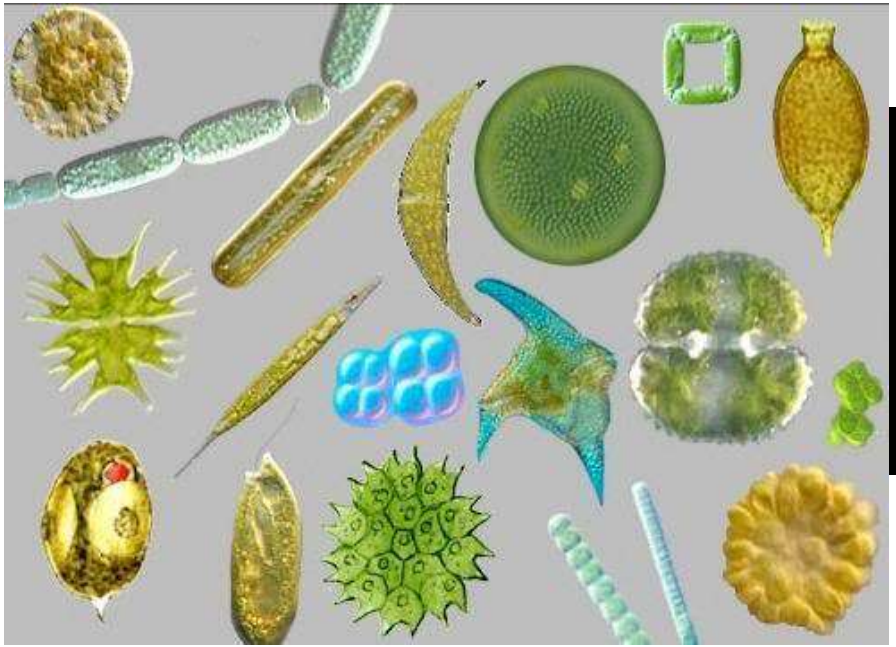
Maree Rosse

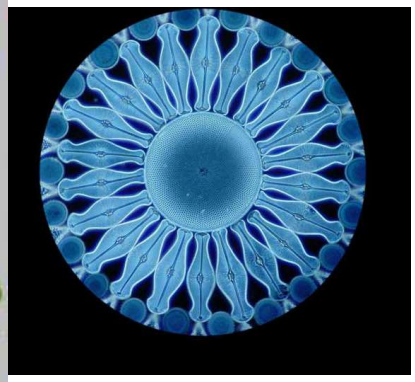
Le **maree rosse** sono formazioni di alghe (fitoplancton) di colore rosso, molto fitte, che si riproducono in abbondanza; il loro ambiente ideale è l'inquinamento urbano, gli scarichi industriali, i rifiuti delle aziende agricole e il deflusso dei fertilizzanti che scorrono da fiumi e torrenti nelle acque costiere, oltre che il graduale aumento della temperatura dei mari, anche se le cause di queste "esplosioni" non sono sempre facilmente individuabili.

E' giusto precisare però che numerose specie di fitoplancton possono causare maree rosse ma soltanto poche producono tossine.
E' possibile rimanere intossicati a causa delle maree rosse, ma è raro che accada in maniera "diretta"; infatti l'intossicazione da marea rossa è sovente ritardata rispetto all'evento marino in quanto la tossina deve passare nella catena alimentare.

Principali organismi costituenti il fitoplancton







cianobatteri

cloroficee

criptoficee

crisoficee

dinoflagellati

diatomee

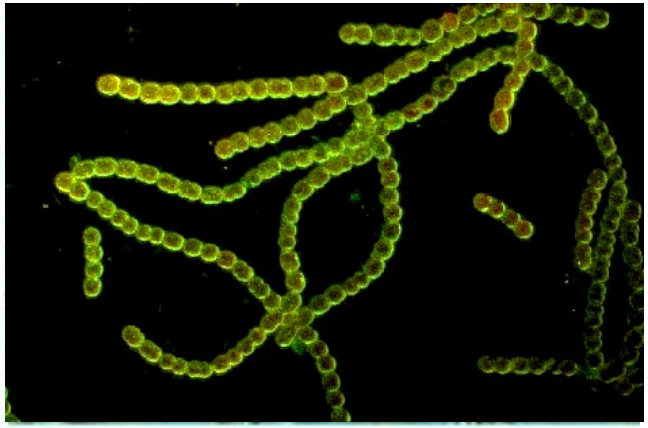
Organismi autotrofi fotosintetizzanti

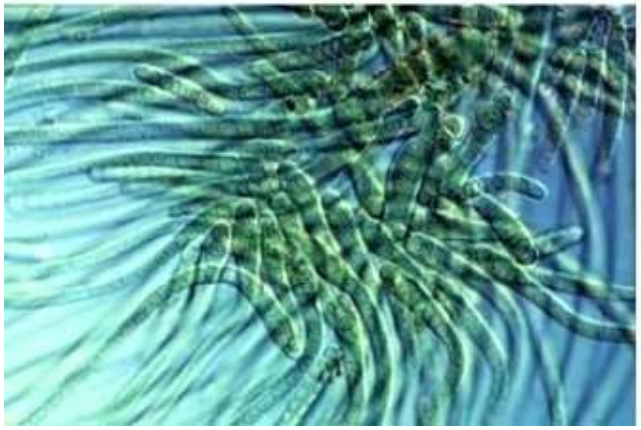
Cianobatteri

Anatossina-a

Saxitossina (lyngbya)

I cianobatteri (Cyanobacteria, 2002), chiamati un tempo, impropriamente, anche alghe azzurre, alghe verdi-azzurre o Cianoficee, sono un phylum di batteri fotosintetici, uno dei 23 phyla del dominio dei Bacteria. Sono organismi unicellulari procarioti, fotoautotrofi.





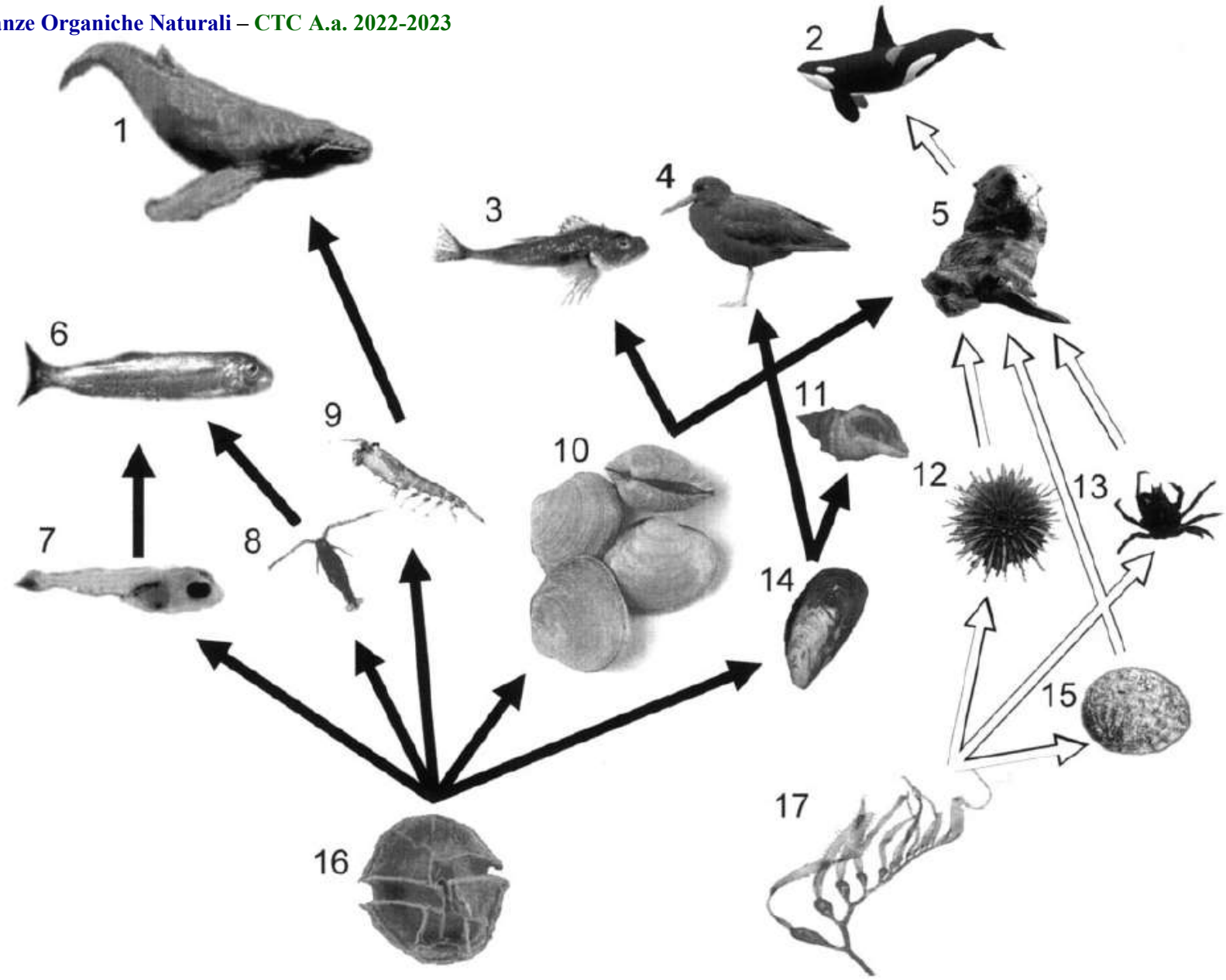
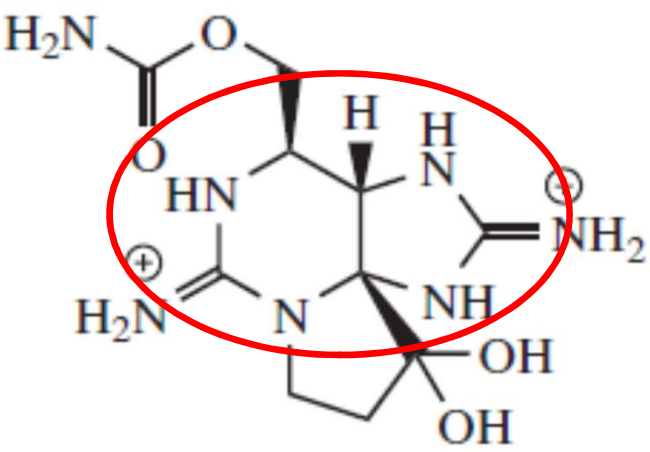


Figure 6. Energy flow within a simplified trophic web, coupling benthic and pelagic communities in coastal habitats of the northeast Pacific Ocean. Hypothesized interactions between species are denoted by arrows, including those mediated directly by saxitoxin (black). Numbered organisms are (1) humpback whale (*Megaptera novaeangilae*), (2) killer whale (*Orcinus orca*), (3) staghorn sculpin (*Lepticotus armatus*), (4) oystercatcher (*Haematopus bachmani*), (5) sea otter (*Enhydra lutris*), (6) mackerel adult (*Scomber scombrus*), (7) mackerel larva (*Scomber scombrus*), (8) copepod (*Calanus* spp.), (9) krill (*Euphausia* spp.), (10) butter clam (*Saxidomus giganteus*), (11) whelk (*Nucella* spp.), (12) sea urchin (*Strongylocentrotus* spp.), (13) kelp crab (*Pugettia producta*), (14) mussel (*Mytilus* spp.), (15) abalone (*Haliotis* spp.), (16) toxic dinoflagellate (*Alexandrium* spp.), and (17) giant kelp (*Macrocystis* spp).

Maree Rosse: tossine



Saxitossina (STX)

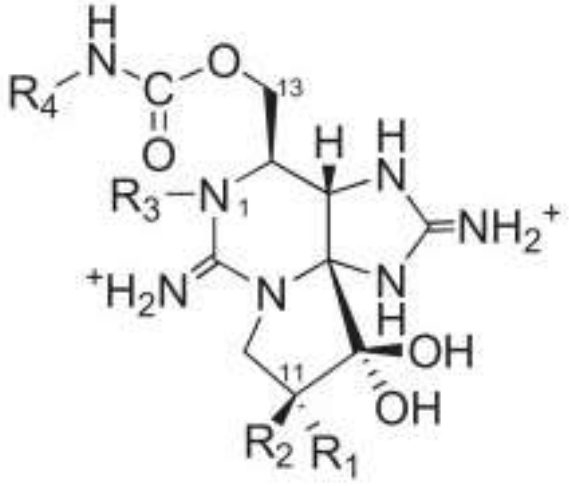
La **saxitossina** è caratterizzata da un sistema purinico ridotto, funzionalizzato da due gruppi guanidinici.

Appartiene al gruppo delle tossine marine definite come "paralizzanti", isolate da molluschi **PSP**, ma prodotte da ceppi tossici di dinoflagellati.

