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REVIEW ARTICLE

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Antioxidant effects of astaxanthin in various diseases—a review

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ABSTRACT

Background: Astaxanthin, a potent antioxidant carotenoid has been found to be highly effective in mopping up free radicals as it possesses anti-oxidative, anti-inflammatory, anti-apoptotic, and other beneficial pharmacological properties. Many chemical reactions produce free radicals which are injurious to body cells, as they are the causes of many diseases, disabilities, and death. Antioxidants suppress and mop up these circulating free radicals.

Method: This review was done by a comprehensive literature search using internet search engines linked to academics such as EBSCO, PubMed, Google Scholar, etc. They were assessed on topics related to astaxanthin. Articles related and linked to studies involving astaxanthin were thoroughly searched and the references of such articles were also searched for information about astaxanthin in relation to the medical application.

Results: In various studies, astaxanthin has been found to be a potent carotenoid as an antioxidant thereby protective to the body as it prevents cancer, enhances eye health, suppresses lipid peroxidation and atherosclerosis, enhances skin and brain health, and suppresses the formation of complications of diabetes mellitus.

Conclusion: Astaxanthin, a highly potent xanthophylls carotenoid has multiple pharmacological properties, and oral supplements of this anti-oxidant are protective against a wide range of diseases.

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Introduction

Free radicals

Free radicals are molecules containing one or more unpaired electrons which give a considerable degree of chemical reactivity to it [1,2]. Most of these free radicals come from intracellular and extracellular processes in biological fluids. The plasma membranes of cells are potential sources of free radicals [3,4]. Other ways of free radical generation are exposure to ionizing radiation, cigarette smoking, sunlight, drug ingestion, and exposure of red blood cells to chemicals such as acetyl phenylhydrazine and hydrogen peroxide (H_2O_2) [5]. Exposure of some neonates to oxidants such as dusting powder and camphor balls results in increased hemolysis due to the generation of free radicals [6]. Free radicals are injurious to body cells and tissues and need to be mopped up by antioxidants. Various sources of antioxidants exist such as vitamins C and E and glutathione. Astaxanthin is considered a potent antioxidant.

Antioxidants

Antioxidants are protective against free radicals such that the possible detrimental effects of these free radicals that are generated are kept on check. Hence, antioxidants stabilize free radicals' reaction. Some antioxidants may be enzymes such as glutathione reductase, superoxide dismutase, and catalase [7]. Dietary antioxidants also exist such as vitamins A, C, E, and beta-carotene. Generally, antioxidants are divided into two major groups:

Water soluble (hydrophilic)

Which are potent in blood, intracellular fluid, and extracellular fluid. They react with oxidants in the cell cytosol and blood plasma. Examples of such are vitamin C, glutathione, and catechins.

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Lipid soluble (hydrophobic)

They are localized to cellular membranes and lipoproteins. These include vitamins A, E, and beta-carotene [5,8]. Generally, antioxidants are helpful in preventing or delaying cell damage as they mop up free radicals generated from cellular processes. Several antioxidants have been evaluated such as vitamin C (ascorbic acid), vitamin E (tocopherol), beta-carotene, selenium, lycopene, and astaxanthin [8,9].

Astaxanthin

Astaxanthin is a lipophilic terpene which is made up of carbon precursors [10,11]. It is a metabolite of zeaxanthin and canthaxanthin, containing hydroxyl and ketone functional groups [10,11]. Astaxanthin, being a xanthophyll carotenoid is chemically identified as 3,3'-dihydroxy-β,β'-carotene-4,4'-dione. It is lipid soluble and distinguished from all other carotenoids and has a molecular mass of 596.84 g/mol with a formula of $C_{40}H_{52}O_4$. It has conjugated double bonds at its center—giving it, its antioxidant effects [10,12].

