Original Article

Astaxanthin improves glucose metabolism and reduces blood pressure in patients with type 2 diabetes mellitus

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Background and Objectives: This randomized, placebo-controlled trial was performed for 8 weeks to investigate the potential effects of astaxanthin (AST) supplementation on the adiponectin concentration, lipid peroxidation, glycemic control, insulin sensitivity, and anthropometric indices in participants with type 2 diabetes mellitus. **Methods and Study Design:** We enrolled 44 participants with type 2 diabetes who met our inclusion criteria. Eight milligrams of AST supplementation or a placebo were randomly administered once daily for 8 weeks to these participants. **Results:** The 8-week administration of AST supplementation increased the serum adiponectin concentration and reduced visceral body fat mass ($p<0.01$), serum triglyceride and very-low-density lipoprotein cholesterol concentrations, and systolic blood pressure ($p<0.05$). Furthermore, AST significantly reduced the fructosamine concentration ($p<0.05$) and marginally reduced the plasma glucose concentration ($p=0.057$). **Conclusions:** We demonstrated that because participants with type 2 diabetes often have hypertriglycemia and uncontrolled glucose metabolism; our findings of dual beneficial effects are clinically valuable. Our results may provide a novel complementary treatment with potential impacts on diabetic complications without adverse effects.

Key Words: astaxanthin, dyslipidemia, hypertriglycemia, adiponectin, diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus is caused by an imbalance between insulin supply and demand, which is indicated by glucose and lipid abnormalities.[1] The etiology of the development of insulin resistance is complex and not fully understood.[2] However, many studies have indicated that deregulation of adipocytokines such as adiponectin, secreted from the adipose tissue, affects insulin sensitivity involved in glucose and lipid metabolism.[3] The clinical management of diabetes focuses on the control of hyperglycemia and insulin resistance by using a combination of nutritional and pharmacological therapies to control non-insulin-dependent diabetes mellitus because of increased significant microvascular and macrovascular complications.[4] Therefore, several natural products such as antioxidants are extensively used to arrest the progression of diabetic complications or potentially prevent or delay the development of diabetic disorders.[5]

Astaxanthin (AST) is a natural carotenoid compound present in various microorganisms and seafoods.[6] A major dietary source of AST is Haematococcuspluvialis, a green microalga that has a high AST content, and is eaten as food by fish and marine organisms.

Studies have reported that AST can perform various biological activities. The effects of AST on lipid metabolism and antioxidant defense mechanisms are several times higher than those of alpha-tocopherol and vitamin C.[7,8] Moreover, AST has positive effects on cholesterol and lipid metabolism, as well as on the immune response

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that occurs through antioxidant defense mechanisms in healthy humans or participants with cardiovascular diseases who have enhanced antioxidant properties.[9,10]

Clinical trials have evaluated AST as a scavenger of free radicals and protective agents, especially in cardiovascular diseases. To the best of our knowledge, no human studies have evaluated the effects of the dietary intake of AST on the lipid profile and blood sugar, particularly in high-risk participants with type 2 diabetes mellitus who have enhanced oxidative stress and inflammation.

Thus, we conducted a trial for 8 weeks to assess the potential effects of 8 mg of the AST supplement on lipid peroxidation, glycemic control, serum adiponectin concentration, anthropometric indices, and blood pressure in participants with type 2 diabetes mellitus receiving oral antidiabetic drugs to control hyperglycemia.

PARTICIPANTS AND METHODS

Study population

This study was a single-center, double-blind (participants and study staff), randomized (1:1 allocation), parallel, placebo-controlled trial. Forty four volunteers with type 2 diabetes were referred to the Diabetes Research Center at the Ahvaz University of Medical Sciences. The patients who met our inclusion criteria were then enrolled after written consent was obtained. The inclusion criteria were as follows: age of 30–60 years; definitive diagnosis of type 2 diabetes with no insulin therapy; no pregnancy or lactation; absence of self-reported specific diseases and malignancies, kidney failure, heart disease, thyroid, and other inflammatory diseases; not taking vitamin and antioxidant supplements during the last 6 months; and no smoking or drinking.

Moreover, participants were excluded if they were taking antioxidant supplements, unable to follow the study, or participating in another clinical drug study within 30 days before entry in the present study. An equal number of participants were randomly allocated into one of two groups: the AST treatment or identical placebo group. All procedures were performed under the supervision of a nutritionist at each step, during which the participants were advised to eat a specific diet, perform physical activity, and take antidiabetic drugs. The protocol of this randomized clinical trial was approved by the Research Ethics Committee of Ahvaz University of Medical Sciences and was registered with the Iranian Registry of Clinical Trials (IRCT2015081623645N1).

