Effective Inhibition of Skin Cancer, Tyrosinase, and Antioxidative Properties by Astaxanthin and Astaxanthin Esters from the Green Alga Haematococcus pluvialis

Ambati Ranga Rao, H. N. Sindhuja, Shylaja M. Dharmesh, Kadimi Udaya Sankar, Ravi Sarada, and Gokare Aswathanarayana Ravishankar

1Plant Cell Biotechnology Department, 2Biochemistry & Nutrition Department, and 3Food Engineering Department, Central Food Technological Research Institute, CFSRI, Mysore 570 020, Karnataka, India
4Institute of Ocean and Earth Sciences, University of Malaya, Kuala Lumpur 50603, Malaysia
5Daynand Nag Institute of Technology, Dr. C. D. Sagar Center for Life Sciences, SVM Hills, 5th Floor, Viharal, New Delhi 110 065, India

ABSTRACT: Astaxanthin mono- (AXME) and diesters (AXDE) were characterized and examined for anticancer potency with total carotenoids (TC) and astaxanthin (AX) against UV-7,12-dimethylbenz[a]anthracene (DMBA)-induced skin cancer model in rat. At 200 μg/kg bw, AXDE and AXME reduced UV-DMBA-induced tumor incidences up to 90 and 88%, respectively, when compared to AX (66%) and TC (83%). UV-DMBA has been known to generate high levels of free radicals and tyrosinase enzyme, leading to characteristic symptoms of skin pigmentation and tumor initiation. Intriguingly, ~7-fold increase in tyrosinase and 10-fold decrease in antioxidant levels were normalized by AXDE and AXME as opposed to ~1.4–2.2-fold by AX and TC, respectively. This result together with the appearance of 72 and 58 ng/mL of retinol in the serum of respective AXE-treated (AXDE + AXME) and AX-treated animals suggested that better anticancer potency of AXEs could be due to increased bioavailability.

KEYWORDS: microalgae, AX, AXME, AXDE, UV-DMBA, skin cancer, retinol

INTRODUCTION

Developing novel strategies to prevent skin cancer represents a desirable goal due to the rise in the incidence of skin cancer patients throughout the world. According to the World Cancer Report, skin cancer constitutes ~30% of all newly diagnosed cancers in the world. This rise in incidence has been attributed to overexposure of skin to sun/UV light, due to reduction in the ozone in the atmosphere.

Skin cancer thus is a disease in which malignant cells are found in the outer layer of the skin. Melanoma is one of the most serious consequences of skin cancer where melanocytes proliferate actively with enhanced accumulation of melanin pigment leading to pigmentation and discoloration of the skin in addition to tumor formation. Up-regulated levels of tyrosinase enzyme appear to contribute significantly to the enhanced synthesis and accumulation of melanin in melanocytes.

Like most cancers, melanoma is best treated when it is diagnosed early. Melanoma can metastasize quickly to other parts of the body through the lymph system or through the blood. Most of the cytotoxic drugs used presently in cancer therapy are highly toxic to a wide spectrum of tissues such as the gastrointestinal tract, bone marrow, heart, lungs, kidney, and brain. Latrogenic failure of these organs has been observed frequently as a cause of death from cancer. Melanomas are difficult to eradicate by chemotherapy because they exhibit a well-known phenomenon, “chemoresistance”. Expression of survival molecules in the cells appears to cause drug resistance, resulting in very little option for curing the disease. Attempts are underway with the use of tyrosinase inhibitors, particularly from natural sources, to overcome chemoresistance and to avoid side effects. Indeed, much progress is being made in the direction of pharmacological evaluation of various plant products and dietary sources with the hope of achieving effective chemoprevention.

Extensive research has been done on Haematococcus pluvialis, a unicellular green alga, in our laboratory including its biotechnological production, characterization of type of astaxanthin (AX), astaxanthin esters (AXEs), etc. Astaxanthin esters are unique, constituted by 70% of monesters; 15–20% of diesters, and 4–5% of free forms, indicating the predominance of esterified astaxanthin forms in H. pluvialis as opposed to free forms in other plant sources. Antioxidant activities 100 and 10 times greater than those of vitamin E and β-carotene have been reported in AX. Recently developed downstream processing for the large-scale production of AX and AXEs may potentiate their use as anticancer alternatives. Furthermore, intriguing studies by Camera et al. implied that different carotenoids exhibit varied potential to offer protection against UV-induced skin cancer. Among the three important carotenoids, AX, canthaxanthin (CX), and β-carotene (BC), AX, which is an oxocarotenoid, has a superior preventive effect toward photo-oxidative changes in...