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A search for cellular and molecular mechanisms involved in harmful algal bloom, *Cochlodinium polykrikoides* induced mammalian hepatotoxicity

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Background and Aims: In this research, we investigated the cytotoxic mechanisms of algal extract of C. polykrikoides responsible for a severe and widespread HAB in the Persian Gulf and Gulf of Oman (2008-2009) in isolated rat liver hepatocytes.
Methods: Isolated hepatocytes were obtained by collagenase perfusion of the rat liver.
Results: Incubation of algal extract with isolated rat hepatocytes caused hepatocyte membrane lysis, reactive oxygen species formation (ROS), glutathione depletion, collapse of mitochondrial membrane potential, ATP depletion and increase in ADP/ATP ratio, cytochrome c release in to the hepatocyte cytosol, activation of caspases cascade and appearance of apoptosis phenotype. Antioxidants (α-tocopherol succinate and BHT), hydroxyl radical scavenger (mannitol and DMSO), Mitochondrial permeability transition (MPT) pore sealing agents (cyclosporine A, carnitine and trifluoperazine), NADPH P450 reductase inhibitor (Diphenyliodonium chloride), CYP2E1 inhibitors (Phenylimidazole and 4-Methylpyrazole) and ATP generators (L-glutamine, Fructose and Xylitol) inhibited the activation of caspase-3 and cell death.
Conclusions: Our data showed, that algal extract activate apoptosis signaling via oxidative stress and mitochondrial pathway. ROS formation could directly be involved in mitochondrial MPT pore opening and activation of caspases cascade leading to toxic effect of C.polykrikoides extract on rat hepatocytes. These findings contribute to a better understanding of C.polykrikoides-toxic effects on mammalian liver cells.

Keywords: Cochlodinium polykrikoides; Rat hepatocytes; Oxidative stress; ROS; Mitochondria; Apoptosis