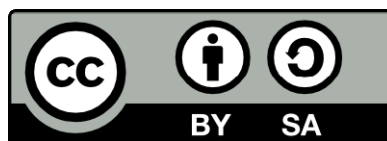




**Optimización de ensayos celulares para la detección de toxinas marinas responsables de intoxicaciones alimentarias. Aplicación en extractos lipofílicos de muestras naturales de *Mytilus galloprovincialis***

Elisabet Cañete Ortiz



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## **REFERENCIAS**



## 6 REFERENCIAS

- Alfonso, A., Alfonso, C., 2008. Pharmacology and mechanism of action: biological detection. Botana, L.M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 315-328.
- Alfonso, A., de la Rosa, L., Vieytes, M.R., Yasumoto, T., Botana, L.M., 2003. Yessotoxin, a novel phycotoxin, activates phosphodiesterase activity effect of yessotoxin on camp levels in human lymphocytes *Biochemical Pharmacology* 65, 193-208.
- Alfonso, A., Román, Y., Vieytes, M.R., Ofuji, K., Satake, M., Yasumoto, T., 2005. Azaspiracid-4 inhibits  $Ca^{2+}$  entry by stored operated channels in human t lymphocytes. *Biochemical Pharmacology* 69 (11), 1627-1636.
- Alfonso, A., Vieytes, M.R., Ofuji, K., Satake, M., Nicolaou, K.C., Frederick, M.O., Botana, L.M., 2006. Azaspiracids modulate intracellular ph levels in human lymphocytes. *Biochemical and Biophysical Research Communications* 346, 1091-1099.
- Allingham, J.S., Miles, C.O., Rayment, I., 2007. A structural basis for regulation of actin polymerization by pectenotoxins. *Journal of Molecular Biology* 371 (4), 959-970.
- Aonuma, S., Ushijima, T., Nakayasu, M., Shima, H., Sugimura, T., Nagao, M., 1991. Mutation induction by okadaic acid, a protein phosphatase inhibitor in CHL cells, but not in *S. Typhimurium*. *Mutation research* 250 (1-2), 375-381.
- Aune, T., Larsen, S., Aasen, J.A.B., Rehmann, N., Satake, M., Hess, P., 2007. Relative toxicity of dinophysistoxin-2 (dtx-2) compared with okadaic acid, based on acute intraperitoneal toxicity in mice *Toxicon* 49, 1-7.
- Aune, T., Sørby, R., Yasumoto, T., Ramstad, H., Landsverk, T., 2002. Comparison of oral and intraperitoneal toxicity of yessotoxin towards mice. *Toxicon* 40, 77-82.
- Aune, T., Yasumoto, T., Engeland, E., 1991. Light and scanning electron microscopic studies on effect of marine algal toxins toward freshly prepared hepatocytes. *Journal of Toxicology and Environmental Health* 34, 1-9.
- Beani, L., Bianchi, C., Guerrini, F., Marani, L., Pistocchi, R., Tomasini, M.C., Ceredi, A., Milandri, A., Poletti, R., Boni, L., 2000. High sensitivity bioassay of paralytic (PSP) and amnesic (ASP) algal toxins based on the fluorimetric detection of  $[Ca^{2+}]_i$  in rat cortical primary cultures. *Toxicon* 38, 1283-1297.
- Bellocci, M., Ronzitti, G., Milandri, A., Melchiorre, N., Grillo, C., Poletti, R., Yasumoto, T., Rossini, G.P., 2008. A cytolytic assay for the measurement of palytoxin based on a cultured monolayer cell line. *Analytical Biochemistry* 374, 48-55.
- Berman, F.W., Muray, T.F., 1997. Domoic acid neurotoxicity in culture cerebellar granule neurons is mediated predominantly by nmda receptors that are activate as a consequence of excitatory amino acid release. *Journal of Neurochemistry* 69, 693-703.

Bialojan, C., Takai, A., 1988. Inhibitory effect of a marine-sponge toxin, okadaic acid, on protein phosphatases. Specificity and kinetics *Biochemical Journal* 256, 283-290.

Botana, L.M., 2008. Seafood and freshwater toxins: pharmacology, physiology, and detection. Botana, L.M. (Eds.). CRC Press.

Bottein Dechraoui, M.Y., Naar, J., Pauillac, S., Legrand, A.M., 1999. Ciguatoxins and brevetoxins, neurotoxic polyether compounds active on sodium channels. *Toxicon* 37, 125-143.

Bottein Dechraoui, M.Y., Tiedeken, J.A., Persad, R., Wang, Z., Granade, H.R., Dickey, R.W., Ramsdell, J.S., 2005. Use of two detection methods to discriminate ciguatoxins from brevetoxins: application to great barracuda from florida keys. *Toxicon* 46, 261-270.