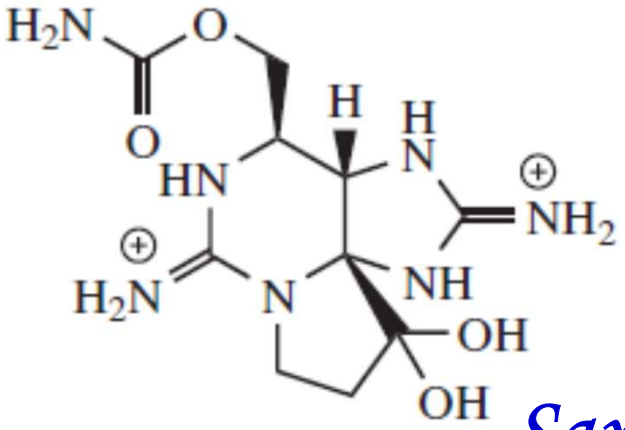
PSP (Paralytic Shellfish Poisoning)

Saxidomus

Gonyautossina (GTX)



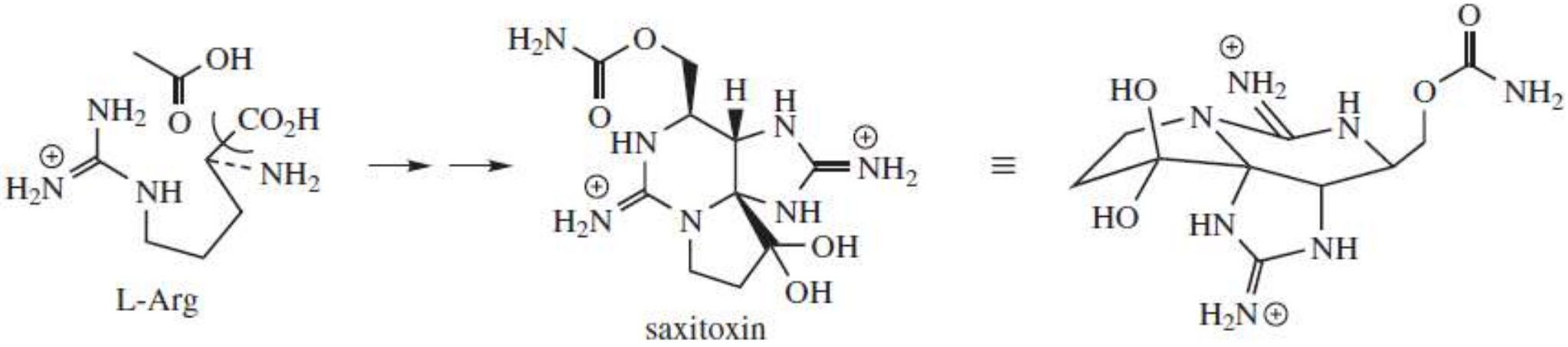
Compound	R_1	R_2	R_3	R_4
C1	OSO_3^-	H	H	SO_3^-
C2	H	OSO_3^-	H	SO_3^-
GTX1	H	H	OH	H
GTX4	H	H	OH	H
neoSTX	H	H	OH	H



Saxitossina (STX)

Gonyaulax (dinoflagellato)

Sintesi della saxitossina a partire dall'arginina



Biol. Bull. **213**: 208–225. (December 2007)

Chem., Eur. J. **2015**, *21*, 7835-7840

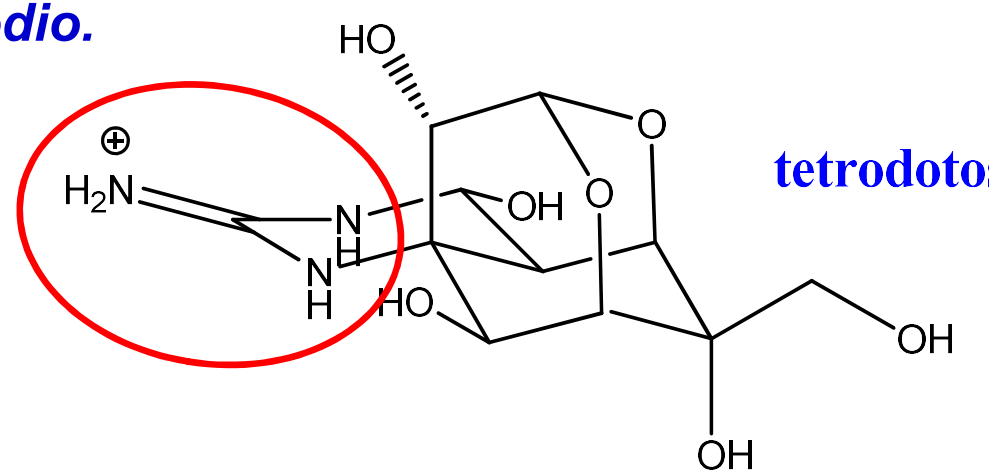
Among the most toxic non-protein substances known, the occurrence of saxitoxin can be traced through the medical literature for centuries. The first documented report of paralytic shellfish poisoning was in 1798,[17] and gives an evocative account of a sickness caused by toxic mussels to several crewmembers exploring the Canadian coast of British Columbia. Based on other writings from this period, the poisonous nature of shellfish during certain seasonal periods was recognized among local inhabitants of coastal regions of Alaska, a unique description of which was preserved by Heinrich Johan Holmberg:[18]

> *"When we found ourselves in Pogibshii proliv (Peril Strait), we turned to eating mussels (Mytilis) because of a shortage of fresh fish. They must have been poisonous at this time of year for a few hours later more than half of our men died. Even I was near death, but remembering my father's advice, to eat smelt (korushki) at such times, I vomited and recovered my health."*

Heinrich Johann Holmberg (1818 -1864) was a Finnish naturalist, geologist (mineralogist) and ethnographer.

Allo stesso gruppo di alcaloidi marini della saxitossina appartiene la **tetrodotossina (*TTX*)**, principio tossico del pesce palla (Tetraodon).

Deriva anch'essa dalla L-Arg e agisce come potente bloccante dei canali del sodio.



tetrodotossina

La Tetrodotossina è 100 volte più tossica rispetto al cianuro di potassio. Un milligrammo (quantità che può essere contenuta nella capocchia di uno spillo) è sufficiente ad uccidere una persona.

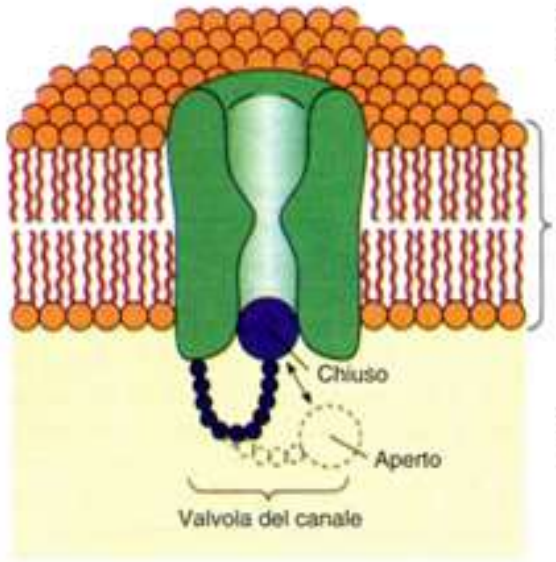
FUGU – Piatto tipico della cucina giapponese.

Dal 1993 al 2006 i casi di avvelenamento sono notevolmente diminuiti; si sono registrati appena 23 casi di cui uno solo avvenuto in un ristorante; tutti gli altri erano pescatori che avevano ingerito ciò che avevano pescato.

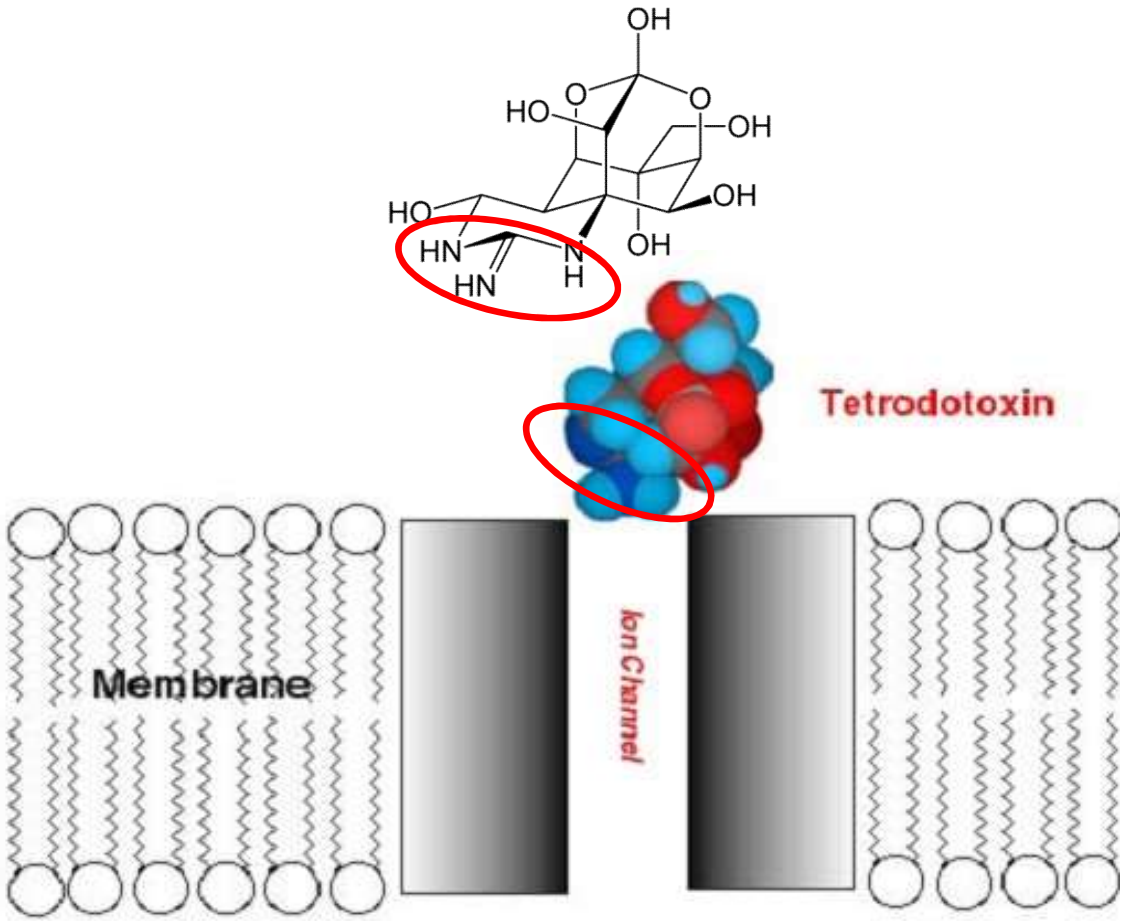
In passato i decessi oscillavano fra i 50 e i 200 all'anno.

*La stessa caratteristica e lo stesso veleno sono presenti nei Diodontidae (**pesci istrice**) muniti per di più anche di aculei su tutto il corpo.*

Meccanismo di azione della Tetrodotossina



La struttura di un canale ionico regolato. La strozzatura al centro del canale può funzionare come filtro selettivo che permette soltanto il trasporto di ioni di un certo tipo. Transizioni conformazionali indotte da modificazioni di potenziale, dall'interazione con ligandi o da stimoli di tipo meccanico aprono il canale al passaggio degli ioni. Nella maggior parte dei canali, la "valvola" è sul lato citoplasmatico della membrana, come mostrato nella figura.



Legame fortissimo tra TTX e canale del sodio voltaggio-dipendente

Il legame permane per 10 secondi

Il sodio non è in grado di entrare nel canale

Morte per insufficienza respiratoria e paralisi del diaframma

Tetrodotossina (TTX)

- Isolata nel 1909 da Yoshizumi Tahara
- Identificata strutturalmente da Robert Woorward, che, per i suoi studi sui composti organici naturali, in particolare proprio sulla TTX, ottenne il premio Nobel per la Chimica nel 1965
- Meccanismo d'azione (blocco selettivo del canale del sodio) dimostrato nel 1964 da Toshio Narahashi e John Moore
- Prima sintesi totale riportata nel 1972 dal giapponese Kishi
- Impegno massiccio nella ricerca di sintesi in laboratorio sempre più mirate ed efficaci negli ultimi 15 anni
- Viene utilizzata per studiare e comprendere il funzionamento della trasmissione nervosa
- Si è rivelata particolarmente efficace per il trattamento del dolore cronico, soprattutto in pazienti con metastasi ossee

DSP (Diarrhetic Shellfish Poisoning)

PSP (Paralytic Shellfish Poisoning)

ASP (Amnesic Shellfish Poisoning)