Humans cannot synthesize astaxanthin in the body [13]. Historically, Professor Basil Weedon's group was the first to prove the structure of astaxanthin by synthesis in 1970 [14]. Like all other carotenoids, astaxanthin is absorbed alongside fatty acids via passive diffusion into the intestinal epithelium [15]. Sources of astaxanthin are yeasts, krill, trout, microalgae, shrimps, and crayfish. Astaxanthin is present in most red-colored aquatic organisms [13,15]. The primary sources of astaxanthin in high concentrations are given below in Table 1 [10].

Algae are the primary natural sources of astaxanthin in the aquatic food chain. The primary industrial sources for natural astaxanthin are the microalgae and *Haematococcus pluvialis*. Commercial astaxanthin for aquaculture is produced synthetically [10].

Table 1. Showing the sources of astaxanthin.

Natural sources	Concentration of astaxanthin (Parts per million)
Salmonids	5
Plankton	60
Krill	120
Arctic shrimp (*P. borealis*)	1,200
Phaffia yeast (*Xanthophyllomyces dendrorhous*)	10,000
Haematococcus pluvialis	40,000

Historical Evolvement of Astaxanthin in Medical Uses

Since its discovery in 1970, astaxanthin has evolved through some technological processes to be useful in everyday life uses. It is now mainly extracted from *Haematococcus pluvialis* using high-pressure liquid chromatography and identified by mass spectrometry [16]. Currently, astaxanthin has been approved as a food colorant in animal and fish feed [17]. Over the years, attempts have been made by scientists to synthetically produce the products of *Haematococcus pluvialis*. Lee et al. [18] demonstrated that adding 1-aminocyclopropane-1-carboxylic acid could enhance the accumulation of astaxanthin while Shang et al. [19] suggested that synthetic *Haematococcus pluvialis* production is enhanced by using butylated hydroxyanisole.

Consumption of astaxanthin can reduce and prevent various disorders in human and animals. Synthetic astaxanthin has a dominant role in agriculture. The consumption of astaxanthin can reduce or prevent the risk of various disorders in human and animals. Synthetic astaxanthin is produced by phaffia yeast and *H. pluvialis* through chemical synthesis [20].

Mechanism of Action of Astaxanthin

Usually, carotenoids are absorbed into body lipids which are enhanced by high cholesterol. On absorption, astaxanthin mixes with bile acid to make micelles and are incorporated into chylomicron. Astaxanthin is then assimilated with lipoprotein and transported to body tissues to protect cells such as skin and lipid-based membrane against oxidative damage [21]. Also, astaxanthin contains polyene chain and multiple double bonds which quench singlet oxygen and radicals to stop the reaction. Antioxidant properties have been linked to their chemical and physical interactions with cell membranes. The polyene chain in astaxanthin mops up free radicals in the cell membrane [22].

Review of Medical Uses of Astaxanthin

Over 50 clinical and experimental studies show that astaxanthin is important in cardiovascular health, eye health, brain health, sports-related activities, skin health, diabetes mellitus and metabolic syndrome, cancer health, and a whole lot of other disease entities [23,24]. In general, with regards to general antioxidant effects (free radical scavenging), astaxanthin is more than 65 times

stronger than vitamin C and 50 times more powerful than vitamin E in protecting cell membranes. In addition, astaxanthin has been shown to be more effective than other carotenoids and other nutrients at singlet oxygen quenching by being up to 800 times stronger than coenzyme Q, 6,000 times greater than vitamin C, 550 times more powerful than green tea catechins, and 11 times stronger than beta-carotene. It is also found to be 2.75 times stronger than lutein [25]. Research suggests that astaxanthin may be beneficial in immune, inflammatory, and neurodegenerative diseases [26,27]. Astaxanthin has been shown to play a role in several diseases.