Caillaud, A., de la Iglesia, P., Darius, H.T., Pauillac, S., Aligizaki, K., Fraga, S., Chinain, M., Diogène, J., 2010. Update on methodologies available for ciguatoxin determination: perspectives to confront the onset of ciguatera fish poisoning in europe. *Marine Drugs* 8 (6), 1838-1907.

Catterall, W.A., Gainer, M., 1985. Interaction of brevetoxin a with a new receptor site on the sodium channel. *Toxicon* 23 (3), 497-504.

Catterall, W.A., Morrow, C.S., Hartshorne, R.P., 1979. Neurotoxins binding to receptor sites associated with voltage-sensitive sodium channels in intact, lysed, and detergent-solubilized brain membranes. *The Journal of Biological Chemistry* 254 (22), 11379-11387.

Cestèle, S., Catterall, W.A., 2000. Molecular mechanisms of neurotoxin action on voltage-gated sodium channels. *Biochimie* 82, 883-892.

Ciminiello, P., Dell'Aversano, C., Fattorusso, E., Forino, M., Magno, G.S., Tartaglione, L., Grillo, C., Melchiorre, N., 2006. The genoa 2005 outbreak. Determination of putative palytoxin in mediterranean *ostreopsis ovata* by a new liquid chromatography tandem mass spectrometry method. *Analytical Chemistry* 78 (17), 6153-6159.

Croci, L., Stacchini, A., Cozzi, L., Ciccaglioni, G., Mazzei, F., Botrè, F., Toti, L., 2001. Evaluation of rapid methods for the determination of okadaic acid on mussels. *Journal of Applied Microbiology* 90, 73-77.

Cuyper, E., Abdel-Mottaleb, Y., Kopljar, I., Rainier, J.D., Raes, A.L., Snyders, D.J., Tytgat, J., 2008. Gambierol, a toxin produced by the dinoflagellate *gambierdiscus toxicus*, is a potent blocker of voltage-gated potassium channels. *Toxicon* 51 (6), 974-983.

Cha, K., Christ, W.J., Finan, J.M., Fujioka, H., Kishi, Y., Klein, L.L., Ko, S.S., Leder, J., McWhorter Jr., W.W., Pfaff, K.-P., Yonaga, M., 1982. Stereochemistry of palytoxin. 4. Complete structure. *Journal of the American Chemical Society*, 7369-7371.

Dakshinamurti, K., Sharma, S.K., Geiger, D.J., 2003. Neuroprotective actions of pyridoxine. *Biochimica et Biophysica Acta* 1647, 225-229.

- Dickey, R.W., 2008. Ciguatera toxins: chemistry, toxicology, and detection. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 479-500.
- Dickey, R.W., Jester, E., Granade, R., Mowdy, D., Moncreiff, C., Rebarchik, D., Robl, M., Musser, S., Poli, M., 1999. Monitoring brevetoxins during a *Gymnodinium breve* red tide: comparison of sodium channel specific cytotoxicity assay and mouse bioassay for determination of neurotoxic shellfish toxins in shellfish extracts. *Natural Toxins* 7, 157-165.
- Diogène, G., Fessard, V., Dubreuil, A., Puiseux-Dao, S., 1995. Comparative studies of the actin cytoskeleton response to maitotoxin and okadaic acid. *Toxicology in Vitro* 9 (1), 1-10.
- Doucette, T.A., Tasker, A., 2008. Domoic acid: detection methods, pharmacology, and toxicology. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 397-430.
- Dragunow, M., Trzoss, M., Brimble, M.A., Cameron, R., Beuzenberg, V., Holland, P., Mountfort, D., 2005. Investigations into the cellular actions of the shellfish toxin gymnodimine and analogues. *Environmental Toxicology and Pharmacology* 20 (2), 305-312.
- Echigoya, R., Rhodes, L., Oshima, Y., Satake, M., 2005. The structures of five new antifungal and hemolytic amphidinol analogs from *Amphidinium carterae* collected in New Zealand. *Harmful Algae* 4 (2), 383-389.
- EFSA, 2008a. Scientific opinion of the panel on contaminants in the food chain on a request from the European Commission on marine biotoxins in shellfish - okadaic acid and analogues. *The EFSA Journal* 589, 1-62.
- EFSA, 2008b. Scientific opinion of the panel on contaminants in the food chain on a request from the European Commission on marine biotoxins in shellfish - yessotoxin group. *The EFSA Journal* 907, 1-62.
- EFSA, 2009a. Scientific opinion of the panel on contaminants in the food chain on a request from the European Commission of marine biotoxins in shellfish - saxitoxin group. *The EFSA Journal* 1019, 1-76.
- EFSA, 2009b. Scientific opinion of the panel on contaminants in the food chain on a request from the European Commission on marine biotoxins in shellfish - azaspiracids. *The EFSA Journal* 723, 1-52.
- EFSA, 2009c. Scientific opinion of the panel on contaminants in the food chain on a request from the European Commission on marine biotoxins in shellfish - pectenotoxin group. *The EFSA Journal* 1109, 1-47.
- European Union Commission Regulation, 2004. Ec 853/2004. *Official Journal of the European Union* L 226, 22-82.
- European Union Commission Regulation, 2005. Ec 2074/2005. *Official Journal of the European Union* L 338, 27-59.
- European Union Commission Regulation, 2011. Ec 15/2011. *Official Journal of the European Union* L 6, 3-6.