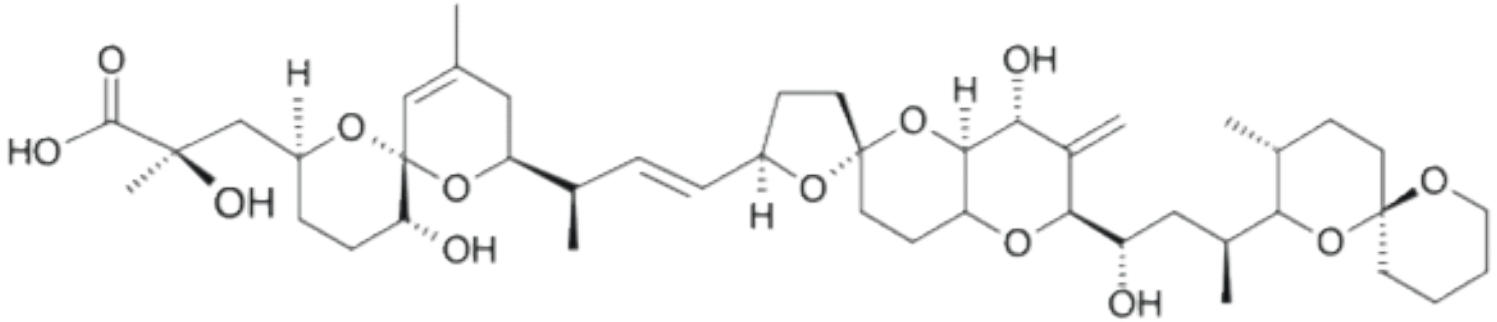
NSP (Neurotoxic Shellfish Poisoning)

CFP (CIGUATERA Fish Poisoning)

Tossine prodotte dai cianobatteri

Tossine di varia natura

DSP (Diarrhetic Shellfish Poisoning)

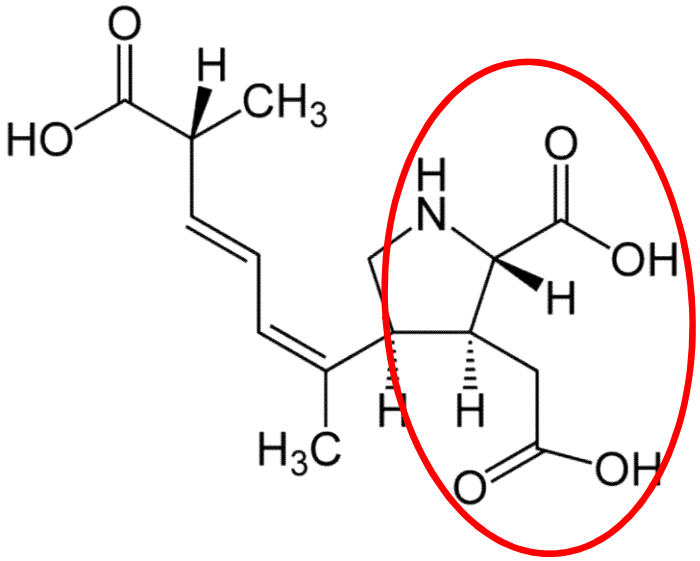


Acido okadaico

Inibisce la defosforilazione cellulare intestinale. Questo fa sì che le cellule diventino molto permeabili all'acqua, provocando una diarrea abbondante con rischio di disidratazione.

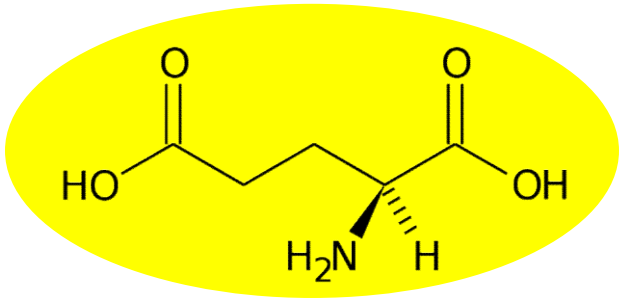
Isolato da alcune specie di spugne del genere Halichondria, ma prodotto, ancora una volta, da dinoflagellati.

ASP (Amnesic Shellfish Poisoning)



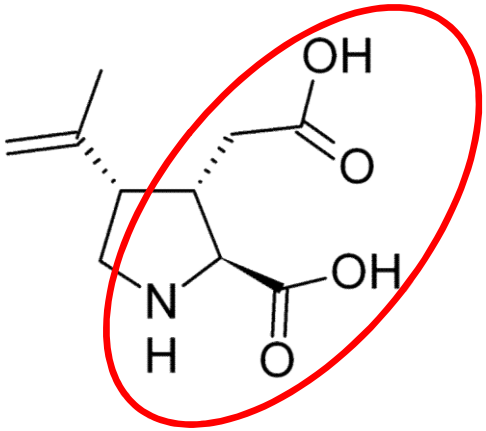
Acido domoico

Originariamente isolato (1958) da un'alga rossa chiamata "doumoi", ma principalmente prodotto da diatomee.



Acido glutammico

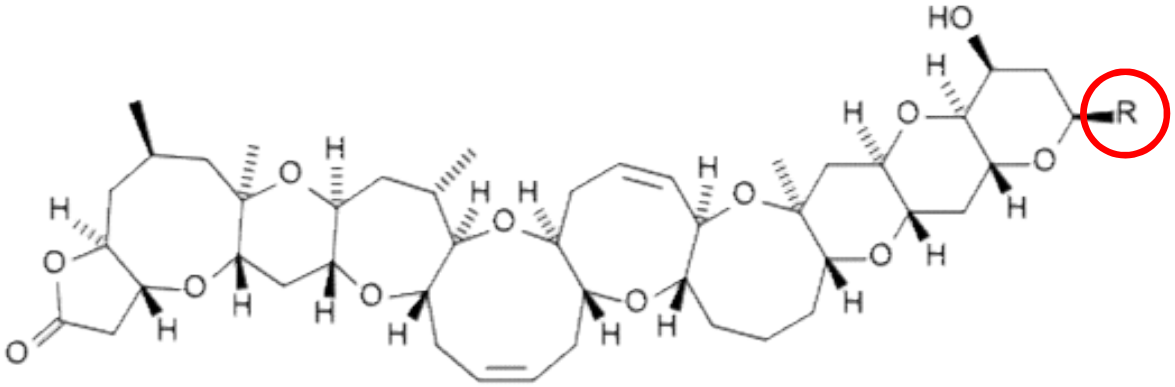
Potenti neurostimolatori in quanto attivano i recettori del glutammato, neurotrasmettitore dell' SNC.



Acido kainico

Sintetizzato da alghe.

NSP (Neurotoxic Shellfish Poisoning)

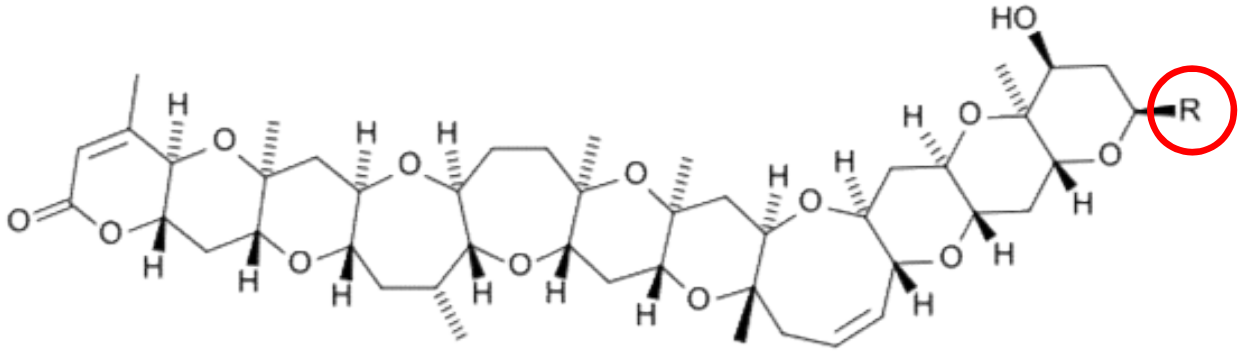


Brevetoxin-5 (PbTx-5): like PbTx-3, but acetylated at hydroxyl group at position 38.

Brevetoxin-6 (PbTx-6): like PbTx-2, but double bond 27-28 is epoxidized.

Brevetossina B

Brevetossina A



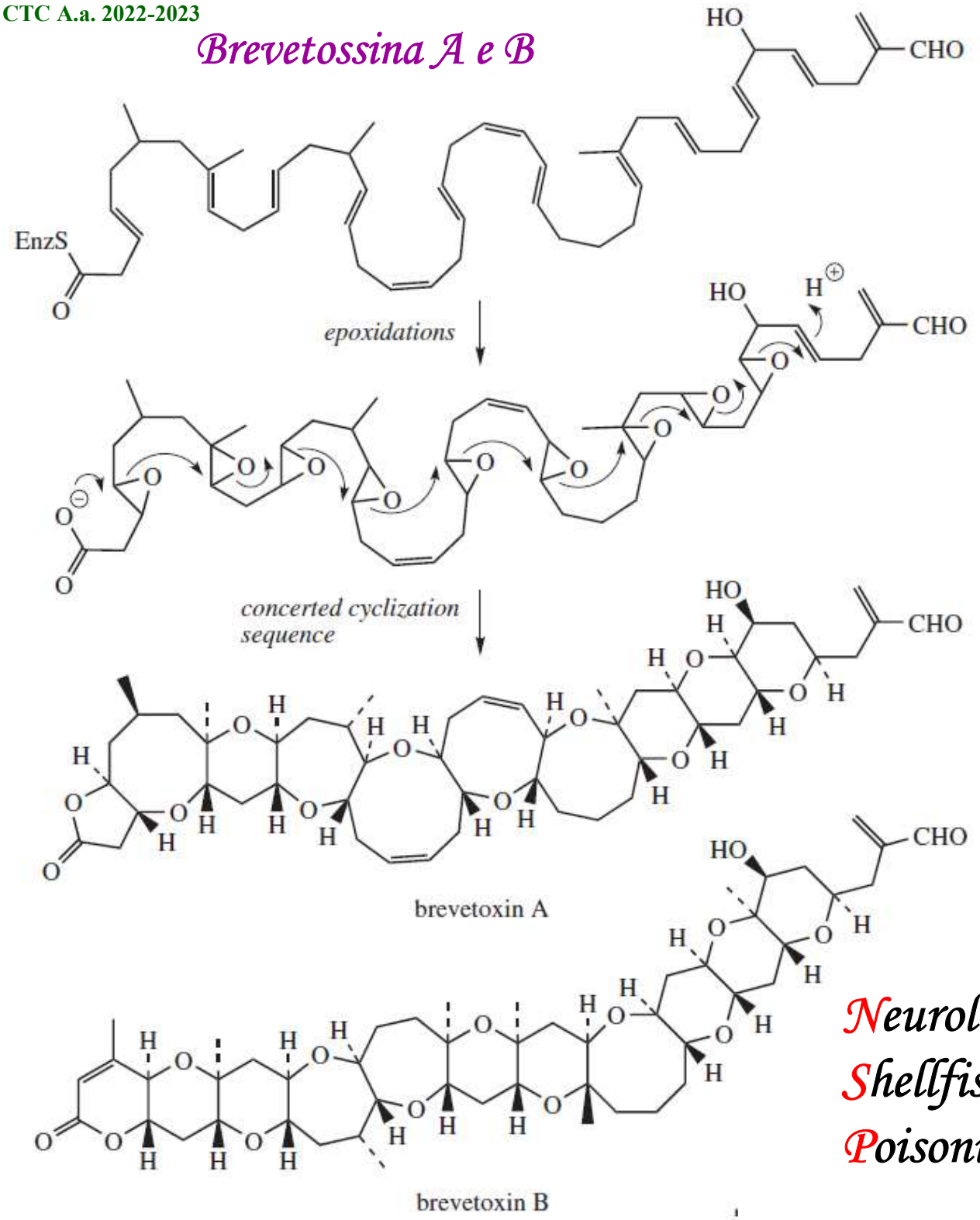
- **Brevetoxin-1 (PbTx-1) R = $-CH_2C(=CH_2)CHO$**
- **Brevetoxin-7 (PbTx-7) R = $-CH_2C(=CH_2)CH_2OH$**
- **Brevetoxin-10 (PbTx-10) R = $-CH_2CH(-CH_3)CH_2OH$**

- **Brevetoxin-2 (PbTx-2) R = $-CH_2C(=CH_2)CHO$**
- **Brevetoxin-3 (PbTx-3) R = $-CH_2C(=CH_2)CH_2OH$**
- **Brevetoxin-8 (PbTx-8) R = $-CH_2COCH_2Cl$**
- **Brevetoxin-9 (PbTx-9) R = $-CH_2CH(CH_3)CH_2OH$**

Brevetossina A e B

Tossine associate al fenomeno delle "maree rosse", ossia fioriture abnormi di dinoflagellati che affliggono pesca e turismo in Florida e nel Golfo del Messico.