Cancer prevention

Several research studies have deciphered that astaxanthin exerts in activity such as anti-proliferation, anti-apoptosis, and anti-invasion via different molecules and pathways including signal transducers and activator of transcription 3 (STAT 3), nuclear factor kappa light chain enhancer of activated β-cell (NF-κβ), peroxisome proliferator activator receptor gamma, and other multiple mechanism of cancer effects. According to Zhang et al., astaxanthin is thought to protect body tissues from oxidation and ultraviolet (UV) damage through suppression of NF-κB activation [28,29]. Astaxanthin also prevents cancer initiation by protecting the body DNA from UV oxidant damage. It does this by promoting early detection and destruction of cells that have undergone malignant transformation by avoiding immune surveillance [30,31]. Also, Jacobsson et al. [58], Palozza et al. [28], and Nagendraprablu and Sudhondranm [29] confirm that astaxanthin prevents the tumor from spreading by reducing tumor production of tissue-melting proteins and blocks the rapid cell replication of tumors in their growth phase by stopping the cancer cell reproductive cycle and enhancing apoptosis [13,32,33].

Eye health

Health benefits of astaxanthin include protection against eye-related macular degeneration (the most common cause of blindness) and inflammatory eye conditions. Astaxanthin protects the eye against eye fatigue, improves visual activity and depth perception, and increases blood flow to eye tissues.

Astaxanthin does this because it crosses the blood–retinal barrier; hence, protecting the eyes. These antioxidant properties have protective effects on the eyes, protecting it against cataract, macular degeneration, and even blindness. Iwasaki and Tahara [34] concluded that astaxanthin reduces cataract formation, glaucoma, and macular degeneration.

Prevention of complications of diabetes mellitus

In 2015, a meta-analysis of data from 10 randomized control studies showed a significant effect of supplementation with astaxanthin on plasma lipid profile and fasting glucose. In another research, involving db/db mice, prevention of diabetic nephropathy was noted on treatment with astaxanthin. It is found that chronic administration of astaxanthin reduces the oxidative stress on the kidneys and prevents renal cell damage. A dose of 6.8 mg a day decreased the level of blood glucose [35–37]. Uchiyama et al. [38] and Ambati et al. [39] noted that giving astaxanthin to obese or/and diabetic animals experienced lower plasma glucose levels, improved insulin sensitivity, and reduced inflammation and oxidative stress. In addition, astaxanthin enhanced the ability of the pancreas to secrete insulin and slowed down the rate of diabetic nephropathy [27,38,39].

Brain health/stroke/hypertension prevention

Neuroprotective effects of astaxanthin have also been noted in experimental animals. It is known to protect against stroke and hypertension and in improving memory in vascular dementia [40–43]. Astaxanthin crosses the blood–brain barrier; hence, protecting the brain [42]. At a given dose of 6–8 mg daily, there was a reduction in blood pressure in studied individuals [35–37]. Neuroprotective properties of the marine carotenoid, astaxanthin and omega-3-fatty acid, are seen as prospective future combinations [44]. Fassett et al. further noted that astaxanthin protects against aging and improves mental functions in rats, 50 mg/kg astaxanthin oil reduced both systolic and diastolic blood pressure in spontaneously hypertensive rats/mrc-cp rats (a model for metabolic syndrome) [45].

Sports-related activities

Astaxanthin is known to promote muscle endurance and protects against muscle damage [46,47]. Astaxanthin limits exercise-induced skeletal muscle damage in mice. It is now used by athletes to enhance performance. The same properties that it has made it beneficial for salmon to swim upstream and are also beneficial to humans looking to

accomplish feats of endurance. This finding is well supported [47–49]. This it does by reducing the production and storage of lactic acid, reducing free radical, and supporting mitochondrial function [50].

Skin health

Astaxanthin reduces the fine lines and wrinkles, improves skin elasticity, protects against sun damage, and prevents age spots and hyperpigmentation. Astaxanthin works as an internal sunscreen of the sort; since it reduces inflammation, and reduces UV damage to skin cells [51]. It is a potent UV radiation absorber [27]. Tominaga et al. in a study involving 38 healthy females gave 6 mg/day of astaxanthin oral supplement and 2 ml/day topical astaxanthin to the participating subjects. Their results showed that the *H. pluvialis*-derived astaxanthin improved skin conditions in all layers such as corneocyte layer, epidermis, basal and dermis layer by combining oral and topical treatment [52]. Astaxanthin is believed to offer skin protection through a number of mechanisms. First, it is believed to block a certain amount of the UV radiation acting directly on the skin. Secondly, it neutralizes the free radicals induced by the UV radiation. Thirdly, it appears to inhibit the induction of matrix metalloproteinase (MMP) by UV light. MMP is thought to be an important factor in sun damage and skin aging [53]. In yet another study in 1998, Savoure et al. also noted that astaxanthin, when given alone or in combination with retinol, substantially reduced/prevented photo-aging of the skin. This study in rats also showed that astaxanthin was found to be 100 times stronger than beta-carotene and 1,000 times stronger than lutein in preventing UV light-induced oxidative stress [54].