Methods

Trained researchers performed all the data collection and measurements. Several demographic characteristics were collected by the interviewers, including age, sex, diabetes duration, medical history, education status, economic status, and type of antidiabetic or antihypertensive drugs received. Height was measured to the nearest 0.5 cm without shoes using a Seca stadiometer. Body mass index was calculated as weight in kg/height^2 in meters for each patient, and waist and hip circumferences were measured on a horizontal plane at the level of the iliac crest in centimeters. A body state device (Omron BF511 Body Composition Monitor) based on the bioelectrical impedance method was applied to measure body fat and body weight. The participants' physical activity levels were assessed using the short version of the International Physical Activity Questionnaire and reported as metabolic equivalent; finally, blood pressure was measured using a mercury sphygmomanometer after 15 min of resting (sitting) in a stress-free condition.

Dietary assessment

Food intake was recorded before, after, and during the study period (3-day food records), according to volume or weight and type of food. To assess energy and macronutrient intake, the dietary data were analyzed using Nutritionist IV software (Version 4.1, First Databank Division, The Hearst Corporation, San Bruno, CA, USA). During each 2-week visit, adherence of the participants to the study protocol was assessed by counting the remaining AST tablets, and asking them to maintain their habitual diet, lifestyle, and medication ingestion.

Blood sampling and primary measures

Venous blood samples were collected during the fasting state for biochemical measurements. The samples were centrifuged, and serums were frozen and stored at −80°C. Fasting blood glucose was measured using a colorimetric method (Pars Azmoon commercial kits, Iran), while lipid profiles were measured using an auto analyzer based on the colorimetric method (Pars Azmoon commercial kit). Fructosamine concentrations were analyzed using an enzyme-linked immunosorbent assay (human "buster" Elisa kit [USA] and eastbiopharm Elisa kit [China]). AST concentrations in the plasma were then analyzed through reverse-phase high-performance liquid chromatography (Alliance 2690, Waters, Milford, MA), where the Trans-b-apo-8′-carotenal (Sigma Chem. Co., St. Louis, MO) was used as an internal standard. Notably, the plasma elimination half-time (T1/2) of AST is generally 16 h after oral administration in the circulation.[6] Thus, the participants were asked to ingest one tablet of AST once each day after lunch (i.e., the main course that contains usual dietary fat) for enhanced oral bioavailability. Samples were withdrawn after overnight fasting for 10–12 h, and the plasma concentration of AST was determined 20 h after last supplement intake.

Study medication and dosing

Active treatment entailed 8 mg of orally administered AST (Nature Vision; USA), which was derived from H. pluvialis (microalgae). Inactive ingredients used as both a supplement and placebo included dicalcium phosphate, microcrystalline cellulose, stearic acid, silicon dioxide, and magnesium stearate. Each patient was required to take one 8-mg tablet of either the placebo (containing the basic material of supplement, except AST) or AST supplement immediately after lunch to ensure its optimal absorption for 8 weeks.

Statistical analysis

The results are presented as a mean±standarderror for continuous variables, and as numbers (percentages) for categorical variables. A one way multivariate analysis of covariance was used to control the pretest differences,

Table 1. Baseline characteristics of subjects

		Placebo (n=22)	Astaxanthin (n=22)	*p*
Sex (men/women)[b]		9/13	8/14	0.76
Age[a], y		54±8	51±9.7	0.24
Diabetic duration[a], y		4.5±4.6	3.6± 3.5	0.47
BMI[a], kg/m^2		30.4±5	30.0±5.11	0.42
BMR[a], K cal		1517±174	1579±231	0.15
Total body fat[a], %		39.7±9.8	35.5±10.6	0.08
Visceral body fat mass[a], %		11±3.4	11.9±3.4	0.33
Oral antihyperttentiondrug[b], n (%)		8 (36.4)	7 (32)	0.47
Oral gluocose-lowering drug,rosiglitazone, n (%)[b]	0[†]	7 (31.8)	6 (27.4)	0.72
	1	7 (31.8)	4 (18.2)	
	2	1 (4.5)	4 (18.2)	
	3	3 (13.6)	4 (18.2)	
	4	3 (13.6)	4 (18.2)	
	5	1 (4.5)	0	
Oral gluocose-lowering drug, metformin, n (%)[b]	0[†]	2 (9.1)	1 (4.5)	0.63
	1	1 (4.5)	1 (4.5)	
	2	5 (22.7)	5 (22.8)	
	3	9 (40.9)	9 (40.9)	
	4	2 (18.2)	4 (9.1)	
	5	3 (9.1)	2 (13.6)	

Values are mans±SD unless otherwise indicated. [a]Independent-samples t test, [b]Mann–Whitney test.
[†]The number of oral glucose lowering pills.

followed by Dunnett's post hoc comparison for multiple comparisons between the groups and paired-sample student t tests for comparisons within each group. Finally the data were tested for normality using the Kolmogorov–Smirnov test. Because of the non normality of the studied variables (positively skewed distribution), logarithmic transformation was performed and homogeneity of the covariance matrix was examined using Box's M statistics. All statistical analyses were performed using SPSS, (Version 20, SPSS Inc., Chicago, IL), and significance was set at $p<0.05$.