Prodotti del metabolismo del *Gymnodymium breve*, (dinoflagellato) sono causa di ***NSP***, con problemi neurologici e gastrointestinali

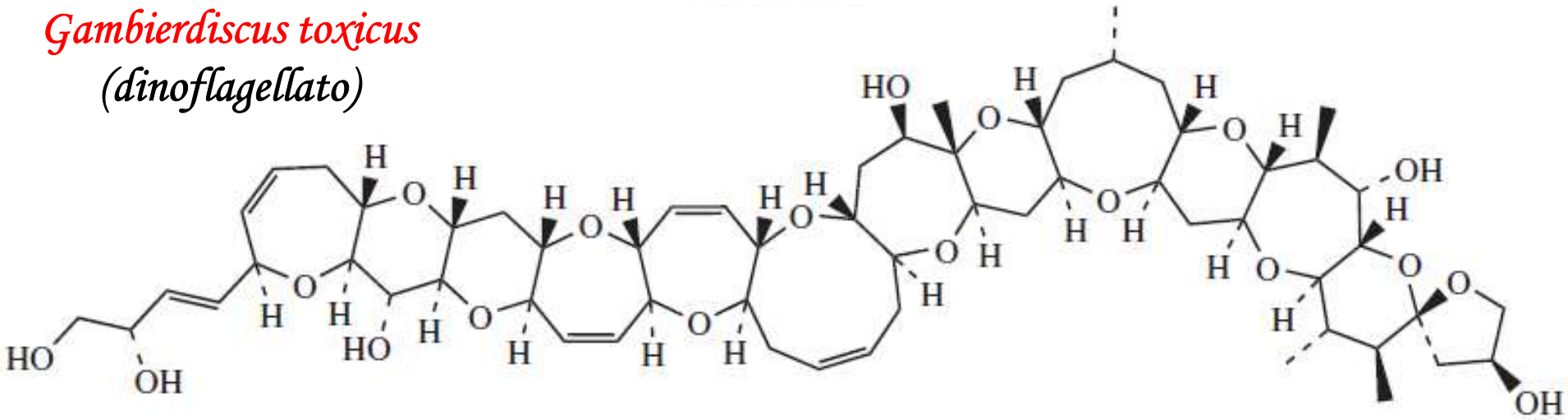


Neurological Shellfish Poisoning

CFP (CIGUATERA Fish Poisoning)

Ciguatera fish poisoning (CFP) produces gastrointestinal, neurological, and cardiovascular symptoms which usually begin developing within 12 to 24 hours of eating contaminated fish. Initially, gastrointestinal symptoms of diarrhea, abdominal pain, nausea, and vomiting occur, followed by neurological symptoms of numbness and tingling of hands and feet, dizziness, altered hot/cold perception, muscle aches, and low heart rates and blood pressure.
In extreme cases, death occurs through respiratory failure.

Gambierdiscus toxicus
(dinoflagellato)



ciguatoxin

Vector fish of ciguatera toxins


Ctenochaetus striatus


Naso unicornis


Cheilinus undulatus


Lethrinus miniatus


Naso brevirostris


Caranx sexfasciatus


Lutjanus bohar


Lutjanus monostigma


Lutjanus rivulatus


Glabrilutjanus nematophorus


Scarus gibbus


Epinephelus fuscoguttatus


Gymnothorax undulatus


Plectorhynchus punctatissimus


Plectropomus leopardus


Cephalopholis argus


Sphyraena barracuda

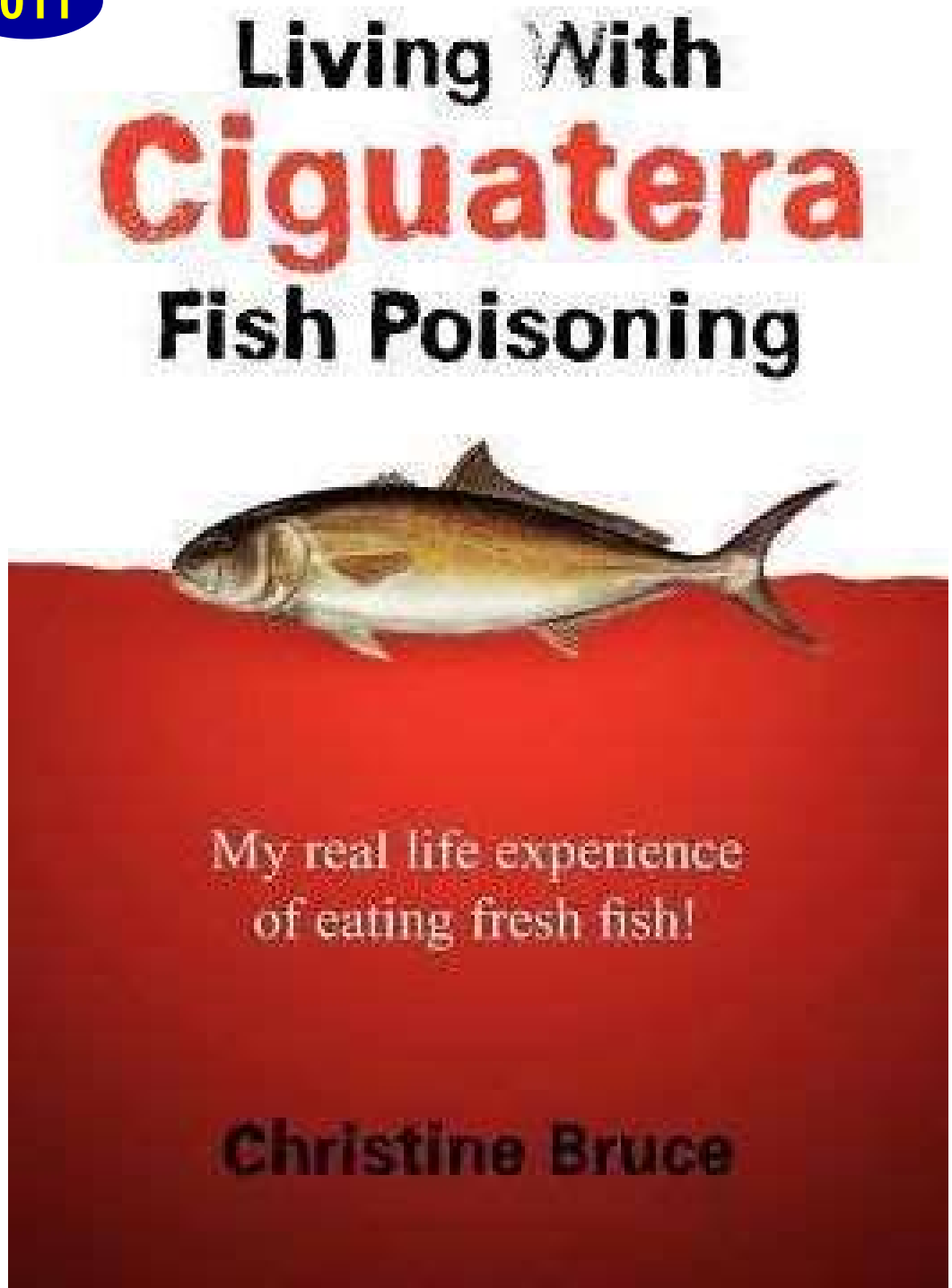
Circa 50.000 persone vengono intossicate ogni anno da organismi marini contaminati da ciguatossine.

Le ciguatossine non vengono distrutte dalle cottura e non esistono test sicuri che possano individuare pesci contaminati o predire quando e dove si avrà lo sviluppo di ciguatossine nelle barriere coralline.

‘Eating fish is like playing russian roulette with your life’ **Ciguatoxins are amongst the deadliest mammalian poison known to us**, volume for volume, **1000 times more potent than arsenic**. THIS FRIGHTENING POISON has been around for centuries - WE ARE NOT INFORMED WHAT IT IS OR MORE IMPORTANTLY, WHAT DO YOU DO ABOUT IT?! I ATE FISH CONTAMINATED WITH CIGUATERA. **THIS POISON IS CONSUMED EASILY BUT NEVER GOES AWAY** - LONG TERM DISABILITY - LONG TERM PAIN - LONG TERM COMPLICATIONS

Ciguatera DAMAGED my life completely; nothing I used to do is possible now.

2011



Contents

MY EXPERIENCE

In October 1999, my partner at the time and I, along with two other friends were off to a wonderful holiday for two weeks to a tropical island destination in one of our safest and most gorgeous places in the world—beautiful Fiji—not too far outside of Australia. It was a quick flight, and before we knew it, we were at a secluded private resort or house in the delicious jungle of Fiji. I had travelled previously to Fiji and wanted to return, so this was a special treat holiday. It was our seventh wedding anniversary, and we had planned for two weeks of enjoyment: one week in this lovely jungle home and a week on a private island up off the north tip of Fiji. It was a two—to three-hour drive from the airport in rugged land, so it was also slow going, and I was quite relieved to get there. It was a bit scary for me, at the time—no road, big ditches, but adventure just the same . . .

We arrived late, and the owners had a fresh, very large platter of seafood delights for our first meal. It looked stunning; however, as I was already allergic to seafood, I could not consume crustaceans, but there was a lovely variety, and I remember the others being delighted with it. Along with that was a fresh fish caught just two hours earlier: scaled, cleaned, and ready for cooking. There were not necessarily large pieces of fish, but the fish was large initially, and there was plenty for the next day with four of us eating lots as our journey had made us ravenous. The others began eating immediately, but I had to wait a while, which made me very hungry, and therefore I ate more than I might have normally. We finally got the pieces of fish on the BBQ and cooked it.

Everyone knows that fish on the BBQ takes only a couple of minutes' cooking on each side after which it's usually done. We did this, and on eating it, we all realised or thought that it wasn't cooked through. It looked cooked enough, but it was 'spongy' or tough instead of melting in the mouth, so we returned it back to the BBQ for more cooking. Well, I recall we cooked these few pieces of fish several times, each time finding it 'spongy', so assuming it was fresh as it had been only recently caught by a Fijian fisherman, and the owners served it up, it had to be OK. We thought, maybe, it was the type of fish in the area and thought no more about it. I didn't enjoy it because it was so strange, and that is all I can say. It tasted fine, and it looked and smelt fine. It seemed fine except for this strange texture when eating it; ...

Ciguatera Fish Poison awareness & support

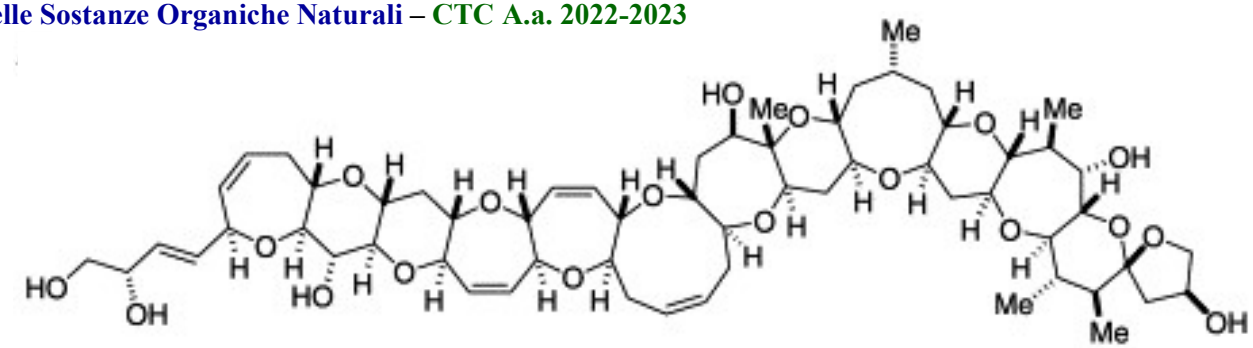
26 NOV 2014
1 *Comment*

FISH & CHIPS FOR DINNER IS NO LONGER SAFE !!

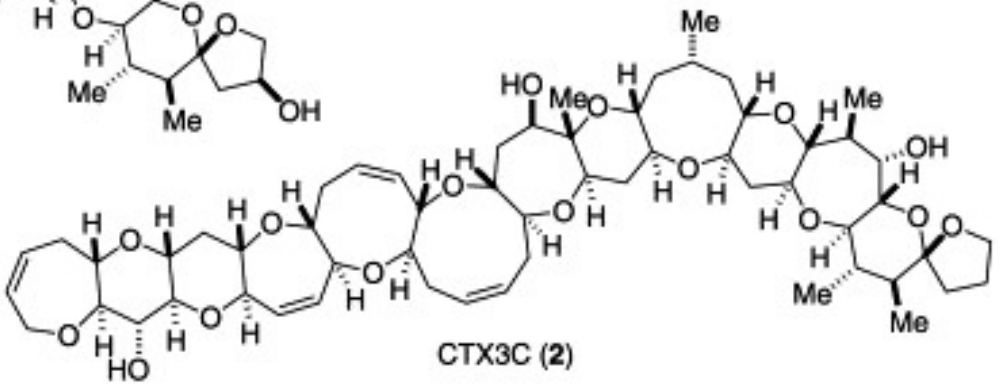
18 March, 2014 3:37PM AEST
Call for ciguatera awareness after 17 cases in Townsville
By Nathalie Fernbach with Paula Tapiolas

The partner of a woman who developed ciguatera poisoning after eating fish and chips is calling for greater awareness of the toxin.