Fairey, E.R., Edmunds, J.S.G., Ramsdell, J.S., 1997. A cell-based assay for brevetoxins, saxitoxins, and ciguatoxins using a stably expressed c-fos-luciferase reporter gene. *Analytical Biochemistry* 251, 129-132.

FAO/IOC/WHO, 2004. Report of the joint fao/ioc/who ad hoc expert consultation on biotoxins in bivalve molluscs.

Fernández-Sánchez, M.T., Novelli, A., 1993. Basic fibroblast growth factor protects cerebellar neurons in primary culture from NMDA and non-NMDA receptor mediated neurotoxicity. *FEBS Letters* 335 (1), 124-131.

Fernández, M.T., Zitko, V., Gascón, S., Novelli, A., 1991. The marine toxin okadaic acid is a potent neurotoxin for cultured cerebellar neurons. *Life Sciences* 49, 157-162.

Fessard V., D.G., Dubreil A., Quod j.P., Durand-Clément M., Legay C., Puiseux-Dao S.,, 1994. Selection of cytotoxic responses to maitotoxin and okadaic acid and evaluation of toxicity of dinoflagellate extracts. *Natural Toxins* 2, 322-328.

Fladmark, K.E., Serres, M.H., Larsen, N.L., Yasumoto, T., Aune, T., Doskeland, S.O., 1998. Sensitive detection of apoptogenic toxins in suspension cultures of rat and salmon hepatocytes. *Toxicon* 36 (8), 1101-1114.

Flanagan, A.F., Callanan, K.R., Donlon, J., Palmer, R., Forde, A., Kane, M., 2001. A cytotoxicity assay for the detection and differentiation of two families of shellfish toxins. *Toxicon* 39 (7), 1021-1027.

Frelin, C., Van Renterghem, C., 1995. Palytoxin. Recent electrophysiological and pharmacological evidence for several mechanisms of action. *General Pharmacology: The Vascular System* 26 (1), 33-37.

Gallacher, S., Birkbeck, T.H., 1992. A tissue culture assay for direct detection of sodium channel blocking toxins in bacterial culture supernates. *FEMS Microbiology Letters* 92 (1), 107-107.

Gill, S., Murphy, M., Clausen, J., Richard, D., Quilliam, M., MacKinnon, S., LaBlanc, P., Mueller, R., Pulido, O., 2003. Neural injury biomarkers of novel shellfish toxins, spirolides: a pilot study using immunochemical and transcriptional analysis. *Neurotoxicology* 24 (4-5), 593-604.

Gusovsky, F., Daly, J.W., 1990. Maitotoxin: a unique pharmacological tool for research on calcium-dependent mechanisms. *Biochemical Pharmacology* 39 (11), 1633-1639.

Habermann, E., 1989. Palytoxin acts through Na<sup>+</sup>, k<sup>+</sup> -ATPase. *Toxicon* 27 (11), 1171-1187.

Habermann, E., Chhatwal, G.S., 1982. Ouabain inhibits the increase due to palytoxin of cation permeability of erythrocytes. *Naunyn Schmiedeberg's Archives of Pharmacology* 319, 101-107.

Hamano, Y., Kinoshita, Y., Yasumoto, T., 1985. Suckling mice assay for diarrhetic shellfish toxins. *Toxic Dinoflagellates*, 383-388.

Hayashi, R., Saito, H., Okumura, M., Kondo, F., 2006. Cell bioassay for paralytic shellfish poisoning (PSP): comparison with postcolumn derivatization liquid

chromatographic analysis and application to the monitoring of PSP in shellfish. *Journal of Agricultural and Food Chemistry* 54 (2), 269-273.

Hess, P., Aasen, J.A.B., 2007. Chemistry, origins, and distribution of yessotoxin and its analogues. Luis, M.B. (Eds.). *Phycotoxins: chemistry and Biochemistry*. 187-202.