Peptic ulcer disease prevention

The ulcer-preventing ability was studied in India when researchers [55,56] at Central Food Technological Institute gave carotenoids and astaxanthin esters orally at doses of 100, 250, and 5,000 mcg/kg to rats. After being fed antioxidants, ethanol was then given to induce gastric ulcer in the studied rats. The researchers noted that lipoxygenase inhibitors in the rat cells were 23 times greater when astaxanthin was given compared to administration of omeprazole, a proton-pump inhibitor used for peptic ulcer disease management. They concluded that free radicals scavenging activity of astaxanthin found in *H. pluvialis* protects against gastric mucosal injury [27,55,56].

Lipid peroxidation/atherosclerosis prevention

Astaxanthin is thought to inhibit lipid peroxidation and simultaneously simulate cancer cells, making it effective for treating breast, colon, and bladder cancers. Also, astaxanthin reduces C-reactive protein in the cardiovascular system, reducing triglycerides, increasing high-density lipoprotein cholesterol and adiponectin levels. In another study done in Finland, Karppi et al. assessed the effect of 3-month astaxanthin supplementation on certain healthy non-smokers aged between 19 and 33 years. The intervention group received two 4 mg capsules daily while the control received placebo. Their findings suggest that the supplementation with astaxanthin decreased the *in vivo* oxidation of fatty acids in the healthy men [57]. In another study by Jacobsson et al. [58], taking 6–8 mg daily of astaxanthin decreased the oxidation of low-density lipoprotein cholesterol and prevented it from atherogenic effect. It protects the vascular lining, promotes improved blood flow, and protects cholesterol from being oxidized. Astaxanthin is thought to play a role in atherosclerosis prevention due to it antioxidant and anti-inflammatory effects in endothelial cells. Dysfunction of both systems in these cells produces a pro-atherogenic state [17,45,59].

Conclusion

From its discovery till now, astaxanthin has been found to be a useful antioxidant which has the potential of mopping up free radicals. The chemical structure of astaxanthin makes it an excellent antioxidant. This single property has been found to be beneficial to humans. These protective effects range from free radical scavenging, mitochondrial protection, anti-inflammatory effects, and protection from glycation [60,61].

With the advancement in technology, synthetic production of astaxanthin by genetic engineering will go a long way in supplying the needed astaxanthin in both agricultural and medical uses. It is believed that the extraction of astaxanthin from its natural sources and synthetic-based forms will play a great role in the management of patients because of its large pharmacological benefits to humans.

Conflict of interest

None declared.

References

[1] Bolarin DM, Ekpe EL, Saidu KS, Eyam SE. Overview of foods with antioxidant effects-clinical relevance. Eur J Food Sci Technol 2016; 4(2):1–9.

[2] Lobo V, Patil A, Phatak A, Chandra N. Free radicals. Pharmacogn Rev 2010; 4(8):118–26.

[3] Shanon R, Stepan M, Timothy AT, Oleksandra P, Seidel L. Intracellular and extracellular Redox states and free radical generation in primary immune cells from children with austism. Autism Res Treat 2012; 986519:1–10.

[4] Caraceni P, Ryu HS, van Thiel D, Borle AB. Sources of oxygen free radicals produced by rat hepatocytes during postanoxis reoxygenation. Mol Cell Res 1995; 1268(3):249–54.