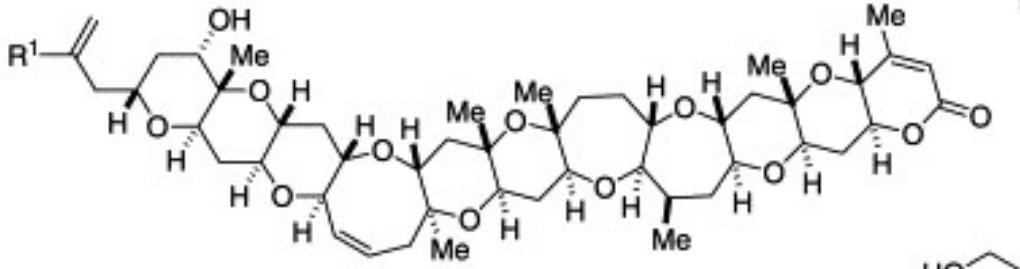
Eteri policiclici di origine marina



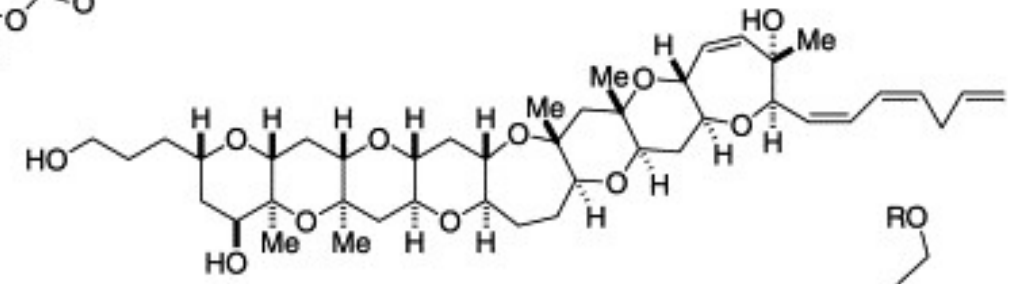
ciguatoxin (CTX, **1**)



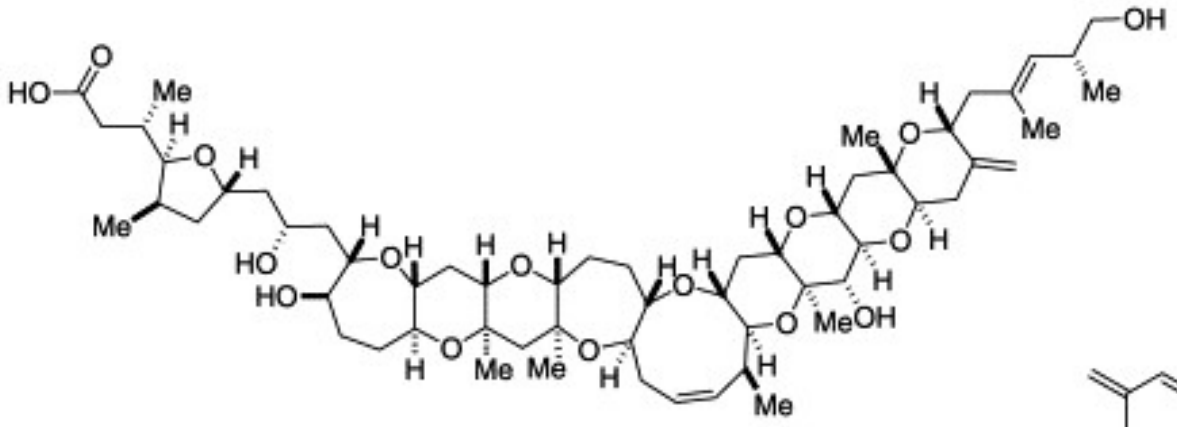
CTX3C (**2**)



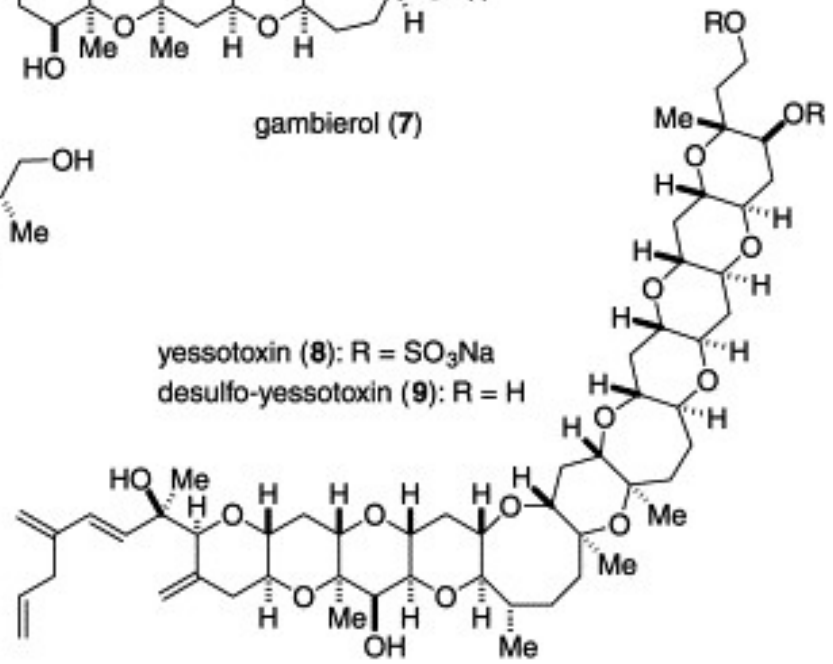
brevetoxin B (BTX B, **3**): R^1 = CHO
PbTx-3 (**4**): R^1 = CH_2OH
[^{3}H]PbTx-3 (**5**): R^1 = CH[^{3}H]OH



gambierol (**7**)

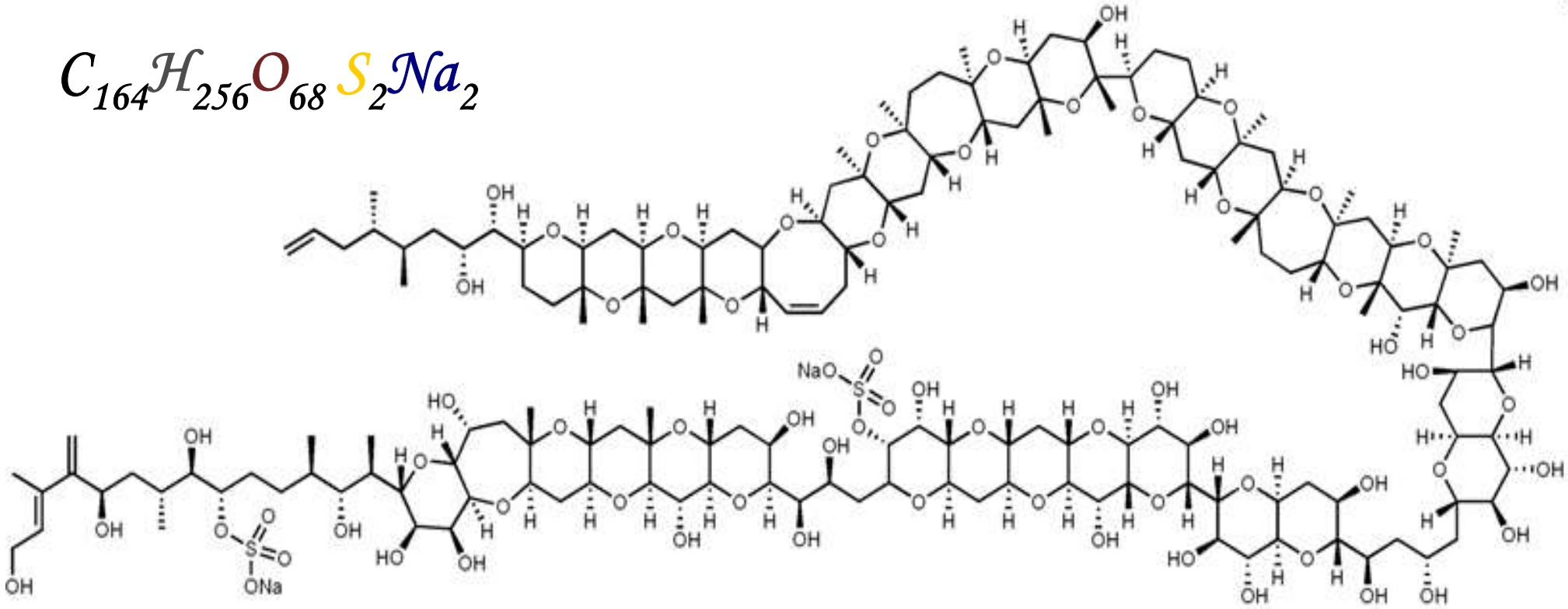


gambieric acid-A (**6**)



yessotoxin (**8**): R = SO_3Na
desulfo-yessotoxin (**9**): R = H

$C_{164}H_{256}O_{68}S_2Na_2$



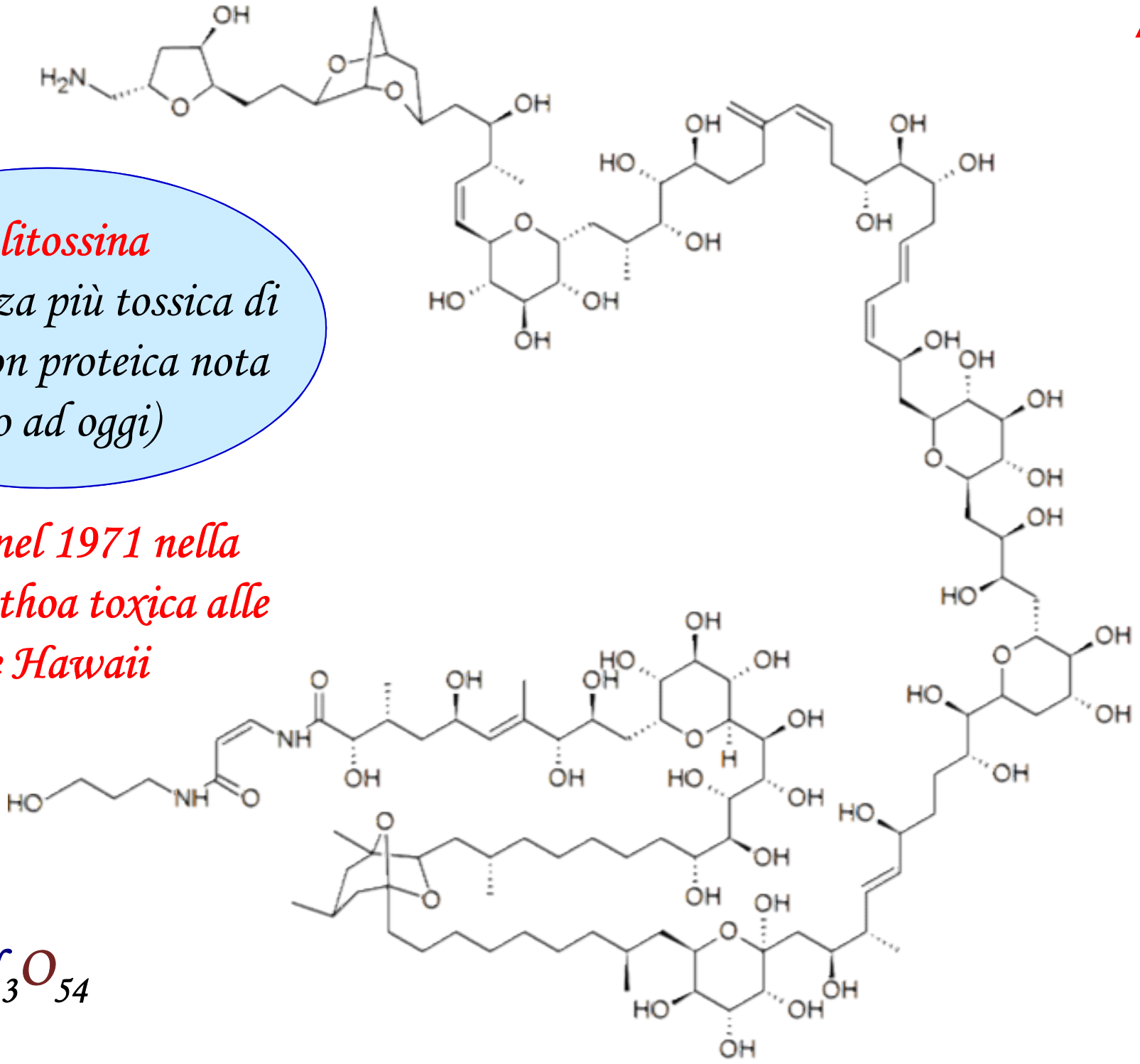
Maitotoxin was named from the ciguatera fish *Ctenochaetus striatus* (called "maito" in Tahiti) from which maitotoxin was isolated for the first time. It was later shown that maitotoxin is actually produced by *Gambierdiscus toxicus*.

Gambierdiscus toxicus
(dinoflagellato)

Palitossina

(la sostanza più tossica di natura non proteica nota sino ad oggi)

scoperta nel 1971 nella specie Palythoa toxica alle isole Hawaii



$C_{129}H_{223}N_3O_{54}$

La potenza dei veleni è misurata utilizzando LD_{50} (cioè la dose che, somministrata in una sola volta, è in grado di uccidere la metà di un gruppo di cavie dopo un'ora).