Hess, P., Grune, B., Anderson, D.B., Aune, T., Botana, L.M., Caricato, P., Egmond, P.V., Halder, M., Hall, S., Lawrence, J.F., Moffat, C., Poletti, R., Richmond, J., Rossini, G.P., Seamer, C., Serratosa Vilageliu, J., 2006. Three Rs approaches in marine biotoxin testing. The report and recommendations of a joint ECVAM/DG sanco workshop (ECVAM workshop 55). *Alternatives to Laboratory Animals* 34, 193-224.

Hirsh, J.K., Wu, C.H., 1997. Palytoxin-induced single-channel currents from the sodium pump synthesized by *in vitro* expression. *Toxicon* 35 (2), 169-176.

Huynh-Delerme, C., Fessard, V., Kiefer-Biasizzo, H., Puiseux-Dao, S., 2003. Characteristics of okadaic acid-induced cytotoxic effects in Cho k1 cells. *Environmental Toxicology* 18 (6), 383-394.

Ito, E., Suzuki, T., Oshima, Y., Yasumoto, T., 2008. Studies of diarrhetic activity on pectenotoxin-6 in the mouse and rat *Toxicon* 51, 707-716.

Jeglitsch, G., Rein, K., Baden, D.G., Adams, D.J., 1998. Brevetoxin-3 (PBTX-3) and its derivatives modulate single tetrodotoxin-sensitive sodium channels in rat sensory neurons. *The Journal of Pharmacology and Experimental Therapeutics* 284 (2), 516-525.

Jellett, J.F., Marks, L.J., Stewart, J.E., Dorey, M.L., Watson-Wright, W., Lawrence, J.F., 1992. Paralytic shellfish poison (saxitoxin family) bioassays: automated endpoint determination and standardization of the *in vitro* tissue culture bioassay, and comparison with the standard mouse bioassay. *Toxicon* 30 (10), 1143-1156.

Jellett, J.F., Wood, C.R., Belland, E.R., Doucette, L.I. The Mist<sup>tm</sup> shippable cell bioassay kits for PSP: an alternative to the mouse bioassay. VIII International Conference on Harmful Algae. 1998, Vigo.

Katsuo, D., Kim, D., Yamaguchi, K., Matsuyama, Y., Oda, T., 2007. A new simple screening method for the detection of cytotoxic substances produced by harmful red tide phytoplankton. *Harmful Algae* 6 (6), 790-798.

Kogure, K., Tamplin, M.L., Simidu, U., Colwell, R.R., 1988. A tissue culture assay for tetrodotoxin, saxitoxin and related toxins. *Toxicon* 26 (2), 191-197.

Landsberg, J.H., 2002. The effects of harmful algal blooms on aquatic organisms *Reviews in Fisheries Science* 10 (2), 113-390.

Larm, J.A., Beart, P.M., Cheung, N.S., 1997. Neurotoxin domoic acid produces cytotoxicity via kainate- and ampa-sensitive receptors in cultured cortical neurones. *Neurochemistry International* 31 (5), 677-682.

Ledreux, A., Krys, S., Bernard, C., 2009. Suitability of the Neuro-2a cell line for the detection of palytoxin and analogues (neurotoxic phycotoxins). *Toxicon* 53, 300-308.



Lee Jong-Soo, I.T., Fraga S., Dahl E., Hovgaard P., Yasumoto T., 1989. Determination of diarrhetic shellfish toxins in various dinoflagellate species. *Journal of Applied Phycology* 1, 147-152.

Leira, F., Alvarez, C., Cabado, A.G., Vieites, J.M., Vieytes, M.R., Botana, L.M., 2003. Development of a F-actin-based live-cell fluorimetric microplate assay for diarrhetic shellfish toxins. *Analytical Biochemistry* 317 (2), 129-135.

Leira, F., Alvarez, C., Vieites, J.M., Vieytes, M.R., Botana, L.M., 2001. Study of cytoskeletal changes induced by okadaic acid in BE(2)-M17 cells by means of a quantitative fluorimetric microplate assay. *Toxicology in Vitro* 15, 277-282.

Leira, F., Vieites, J.M., Vieytes, M.R., Botana, L.M., 2000. Characterization of 9h-(1,3-dichloro-9,9-dimethylacridin-2-ona-7-yl)-phosphate (DDAO) as substrate of PP-2a in a fluorimetric microplate assay for diarrhetic shellfish toxins (DSP). *Toxicon* 38 (12), 1833-1844.

LePage, K.T., Dickey, R.W., Gerwick, W.H., Jester, E.L., Murray, T.F., 2005. On the use of neuro-2a neuroblastoma cells versus intact neurons in primary culture in neurotoxicity studies. *Critical Reviews in Neurobiology* 17 (1), 27-50.