[5] Etukudo MH. Antioxidant: sacrificial lambs to free radicals. Lecture note at 59th UNICAL inaugural lecture, Calabar, Nigeria, 2014.

[6] Flaman Z, Pellachia-Clarke S, McGuigan M, Bailey B. Unintentional exposure of young children to camphor and eucalyptus oils. Paediatr Child Health 2001; 6(2):80–3.

[7] Shahihi F, Zhong YL. Measurement of antioxidant activity. J Function Food 2015; 18(Part B):757–81.

[8] Nimse SB, Pal D. Free radicals, natural antioxidants, and their reaction mechanisms. RSC Adv 2015; 5:27986–8006.

[9] Dizdaroglu M, Faruga P. Mechanism of free radical-induced damage to DNA. Free Radic Res 2012; 46:382–419.

[10] Astaxanthin. Available via https://en.wikipedia.org/wiki/Astaxanthin

[11] Choi S, Koo S. Efficient syntheses of the keto-carotenoids canthaxanthin, astaxanthin, and astacene. J Organ Chem 70(8):3328–31.

[12] Astaxanthin. Available via https://pubchem.ncbi.nlm.nih.gov/compound/Astaxanthin#section=Top (Accessed 18 April 2018).

[13] What is astaxanthin? Availabale via http://astaxanthin.org/about/what-is-astaxanthin/ (Accessed 18 April 2018).

[14] Cooper RDG, Davis JB, Leftwick AP, Price C, Weedon B. Carotenoids and related compounds. XXXII. Synthesis of astaxanthin, hoenicoxanthin, hydroxyechinenone, and the corresponding diosphenols. J Chem Soc Perkin Trans 1975; 1(21):2195–204

[15] Astaxanthin antioxidant. Available via https://astaxanthin-antioxidant.blogspot.com.ng/2017/04/astaxanthin-and-obesity.html (Accessed 18 April 2018).

[16] Du P, Jin M, Yang L, Chen G, Zhan C, Jin F. Determination of astaxanthin in feeds using high performance liquid chromatography and an efficient extraction method. J Chromatogr 2016; 39(1):35–43.

[17] Lim KC, Yussoff FM, Shariff M, Kamarudin MS. Astaxanthin as feed supplement in aquatic animals. Rev Aquacult 2017; doi:10.1111/raq.12200.

[18] Lee CS, Choi YE, Yun YS. Strategy for promoting astaxanthin accumulation in *Haemococcus pluvialis* by 1-aminocyclopropane-1carboxylic acid application. J Biotechnol 2016; 236:120–7.

[19] Shang M, Ding W, Zhao Y. Enhanced astaxanthin production from *H. pluvialis* using butylated hydroxylanisole. J Biotechnol 2016; 236:197–207.

[20] Pashkow FJ, Watumull DG, Campbell CL. Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular diseases. Am J Cardiol 2008; 101:58D–68D.

[21] Komatsu T, Sasaki S, Manabe Y, Hirata T, Sugawara T. Preventive effect of dietary astaxanthin on UVA-induced skin photoaging in hairless mice. PLoS One 2017; 12(2):e0171178.

[22] Ambati RR, Moi PS, Ravi S, Aswathanarayana RG. Astaxanthin: sources, extraction, stability, biological activities and commercial applications. Mar Drugs 2014; 12(1):128–52.

[23] Grimmig B, Kim SH, Shytle RD. Neuro-protective mechanisms of astaxanthin: a potential therapeutic role in preserving cognitive function in age and neuro-degeneration. Geoscience 2017; 39(1):19–32.

[24] Ni Y, Nagashimada M, Zheuge F, Zhan L, Nagata N, Tsutsui A. Astaxanthin prevents and reverses diet-induced insulin resistance and steatohepatitis in mice: a comparison with vitamin E. Sci Rep 2015; 5:17192.

[25] Fassett RG, Coombes JS. Astaxanthin in cardiovascular health and diseases. Molecules 2012; 17(2):2030–48.

[26] Kidd P. Astaxanthin- cell membrane and nutrient with diverse clinical benefits and anti-ageing potentials. Altern Med Rev 2011; 16(4):255–64.

