Biochemical studies on the effect of Astaxanthin and Docosahexaenoic acid on the neurotoxicity caused by occurrence of Penitrem in foods

A thesis Submitted in a fulfillment of the requirements for the Ph.D. degree of Science

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This thesis has not been submitted for a degree at this or any other university.

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I would like to dedicate this work to every member of my faithful family

For their endless love, support and encouragement

And finally to my lovely kids Mohamed, Ahmed and Nouran, that is the most beautiful events in my whole live

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ABSTRACT

Abstract

Penitrem A is a food mycotoxin produced by numerous *Penicillium* species. Penitrem A is a strong tremorgenic through selective antagonism of BK channels. Astaxanthin is a marine natural xanthophyll carotenoid with documented antioxidant interest. In contrast to other common antioxidants. Astaxanthin can cross blood brain barriers, inducing neuroprotective effects. Docosahexaenoic acid is polyunsaturated ω-3 fatty acid certainly occurring in fish and algae. Docosahexaenoic acid is crucial for normal neurological and cellular development. This study evaluated the protective activity of Astaxanthin and Docosahexaenoic against Penitrem A toxicity using Schwann cells CRL-2765 as an *In- vitro* model and two *In- vivo* models *Sprague Dawely rats* and *Caenorhbitidis elegans*. Penitrem A inhibited the viability of Schwann cells with an IC_{50} of 22.6 µM. Treatments with 10-100 µM of Docosahexaenoic acid significantly reversed the Penitrem A toxicity at its IC_{50} dose and improved the survival of Schwann cells to 70.5% and 98.8%, respectively. Treatment with Astaxanthin 10 µM and 20 µM increased the survival percent to 61.7% and 70.5%, respectively. BK channel inhibition in the nematode *Caenorhbitidis elegans* is related to abnormal reversal locomotion. Docosahexaenoic acid and Astaxanthin counteracted the *In- vivo* Penitrem A BK channel antagonistic activity in the *Caenorhbitidis elegans*. Rats fed on Penitrem A-contaminated diet showed high levels of glutamate, aspartate, and Gamma amino butyric acid neurotransmitters, with observed necrosis or complete absence of Purkinjie neurons. Dopamine, serotonin and Norepinephrine levels were abnormal. Nitric oxide, Malondialdehyde levels significantly increased, while Total antioxidant capacity level significantly decreased in serum and brain homogenate in Penitrem A treated rats. Docosahexaenoic and Astaxanthin