Lin, Y., Risk, M., Ray, S.M., Van Engen, D., Clardy, J., Golik, J., James, J.C., Nakanishi, K., 1981. Isolation and structure of brevetoxin b from the "Red tide" Dinoflagellate *ptychodiscus brevis* (gymnodinium breve). *Journal of the American Chemical Society* 103 (22), 6773 - 6775.

Lombet, A., Bidard, J.N., Lazdunski, M., 1987. Ciguatoxin and brevetoxins share a common receptor-site on the neuronal voltage-dependent Na<sup>+</sup> channel. *FEBS Letters*. 219 (2), 355-359.

Louzao, M.C., Cagide, E., Yotsu-Yamashita, M., Sasaki, M., 2008. Polycavernosides and gambierol: chemistry, pharmacology, toxicology, and detection. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 597-628.

Louzao, M.C., Vieytes, M.R., Baptista de Sousa, J.M.V., Leira, F., L.M., B., 2000. A fluorimetric method based on changes in membrane potential for screening paralytic shellfish. *Analytical Biochemistry* 289, 246-250.

Louzao, M.C., Vieytes, M.R., Yasumoto, T., Botana, L.M., 2004. Detection of sodium channel activators by a rapid fluorimetric microplate assay. *Chemical Research in Toxicology* 17, 572-578.

Malaguti, C., Milandri, A., Poletti, R., Rossini, G.P., 2002. Cytotoxic responses to unfractionated extracts from digestive glands of mussels. *Toxicon* 40, 573-578.

Manger R.L., L.S., Lee S. Y., Hungerford J.M., Hokama Y., Dickey R.W., Granade H.R., Lewis R., Yasumoto T., Wekell M.M. Cell bioassay for sodium channel effectors. *Sixième Conférence Internationale sur le Phytoplancton Toxique*. 1993, Nantes.

Manger, R.L., Leja, S., Lee, S.Y., Hungerford, J.M., Hokama, Y., Dickey, R.W., Granade, H.R., Lewis, R., Yasumoto, T., Wekell, M.M. Cell bioassay for sodium channel effectors. *Sixième Conférence Internationale sur le Phytoplancton Toxique*. 1993a, Nantes.

Manger, R.L., Leja, S., Lee, S.Y., Hungerford, J.M., Hokama, Y., Dickey, R.W., Granade, H.R., Lewis, R., Yasumoto, T., Wekell, M.M., 1995. Detection of sodium channel toxins: directed cytotoxicity assays of purified ciguatoxins, brevetoxins, saxitoxins and seafood extracts. *Journal Of AOAC International* 78 (2), 521-527.

Manger, R.L., Leja, S., Lee, S.Y., Hungerford, J.M., Hokama, Y., Wekell, M.M., 1996. Comparative response of human and murine cell lines by cell bioassay to sodium channel active marine toxins and extracts. *Toxicon* 34 (3), 336-337.

Manger, R.L., Leja, S., Lee, S.Y., Hungerford, J.M., Wekell, M.M., 1993b. Tetrazolium-based cell bioassay for neurotoxins active on voltage-sensitive sodium channels: semiautomated assay for saxitoxins, brevetoxins, and ciguatoxins. *Analytical Biochemistry* 214, 190-194.

Matsunaga, K., Nakatani, K., Ishibashi, M., Kobayashi, J., Ohizumi, Y., 1999. Amphidinolide b, a powerful activator of actomyosin atpase enhances skeletal muscle contraction. *Biochimica et Biophysica Acta* 1427, 24-32.

Miles, C.O., Wilkins, A.L., Munday, R., Dines, M.H., Hawkes, A.D., Briggs, L.R., Sandvik, M., Jensen, D.J., Cooney, J.M., Holland, P.T., Quilliam, M.A., Mackenzie, A.L., Beuzenberg, V., Towers, N.R., 2004. Isolation of pectenotoxin-2 from *dinophysis acuta* and its conversion to pectenotoxin-2 seco acid, and preliminary assessment of their acute toxicities. *Toxicon* 43, 1-9.

Molgó, J., Shimahara, T., Legrand, A.M., 1993. Ciguatoxin, extracted from poisonous morays eels, causes sodium-dependent calcium mobilization in NG108-15 neuroblastoma x glioma hybrid cells. *Neuroscience Letters* 158, 147-150.

Munday, R., 2008a. Toxicology of cyclic imines: gymnodimine, spirolides, pinnatoxins, pteriatoxins, prorocontrolide, spiro-prorocentrimine, and symbioimines. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 581-594.

Munday, R., 2008b. Occurrence and toxicology of palytoxins. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 693-714.

Munday, R., Towers, N.R., Mackenzie, L., Beuzenberg, V., Holland, P.T., Miles, C.O., 2004. Acute toxicity of gymnodimine to mice. *Toxicon* 44 (2), 173-178.