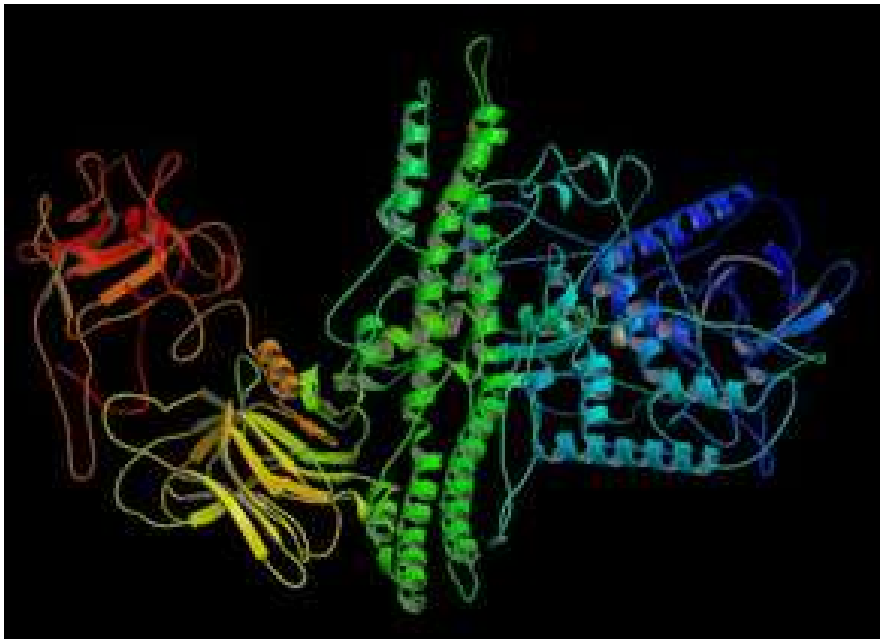
I più potenti veleni dei serpenti hanno un LD_{50} di 25 microgrammi per chilogrammo di peso corporeo.

Per la tetrodotossina, il valore di LD_{50} è di 8 microgrammi per chilogrammo,

per la batracotossina, il veleno dalla pelle delle rane dal dardo, è di 2-7 microgrammi,

per la palitossina, è 0.3 microgrammi (o 300 nanogrammi).

Tossina Botulinica



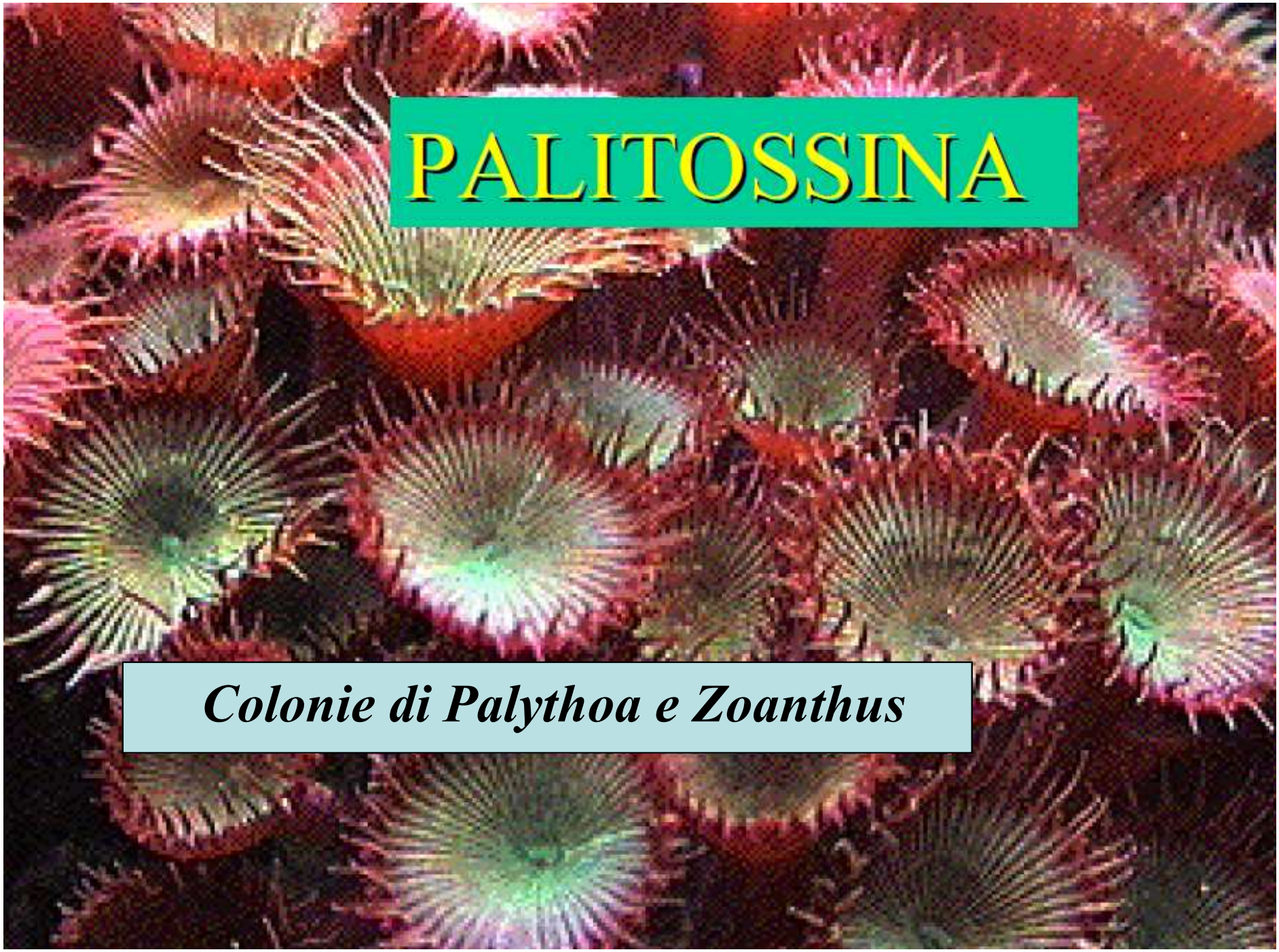
Botulinum toxin is the most toxic substance known to man. It takes only a small amount of botulinum to kill a human.

The lethal dose of botulinum is estimated to be 70 micrograms for an adult human (by comparison, the estimated lethal dose of cyanide is 200,000 micrograms). Botulinum toxin is produced by a bacteria called Clostridium botulinum.

People are exposed to this poison when they eat contaminated food, or if the bacteria gets into a deep wound (the sickness that results from this toxin is called botulismo).

Botulism can cause paralysis of muscles, including the ones that we use to breathe!

LD_{50} 1.3–2.1 ng/kg intravenoso o intramuscolare e 10–13 ng/kg per inalazione

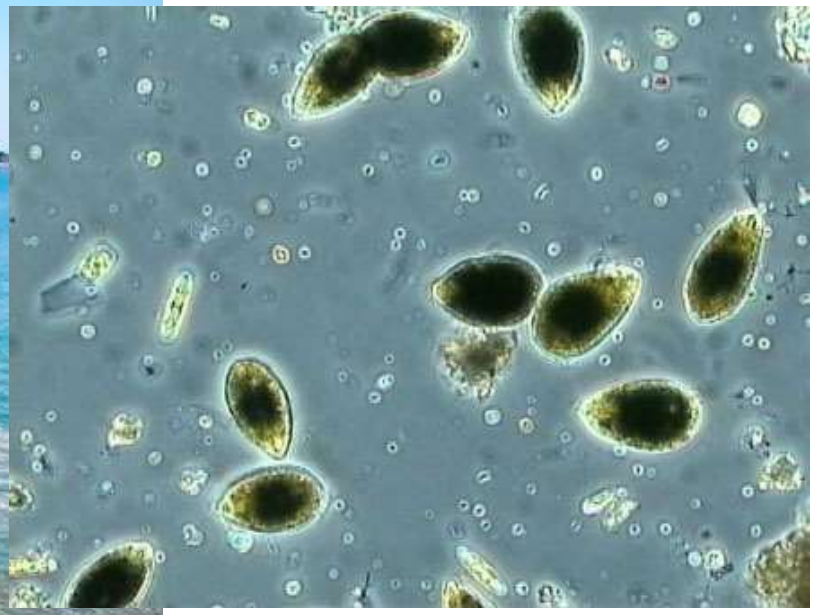

PALITOSSINA
Colonie di Palythoa e Zoanthus

Oceano Pacifico - Polinesia

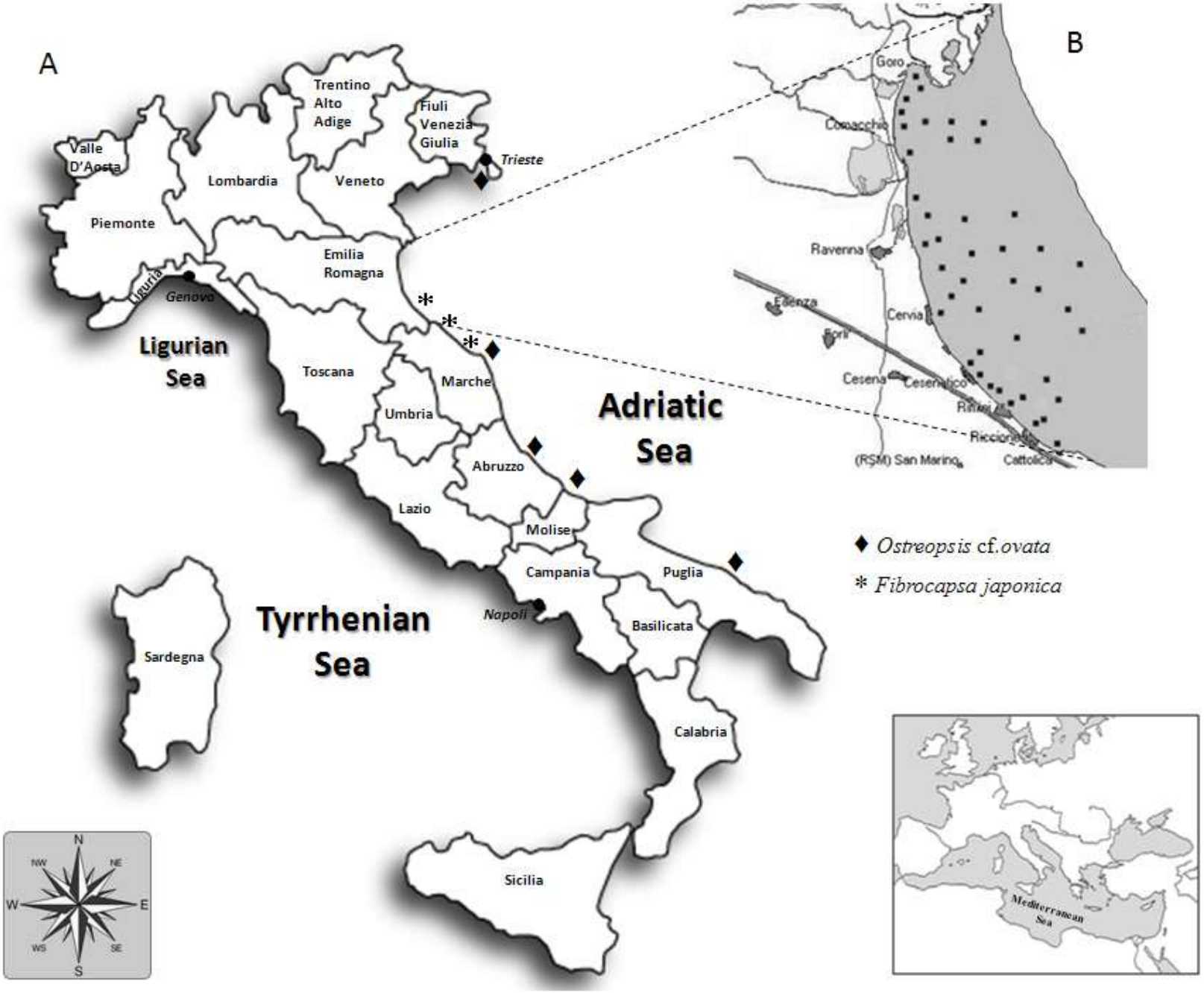
Caraibi


Golfo del Messico
L'Avana
Pinar del Río
BAHAMAS
Santa Clara
OCEANO ATLANTICO
CUBA
Las Tunas
Santiago de Cuba
Campeche
SSICO
CAYMAN
GRANDI ANTILLE
HAITI
Santiago
San Juan
ANGUILLA
Basseterre
Saint John's
BELIZE
GIAMAICA
Santo Domingo
PICCOLE ANTILLE
GUADALUPA
HONDURAS
Fort-de-France
DOMINICA
MARTINICA
Guatemala
SAINT LUCIA
Mar dei Caraibi
(Mar delle Antille)
SAINT VINCENT E GRENADINE
ARUBA
Saint George's
GRENADA
NICARAGUA
Riohacha
Barranquilla
Maracaibo
Caracas
Port-of-Spain
San José
Cartagena
Barquisimeto
Valencia
Maturín
COSTA RICA
Panamá
Montería
Mérida
Barinas
Ciudad Guayana

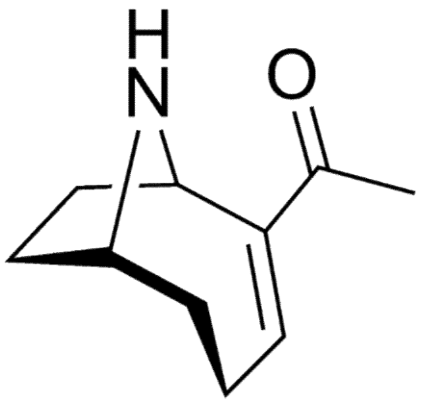
Ostreopsis ovata



La fioritura dell'alga può causare un'intossicazione i cui sintomi sono irritazione delle mucose respiratorie e congiuntivali, con conseguente raffreddore, difficoltà respiratorie (tosse, respiro sibilante) e febbre.