[27] Beutner S, Bloedorn B, Frixel S, Hernández Blanco I, Hoffmann T, Martin H-D, et al. Quantitative assessment of antioxidant properties of natural colorants and phytochemicals: carotenoids, flavonoids, phenols and indigoids. The role of β-carotene in antioxidant functions. J Sci Food Agric 2001; 81:559–68; doi:10.1002/jsfa.849

[28] Palozza P, Torrelli C, Boninsegna A. Growth inhibitory effects of the astaxanthin-rich *H. pluvialis* in human colon cancer cell. Cancer Lett 2009; 283(1):108–17.

[29] Nagendraprablu P, Sudhondranm G. Astaxanthin inhibits tumor invasion by decreasing extracellular matrix pollution and induces apoptosis in experimental rat colon carcinogenesis by modulating the expression of ERK-2, NFK-B, and COX-2. Invest. New Drugs 2011; 29(2):201–24.

[30] Astaxanthin supplement health benefit and side effects. Availabale via http://www.raysahelian.com/astaxanthin.html (Accessed 18 April 2018).

[31] Zhang L, Wang H. Multiple mechanisms of anti-cancer effects exerted by astaxanthin. Mar Drug 2015; 13(7):4310–30.

[32] Camera E, Mastrofrancesco A, Fabbri C, Daubrawa F, Picardo M, Sies H. Astaxanthin, canthaxanthin and

β-carotene differently affect UVA-induced oxidative damage and expression of oxidative stress-responsive enzymes. Exp Dermatol 2009; 18(3):222–31; doi:10.1111/j.1600-0625.2008.00 790

[33] Santocomo M, Zurria M, Berrettini M, Fedeli D, Falcioni G. Lutein, zeaxanthin and astaxanthin protect against DNA damage in SK-N-SH human neuroblastoma cells induced by reactive nitrogen species. J Photochem Photobiol B 2007; 88(1):1–10; doi:10.1016/j.jphotobiol.2007.04.007

[34] Iwasaki T, Tahara A. Effects of astaxanthin on eye strain induced by accommodative dysfunction. J Eye 2006; 23(6):829–34.

[35] Naito Y, Uchiyama K, Aoi W. Prevention of diabetic nephropathy by treatment with astaxanthin in diabetic db/db mice. Biofactors 2004; 20(1):49–53.

[36] Manabe E, Handa W, Naito Y. Astaxanthin protects mesangial cells from hypoglycemia- induced oxidative signaling. J Cell Biochem 2008; 103(6):1925–37.

[37] Astaxanthin may protect against the onset and progression of kidney damage associated with type 2 diabetes mellitus. Available via http://www.fujichemical.co.jp/english/newsletter/newsletter_nutra_0803.html (Accessed 18 April 2018).

[38] Uchiyama R, Ndito Y, Hasegewu G, Nakawuna N, Takahashi J, Yoshikawa T. Astaxanthin protects beta cells against glucose toxicity in diabetic db/db mice. Redox Rep 2002; 7(5):290–3.

[39] Ambati RR, Moi PS, Ravi S, Aswuthnagama G. Astaxanthin, sources, extinction, stability, biological activities and in commercial application—a review. Mar Drugs 2014; 12(1):128–52.

[40] Wu H, Niu H, Shao A, Wu C. Astaxanthin as a potential neuro-protective agent for neurological diseases. Mar Drugs 2015; 13(90):5750–66.

[41] Hussein G, Nakamura M, Zhao Q, Iguchi T, Ceoto H, Sankara U. Anti- hypertensive and neuro-protective effects of astaxanthin in experimental animals. Biol Pharm Bull 2005; 28(1):47–52.

[42] Manabe Y, Komatsu T, Seki S, Sugawara T. Dietary astaxanthin can accumulate in the brain of rats. Biosci Biotechnol Biochem 2018; 82(8):1433–6.

[43] Bahonar A. Carotenoids as potential antioxidant agents in stroke prevention: a systemic review. Int J Pre Med 2017; 8:70.