Murata, M., Masanori, K., Lee, J.-S., Yasumoto, T., 1987. Isolation and structure of yessotoxin, a novel polyether compound implicated in diarrhetic shellfish poisoning. *Tetrahedron Letters* 28, 5869-5872.

Nasser, B., Moustaid, K., Moukha, S., Mobio, T.A., Essamadi, A., Creppy, E.E., 2008. Evaluation of the cytotoxicity and genotoxicity of extracts of mussels originating from moroccan atlantic coast, in human colonic epithelial cells Caco-2. *Environmental Toxicology* 23 (4), 539-547.

Novelli, A., Kispert, J., Fernández, M.T., Torreblanca, A., Zitko, V., 1992. Domoic acid-containing toxic mussels produce neurotoxicity in neuronal cultures through a synergism between excitatory amino acids. *Brain Research* 577 (1), 41-48.

Ofuji, K., Satake, M., McMahon, T., Silke, J., James, K.J., Naoki, H., Oshima, Y., Yasumoto, T., 1999. Two analogs of azaspiracid isolated from mussels, *mytilus edulis*, involved in human intoxication in Ireland. *Natural Toxins* 7, 99-102.

Okumura, M., Tsuzuki, H., Tomita, B.-I., 2005. A rapid detection method for paralytic shellfish poisoning toxins by cell bioassay. *Toxicon* 46 (1), 93-98.

Onuma, Y., Satake, M., Ukena, T., Roux, J., Chanteau, S., Rasolofonirina, N., Ratsimaloto, M., Naoki, H., Yasumoto, T., 1999. Identification of putative palytoxin as the cause of clupeotoxism. *Toxicon* 37 (1), 55-65.

Oteri, G., Stamatii, A., Zampaglioni, F., Zucco, F., 1998. Evaluation of the use of two human cell lines for okadaic acid and DTX-1 determination by cytotoxicity assays and damage characterization. *Natural Toxins* 6 (5), 197-209.

Paz, B., Daranas, A.H., Norte, M., Riobó, P., Franco, J.M., Fernández, J.J., 2008. Yessotoxins, a group of marine polyether toxins: an overview *Marine Drugs* 6 (2), 73-102.

Pérez-Gómez, A., Ferrero-Gutierrez, A., Novelli, A., Franco, J.M., Paz, B., Fernández-Sánchez, M.T., 2006. Potent neurotoxic action of the shellfish biotoxin yessotoxin on cultured cerebellar neurons. *Toxicological Sciences* 90 (1), 168-177.

Pierotti, S., Malaguti, C., Milandri, A., Poletti, R., Rossini, G.P., 2003. Functional assay to measure yessotoxins in contaminated mussel samples. *Analytical Biochemistry* 312, 208-216.

Plakas, S.M., El Said, K.R., Jester, E.L.E., Ganade, H.R., Musser, S.M., Dickey, R.W., 2002. Confirmation of brevetoxin metabolism in the eastern oyster (*Crassostrea virginica*) by controlled exposures to pure toxins and to *Karenia brevis* cultures. *Toxicon* 40, 721-729.

Poli, M.A., Mende, T.J., Baden, D.G., 1986. Brevetoxins, unique activators of voltage-sensitive sodium channels, bind to specific sites in rat brain synaptosomes. *Molecular Pharmacology* 30 (2), 129-135.

Pouchus, Y.F., Amzil, Z., Baut, C.M.-L., James, K.J., Verbist, J.-F., 1997. Specificity of the test based on modification of cell morphology for detection of lipophilic inhibitors of protein phosphatases. *Toxicon* 35 (7), 1137-1142.

Qiu, S., Pak, C.W., Currás-Collazo, M.C., 2005. Sequential involvement of distinct glutamate receptors in domoic acid-induced neurotoxicity in rat mixed cortical cultures: effect of multiple dose/duration paradigms, chronological age, and repeated exposure. *Toxicological Sciences* 89 (1), 243-256.

Riobó, P. Palitoxinas, ensayos biológicos y métodos químicos para su determinación en organismos marinos. Departamento de Biología Funcional y Ciencias de la Salud. Universidad de Vigo. Vigo, 2008.

Román, Y., Alfonso, A., Louzao, M.C., de la Rosa, L.A., Leira, F., Vieites, J.M., Vieytes, M.R., Ofuji, K., Satake, M., Yasumoto, T., Botana, L.M., 2002. Azaspiracid-1, a potent, nonapoptotic new phycotoxin with several cell targets. *Cellular Signalling* 14 (8), 703-716.

Román, Y., Alfonso, A., Vieytes, M.R., Ofuji, K., Satake, M., Yasumoto, T., Botana, L.M., 2004. Effects of azaspiracids 2 and 3 on intracellular cAMP, [Ca<sup>2+</sup>], and pH. *Chemical Research in Toxicology* 17 (10), 1338-1349.