A
B
Trentino Alto Adige
Fiuli Venezia Giulia
Valle D'Aosta
Lombardia
Veneto
Trieste
Piemonte
Emilia Romagna
Liguria
Genova
Ligurian Sea
Toscana
Marche
Umbria
Adriatic Sea
Abruzzo
Lazio
Molise
Campania
Puglia
Napoli
Basilicata
Sardegna
Tyrrhenian Sea
Calabria
Sicilia
Goro
Comacchio
Ravenna
Cervia
Cesena
Cesenatico
Rimini
Riccione
(RSM) San Marino
Cattolica
♦ Ostreopsis cf.ovata
* Fibrocapsa japonica
N
NW
NE
W
E
WS
SE
S
Mediterranean Sea

Tossine di natura diversa



Anatossina-a

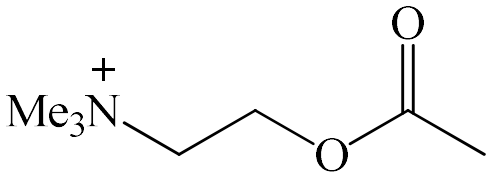
(cianobatteri)

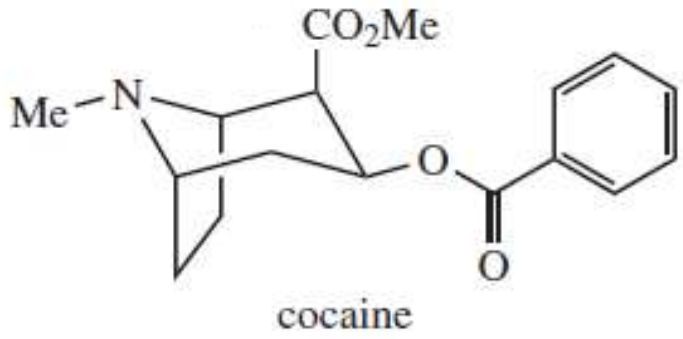
Anatoxin-a was first discovered by P.R Gorham in the early 1960's, after several heads of cattle died as a result of drinking water from Saskatchewan Lake in Canada, which contained toxic algal blooms.

It was later isolated (1972) by J.P. Devlin from the cyanobacteria Anabaena flos aquae.

Symptoms of anatoxin exposure include loss of coordination, convulsions and death by respiratory paralysis.

Agonista dell'acetilcolina nei confronti dei recettori nicotinici





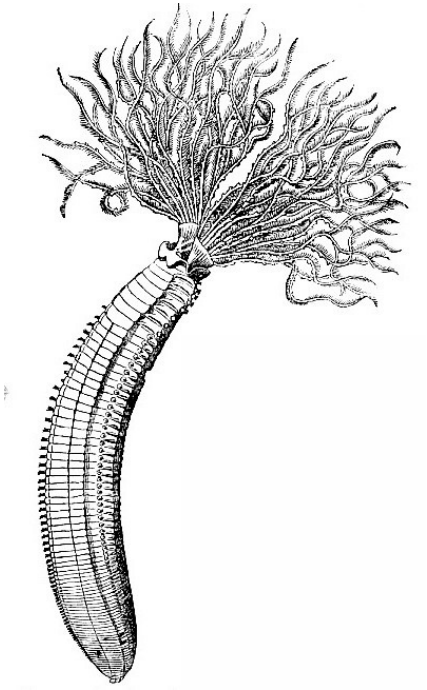
cocaine

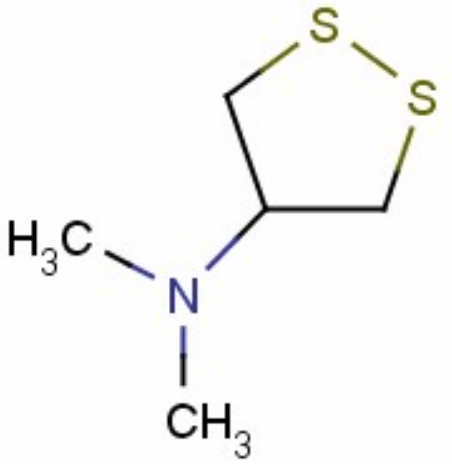
Tossine di natura diversa

Nereistossina

Lumbriconereis heteropoda Marenzeller 1879 (Marine Worm)

Kingdom: Animalia
Phylum: Annelida
Class: Polychaeta
Order: Eunicida
Family: Lumbrineridae





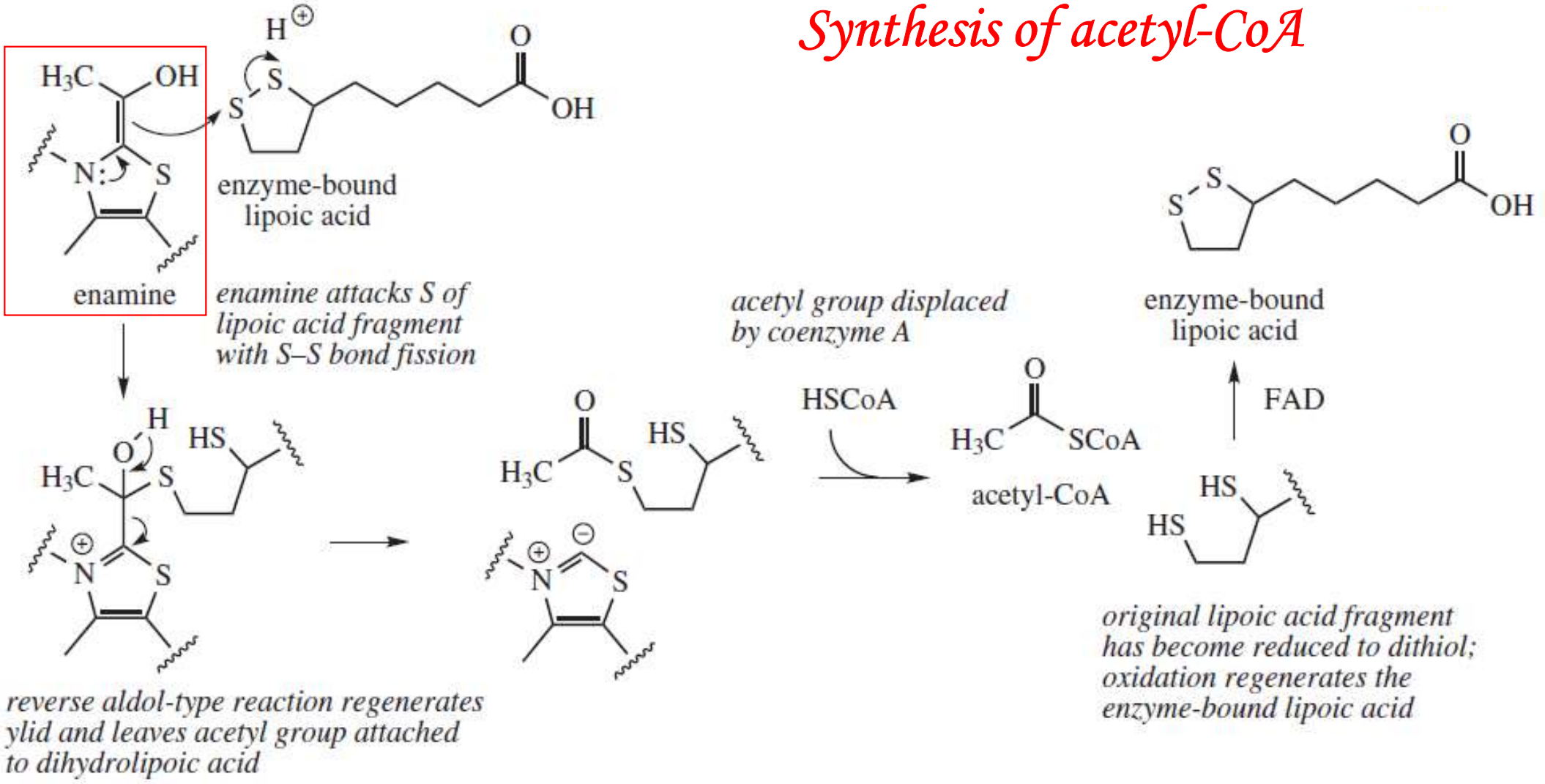
La nereistossina si sostituisce all'acido lipoico, bloccando la sintesi dell'acetil-CoA catalizzata dalla vitamina B_1

Vitamina B_1

Decarboxylation of α-keto acids

pyruvic acid → acetyl-CoA (pyruvate dehydrogenase)

Synthesis of acetyl-CoA



Sostanze Organiche Naturali di origine marina

….non solo tossine!

Alghe

Utilizzate nella dieta delle popolazioni costiere fin dalla notte dei tempi

Cina

Cina, 600 a.C.: "I vegetali marini sono una delicatezza degna di un imperatore"

Giappone

Galles

Caraibi

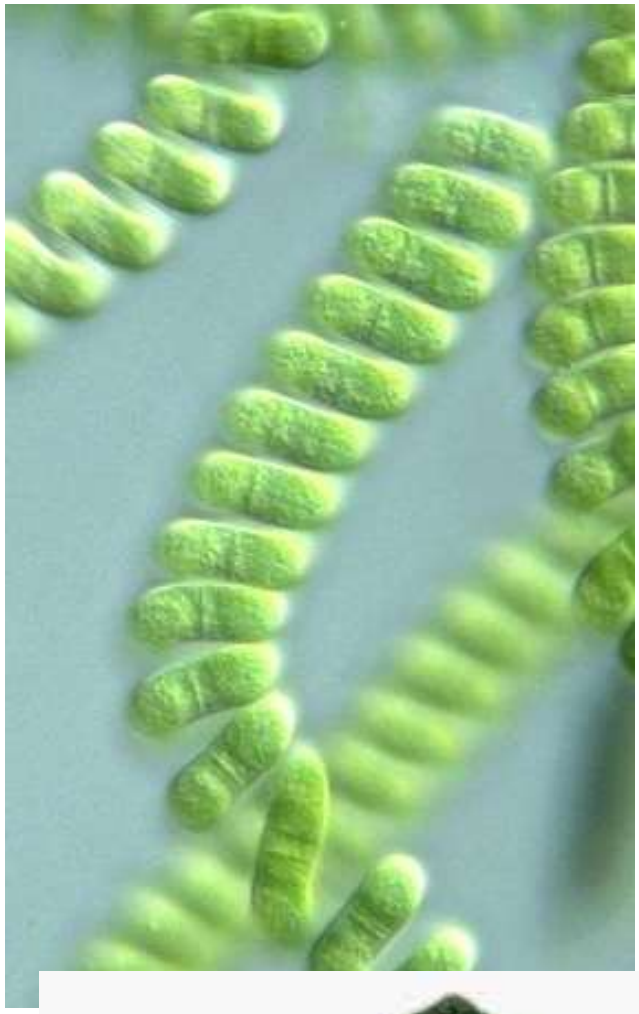
Irlanda

Alaska

Canada

Sicilia

Ricche di vitamine (A, C, complesso B), sali minerali, ammino acidi essenziali, antiossidanti…..



SPIRULINA, UNA PICCOLA ALGA PER COMBATTERE IL COLESTEROLO

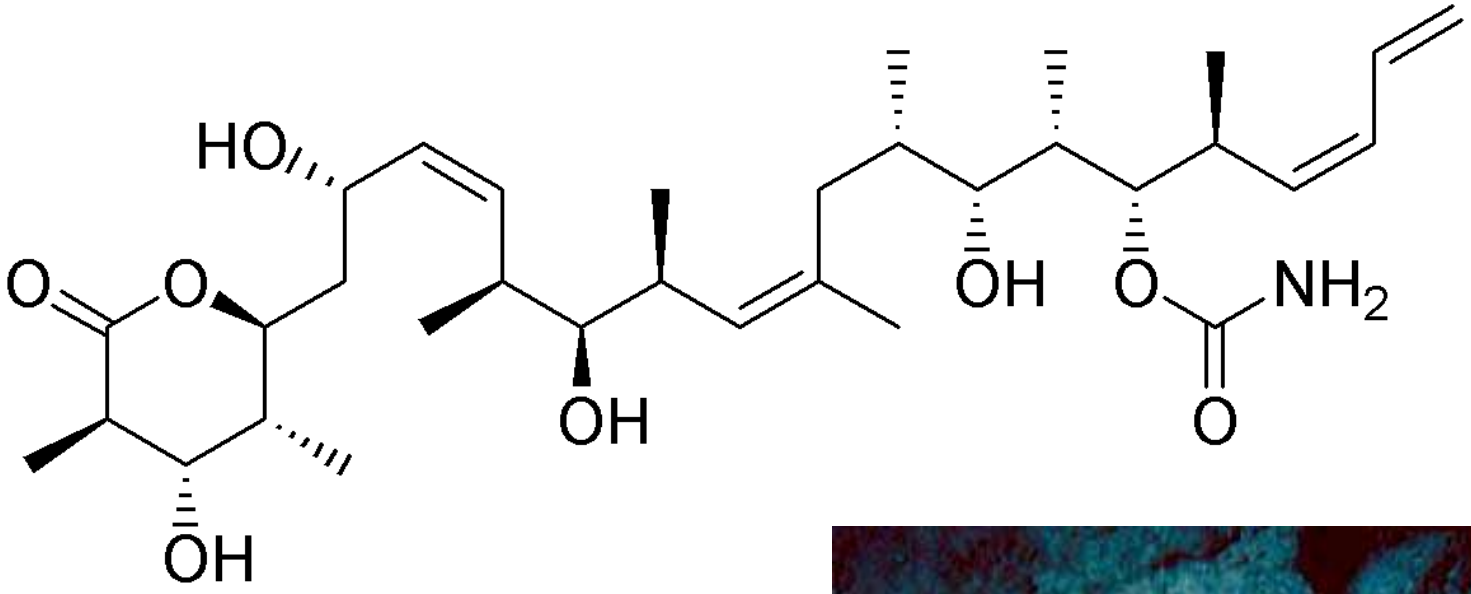
Microscopiche alghe azzurro-verdi, contenenti un pigmento azzurro (ficocianina), così chiamate per via dei filamenti arrotolati a mo' di spirale. Di forte potere nutritivo, oltre a proprietà antiossidanti e antinfiammatorie, possono avere benefici effetti nella prevenzione dei disturbi cardiovascolari.