[44] Fassett RG, Coombes JS. Astaxanthin, oxidative stress, inflammation and cardiovascular disease. Fut Cardiol 2009; 5(3):333–42.

[45] Yanai H, Ito K, Yoshida H, Tada N. Antihypertensive effects of astaxanthin. Integr Blood Press Control 2008; 1:1–3.

[46] Ikeuchi M, Koyama T, Takahashi J, Yazawu K. Effects of astaxanthin supplementation on exercise-induced fatigue in mice. Biol Pharm 2006; 29(10):2106–10.

[47] Astaxanthin supports eye, skin, joints, heart and exercise recovery. Available via https://www.nutritionexpress.com/supplements/astaxanthin (Accessed 18 April 2018).

[48] Djordjevic B, Baralic I, Kotur-Stevuljevic C, Stefanovic A, Ivanisevic J. Effect of astaxanthin supplementation on muscle damage and oxidative stress markers in elite young soccer players. J Sports Med Phys Fitness 2012; 52(4):382–92.

[49] Ikeuchi M, Koyama T, Takahashi J, Yazawa K. Effects of astaxanthin supplementation on exercise-induced fatigue in mice. Biol Pharm Bull 2006; 29(10):2106–10.

[50] Aoi W, Naito Y, Sakuma K, Kuchide M, Tokuda H, Maoka T, et al. Astaxanthin limits exercise-induced skeletal and cardiac muscle damage in mice. Antioxid Redox Signal 2003; 5(1):139–44.

[51] Hama S, Takahasi IY. Protective effects of topical application of poorly soluble antioxidant astaxanthin liposomal formulation on ultraviolet-induced skin damage. J Pharm Sci 2012; 101(8):2909–16.

[52] Tominaga K, Hongo N, Karato M, Yamashita E. Cosmetic benefits of astaxanthin on human subjects. Acta Biochim Pol 2012; 59(1):43–7.

[53] Kumi A. Effect of antioxidant to inhibit UV-induced wrinkles. J Japan Cosmet Sci Soc 2003; 27(4):298–303.

[54] Savoure N, Briand G, Amoury-Touz M, Combre A, Maudati M. Vitamin A status and metabolism of cutaneous polyamines in hairless mouse after UV irradiation: action of beta carotene and astaxanthin. Int J Nutr Res 1995; 65(2):79–86.

[55] Kamath BS, Srikanta BM, Dharmesh SM, Sarada R, Ravishankar GA. Ulcer-preventive and antioxidative properties of astaxanthin from *Haematocuccus pluvialis*. Eur J Pharmacol 2008; 590(1–3):387–95.

[56] Kamath BS, Srinkata BM, Dharmesh SM, Sarada R, Ravishankar VA. Ulcer preventive and anti-oxidative properties of astaxanthin from *Haematococcus pluvialis*. Eur J Pharm 2008; 590(1–3):387–95.

[57] Karppi J, Risanen TH, Nyysonen K, Kikkoren J. Effects of astaxanthin supplementation on lipid peroxidation. Int J Vitamin Nutr Res 2007; 77:3–11.

[58] Jacobsson S, Yuan XM, Zieden B, Olsson AG. Effects of alpha tocopherol and astaxanthin in low density lipoprotein cholesterol-oxidation and atherosclerosis in WHHL rabbits. Atherosclerosis 2004; 173(2):231–7.

[59] Lee PH, Kim CS, Lee YJ. Astaxanthin protects against MPTP/MPP-induced mitochondrial dysfunction and ROS population in vivo and in vitro. Food Chem Toxicol 2011; 49(1):271–80.

[60] Wolf AM, Assoh S, Hirauna H. Astaxanthin protects mitochondrial redox state and functional integrity against oxidative stress. J Nutr Biochem 2010; 21(5):389–91.

[61] Higuera CI, Felix-Valenzuela F, Goycoolea FM. Astaxanthin: a review of its chemistry and application. Crit Rev Food Sci Nat 2006; 46(2):185–96.