Ronzitti, G., Hess, P., Rehmann, N., Rossini, G.P., 2007. Azaspiracid-1 alters the e-cadherin pool in epithelial cells. *Toxicological Sciences* 95 (2), 427-435.

Rossini, G.P., 2005. Functional assays in marine biotoxin detection. *Toxicology* 207, 451-462.

Ryan, G., Cunningham, K., Ryan, M.P., 2008. Pharmacology and epidemiological impact of azaspiracids. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 755-762.

Sasaki, K., Wright, J.L.C., Yasumoto, T., 1997. Identification and characterization of pectenotoxin (PTX) 4 and PTX7 as spiroketal stereoisomer of two previously reported pectenotoxins. *The Journal of Organic Chemistry* 63 (8), 2475-2480.

Satake, M., Ofuji, K., Naoki, H., James, K.J., Furey, A., McMahon, T., Silke, J., Yasumoto, T., 1998. Azaspirazid, a new marine toxin having unique spiro ring assemblies, isolated from irish mussels, *mytilus edulis*. *Journal of the American Chemical Society* 120, 9967-9968.

Scheiner-Bobis, G., Hübschle, T., Diener, M., 2002. Action of palytoxin on apical H<sup>+</sup>/K<sup>+</sup>-ATPase in rat colon. *European Journal of Biochemistry* 269 (16), 3905-3911.

Scheiner-Bobis, G., Meyer Zu Heringdorf, D., Christ, M., Habermann, E., 1994. Palytoxin induces k<sup>+</sup> efflux from yeast cells expressing the mammalian sodium pump. *Molecular Pharmacology* 45, 1132-1136.

Sharp, C.D., Fowler, M., Jackson IV, T.H., Houghton, J., Warren, A., Nanda, A., Chandler, I., Cappell, B., Long, A., Minagar, A., Alexander, J.S., 2003. Human neuroepithelial cells express NMDA receptors. *BMC Neuroscience* 4, 28.

Sheridan, R.E., Despande, S.S., Adler M., 2005. Cytotoxic actions of palytoxin on aortic smooth muscle cells in culture. *Journal of Applied Toxicology*. 25, 365-373.

Shimizu, Y., Chou, H.N., Bando, H., Van Duyne, G., Clardy, J., 1986. Structure of brevetoxin a (gb-1 toxin), the most potent toxin in the florida red tide organism *gymnodinium breve* (*Ptychodiscus brevis*). *Journal of the American Chemical Society* 108 (3), 514 - 515.

Stewart, M., Blunt, J.W., Munro, M.H., Robinson, W.T., Hannah, D.J., 1997. The absolute stereochemistry of the new zealand shellfish toxin gymnodimine. *Tetrahedron Letters* 38 (27), 4889-4890.

Suganuma, M., Fujiki, H., Suguri, H., Yoshizawa, S., Hirota, M., Nakayasu, M., Ojika, M., Wakamatsu, K., Yamada, K., Sugimura, T., 1988. Okadaic acid: an additional non-phorbol-12-tetradecanoate-13-acetate-type tumor promoter. *Proceedings of the National Academy of Sciences* 85 (6), 1768-1771.

Suzuki, T., Mackenzie, L., Stirling, D., Adamson, D.J., 2001. Pectenotoxin-2 seco acid: a toxin converted from pectenotoxin-2 by the new zealand greenshell mussel, *perna canaliculus*. *Toxicon* 39 (4), 507-514.

Suzuki, T., Mitsuya, T., Matsubara, H., Yamasaki, M., 1998. Determination of pectenotoxin-2 after solid phase extraction from seawater and from the dinoflagellate *dinophysis fortii* by liquid chromatography with electrospray mass

spectrometry and ultraviolet detection: evidence of oxidation of pectenotoxin-2 to pectenotoxin-6 in scallops. *Journal of Chromatography A* 815, 155-160.

Taniyama, S., Arakawa, O., Terada, M., Nishio, S., Takatani, T., Mahmud, Y., Noguchi, T., 2003. *Ostreopsis* sp., a possible origin of palytoxin (PTX) in parrotfish *scarus ovifrons*. *Toxicon* 42 (1), 29-33.

Truman, P., Lake, J.R., 1996. Comparison of mouse bioassay and sodium channel cytotoxicity assay for detecting paralytic shellfish poisoning toxins in shellfish extracts. *Journal of AOAC International* 79 (5), 1130-1133.

Tubaro, A., Dell'Ovo, V., Sosa, S., Florio, C., 2010. Yessotoxins: a toxicological overview. *Toxicon* 56 (2), 163-172.