La *Spirulina maxima* ha dimostrato che può far diminuire la pressione arteriosa, i trigliceridi e il colesterolo "cattivo" LDL, riducendone anche l' ossidazione, che gioca un importante ruolo nella formazione della placca arteriosclerotica. Sembra avere anche un effetto di prevenzione della SLA.

Gli Aztechi la chiamavano tecuilat e la consumavano durante i lunghi tragitti per recuperare le forze

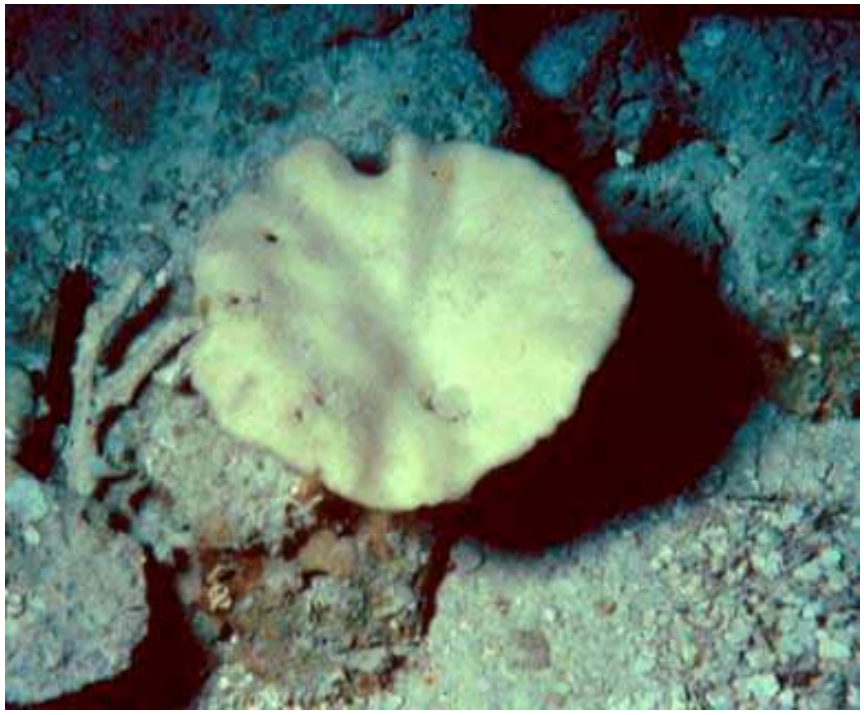
Aztechi: 1300 – 1500 d.C.

Gli Aztechi consideravano il cacao come un dono del loro re QUETZALCOATL ("serpente piumato")

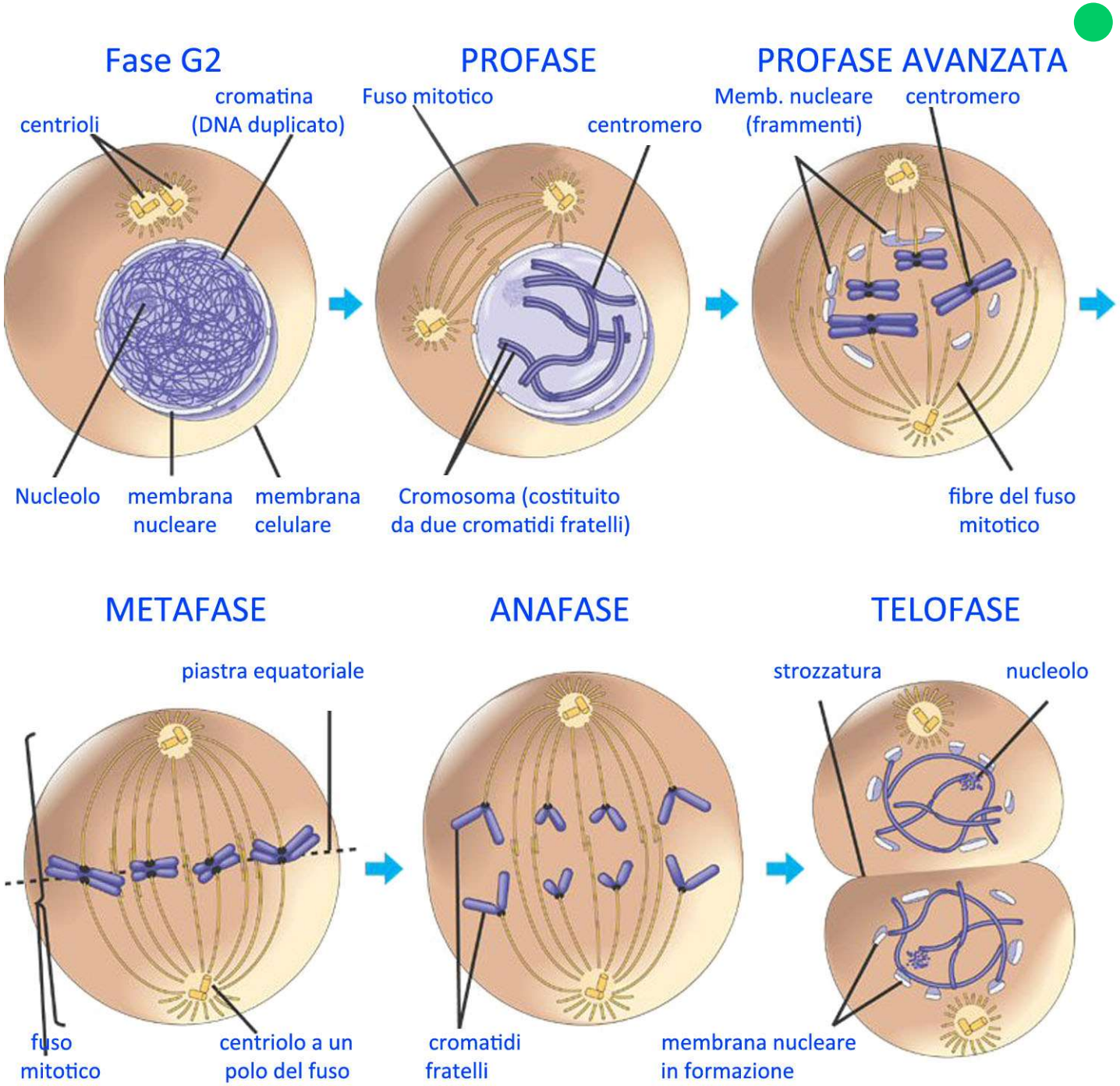


Discodermolide was isolated from the sponge *Discodermia dissoluta*.

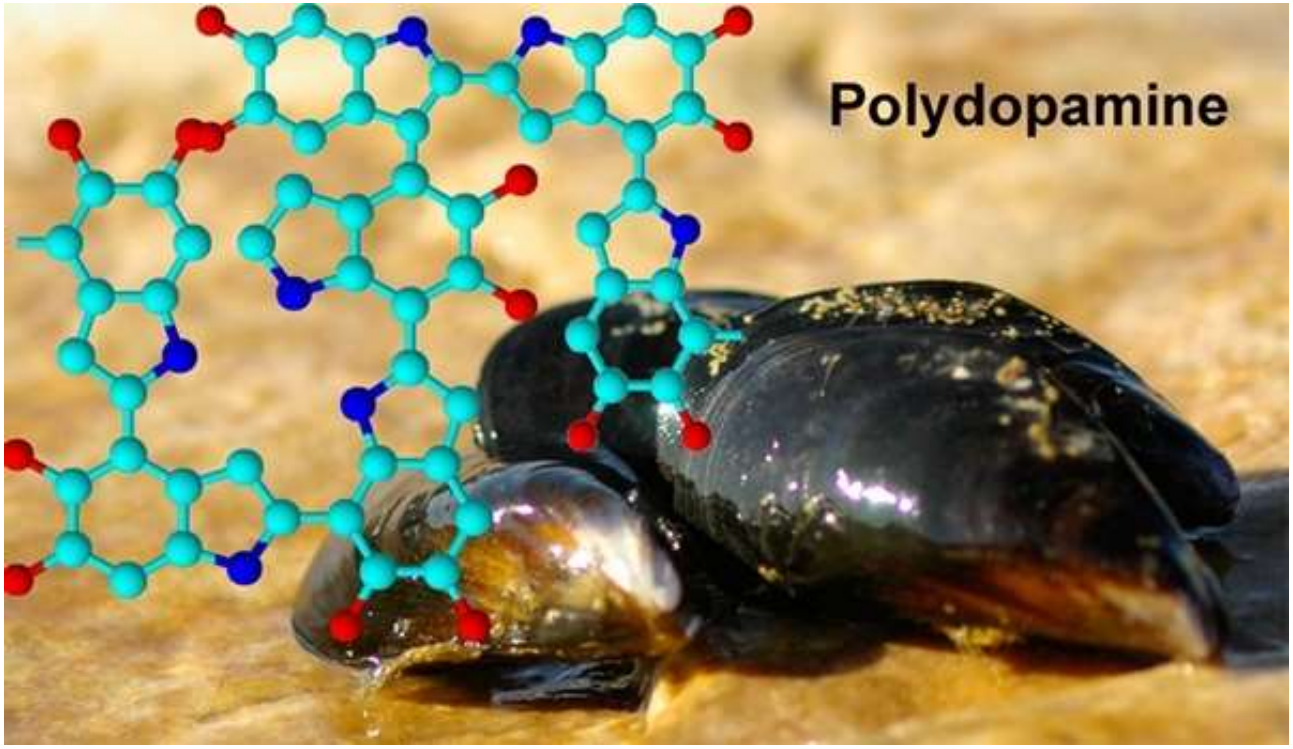
This compound is a potent antitumor agent.



Discodermolide inhibits the proliferation of human cells by arresting the cell cycle in G2- and M-phase. It hyper-stabilizes microtubules during cell division. Hyper-stabilization of the mitotic spindle causes cell cycle arrest and **cell death by apoptosis**. Discodermolide competes with **paclitaxel** for microtubule binding, but with higher affinity, and is also effective in paclitaxel-resistant cancer cells.



2014 Chem. Rev. (114) 5057-5115

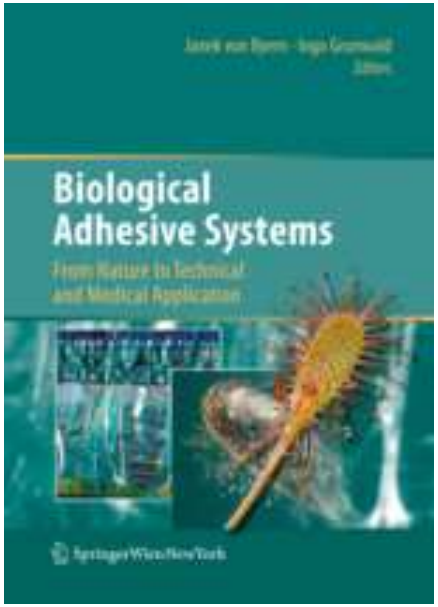


The observation of the adhesion of invertebrate mussels to solid surfaces led to an **important advance in the field of materials science**. Mussels can strongly attach to diverse substrates with high binding strength, even on wet surfaces.

Scientists have long investigated the wet adhesion property of mussels.

It was found that 3,4-dihydroxy-L-phenylalanine (DOPA) and lysine-enriched proteins near the plaque−substrate interface are the major origins of the extraordinarily robust adhesion.

On the basis of these findings, polydopamine, with a molecular structure similar to that of DOPA, moved into the spotlight as a novel coating material in 2007.



2011

Living With Ciguatera Fish Poisoning

My real life experience of eating fresh fish!

Christine Bruce

GIOVANNI SCAPAGNINI

2007

UN OCEANO DI SALUTE

TRA SCIENZA E AVVENTURA,
LE RISORSE
PER IL NOSTRO FUTURO

Sperling & Kupfer Editori