Tubaro, A., Florio, C., Luxich, E., Sosa, S., Della Loggia, R., Yasumoto, T., 1996a. A protein phosphatase 2a inhibition assay for a fast and sensitive assessment of okadaic acid contamination in mussels. *Toxicon* 34 (7), 743-752.

Tubaro, A., Florio, C., Luxich, E., Vertua, R., Della Loggia, R., Yasumoto, T., 1996b. Suitability of the mtt-based cytotoxicity assay to detect okadaic acid contamination of mussels. *Toxicon* 34 (9), 965-974.

Tubaro, A., Sosa, S., Bornancin, A., Hungerford, J.M., 2008. Pharmacology and toxicology of diarrhetic shellfish toxins. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 229-254.

Tubaro, A., Sosa, S., Carbonatto, M., Altinier, G., Vita, F., Melato, M., Satake, M., Yasumoto, T., 2003. Oral and intraperitoneal acute toxicity studies of yessotoxin and homoyessotoxins in mice. *Toxicon* 41, 783-792.

Twiner, J.M., Hess, P., Bottein Dechraoui, M.Y., McMahon, T., Samons, M.S., Satake, M., Yasumoto, T., Ramsdell, J.S., Doucette, G.J., 2005. Cytotoxic and cytoskeletal effects of azaspiracid-1 on mammalian cell lines. *Toxicon* 45, 891-900.

Twiner, J.M., Rehmman, N., Hess, P., Doucette, G.J., 2008. Azaspiracid shellfish poisoning: a review on the chemistry, ecology, and toxicology with an emphasis on human health impacts. *Marine Drugs* 6, 39-72.

Uemura, D., Chou, T., Haino, T., Nagatsu, A., Fukuzawa, S., Zheng, S.-z., Chen, H.-s., 1995. Pinnatoxin A: a toxic amphoteric macrocycle from the okinawan bivalve *pinna muricata*. *Journal of the American Chemical Society* 117, 1155-1156.

Vale, C., Nicolaou, K.C., Frederick, M.O., Gomez-Limia, B., Alfonso, A., Vieytes, M.R., Botana, L.M., 2006. Effects of azaspiracid-1, a potent cytotoxic agent, on primary neuronal cultures. A structure-activity relationship study. *Journal of Medicinal Chemistry* 50 (2), 356-363.

Van Dolah, F.M., 2000. Diversity of marine and freshwater algal toxins. Botana, L.M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology and detection*. CRC Press. 19-43.

Van Dolah, F.M., Leighfield, T.A., Haynes, B.L., Hampson, D.R., Ramsdell, J.S., 1997. A microplate receptor assay for the amnesic shellfish poisoning toxin, domoic acid, utilizing a cloned glutamate receptor. *Analytical Biochemistry* 245, 102-105.

Vélez, P., Sierralta, J., Alcayaga, C., Fonseca, M., Loyola, H., Johns, D.C., Tomaselli, G.F., Marbán, E., Suárez-Isla, B.A., 2001. A functional assay for paralytic shellfish toxins that uses recombinant sodium channels. *Toxicon* 39 (7), 929-935.

Vilariño, N., Espiña, B., 2008. Pharmacology of pectenotoxins. Botana, L. M. (Eds.). *Seafood and freshwater toxins: pharmacology, physiology, and detection*. CRC Press. 361-370.

Vilariño, N., Nicolaou, K.C., Frederick, M.O., Cagide, E., Ares, I.R., Louzao, M.C., Vieytes, M.R., Botana, L.M., 2006. Cell growth inhibition and actin cytoskeleton disorganization induced by azaspiracid-1 structure-activity studies. *Chemical Research in Toxicology* 19 (11), 1459-1466.

Wang, S., Wang, G.K., 2003. Voltage-gated sodium channels as primary targets of diverse lipid-soluble neurotoxins. *Cellular Signalling* 15, 151-159.

Wisnoskey, B.J., Estacion, M., Schilling, W.P., 2004. Maitotoxin-induced cell death cascade in bovine aortic endothelial cells: divalent cation specificity and selectivity *American Journal of Physiology Cell Physiology* 287, C345-C356.

Yasumoto, T., Murata, M. Lee, J.S., Torigoe, K. Polyether toxins produced by dinoflagellates. *Mycotoxins and Phycotoxins 1988*, Amsterdam

Yasumoto, T., Murata, M., Oshima, Y., Sano, M., Matsumoto, G.K., Clardy, J., 1985. Diarrhetic shellfish toxins. *Tetrahedron* 41 (6), 1019-1025.

Yasumoto, T., Oshima, Y., Yamaguchi, M., 1978. Occurrence of a new type of shellfish poisoning in the tohoku district. *Bulletin of the Japanese Society of Scientific Fisheries* 44 (11), 1249-1255.