RESULTS

Baseline anthropometric and demographic characteristics of the participants

We initially included 44 participants, of which 41 completed the study. A summary of their physical characteristics and received medication is presented in Table 1. Notably, the baseline data did not significantly differ between the AST and placebo groups (all data has not been displayed). Therefore, all further analyses were conducted based on the intervention.

Dietary and supplement intake

Dietary records were analysed for total dietary energy, fat, protein, carbohydrate, and micronutrient intake among the participants with type 2 diabetes mellitus before and after the intervention (Table 2). Because the best sources of natural AST are algae, yeast, wild sockeye salmon, trout, krill, and shrimp.[6] these were not included in the daily diet of our participants. Thus, food sources of AST were limited, and the background carotenoid intake could be estimated (Table 2). The aforementioned dietary parameters did not significantly differ before and after the intervention; additionally, the intake of other carotenoids did not differ between the groups during the study. After counting the recalled tablet boxes (either empty or containing AST supplements that were not consumed) at every 2-week visit, we determined that the compliance of our participants was satisfactory; only one participant dropped out of the study because of travel issues. In the placebo group, the plasma AST concentration was undetectable in all the participants at weeks 0 and 8. However, in the AST group, the plasma AST concentration increased from undetectable to 0.01μmol/L. No significant changes were observed in the participants' physical activity during the intervention ($p=0.062$).

The results for the effects of AST on the body composition, serum lipid profile, glycemic control, and adiponectin concentration are listed in Table 3. Overall, the 8-week administration of AST significantly increased serum adiponectin concentration ($p<0.05$) and reduced visceral body fat mass; serum trigylceride (TG), very-low-density lipoprotein (VLDL) cholesterol, and fructosamine concentrations; and systolic blood pressure (SBP; all $p<0.05$; Table 3).

Although the comparison within the groups indicated that AST increased Basal Metabolic Rate (BMR), the comparison between the groups did not provide any significant results ($p>0.05$). Compared with the placebo group, slight changes were observed in the plasma glucose and high-density lipoprotein (HDL) cholesterol concentrations in the AST group ($p=0.06$).

DISCUSSION

The results of this study revealed that 8 mg of the AST supplement, which is a potent antioxidant, subsequently reduced visceral fat and increased adiponectin concentrations. This finding is consistent with the results of previous studies that reported that the concentration of adiponectin (an adipose-specific protein) was inversely correlated with the visceral adipose tissue area,[11] and that extreme fat mass reduction in obese individuals was associated with an increase in plasma adiponectin concentration.[12] A growing body of evidence has indicated that the degree of hypoadiponectinemia is more closely related to the degree of insulin resistance, and that adiponectin can link intra-abdominal fat with insulin resistance and stimu-

Table 2. Average daily macronutrients and some of micronutrients intake

	Placebo(n=21)			Astaxanthin (n=22)		
	Baseline	8 wk	*p*	Baseline	8 wk	*p*
Energy, kcal	3516±1300	3806±1402	0.31	4012±1409	4262±1223	0.32
Protein, g	150±83	160±70	0.71	144.95±76	167±58	0.17
Fat, g	124±58	125±52	0.91	139±59	140±59	0.48
Carbohydrate, g	520±190	549±250	0.52	521±222	559±225	0.48
Fiber, g	31±13	34±15	0.47	30±14	39±17	0.09
Vitamin C, mg	230±106	188±120	0.16	124±69	115±58	0.83
Vitamin E, mg	99±99	94±102	0.26	34±29	27±30	0.28
Vitamin A, µg	219±276	230±340	0.09	349±327	327±302	0.10
Vitamin K, mg	284±149	361±282	0.29	250±218	361±200	0.10
α-carotene , µg	807±140	878±149	0.09	815±140	887±140	0.08
B- carotene, µg	1236±810	1260±770	0.14	1322±819	1332±710	0.23
Lutein & zeaxanthin, µg	1163±819	1220±810	0.17	1263±823	1220±870	0.24
Lycopene, µg	2195±988	2210±870	0.20	2300±1010	2360±810	0.35
Zinc, mg	15±5	17±6	0.16	16±9	19±6	0.12
Calcium, mg	1988±255	1629±382	0.57	1560±228	1587±260	0.89
Sodium, mg	3552±390	2769±146	0.40	3269±329	3042±184	0.82
Cholesterol, mg	398±98	418±102	0.41	549±261	561±265	0.65
Saturated fatty acid, mg	32±13	32±14	0.85	49±23	52±27	0.14
Unsaturated fatty acid, mg	52±28	57±28	0.60	90±41	92±43	0.70

Values are means±SD.
*p<0.05 between groups.
**p<0.05 for change within group baseline to 8 weeks.

Table 3. Anthropometric data, lipid profiles and serum serum biochimical values

	Placebo (n=21)			Astaxanthin (n=22)			*p*
	Baseline	8 wk	*p*	Baseline	8 wk	*p*	
BMI, kg/m^2	30.1±5.1	30.4±5.09	0.04	30.0±5.18	29.9±5.18	0.61	0.18
BMR, kcal	1513±185	1515±222	0.95	1579±231	1595±238	0.06	0.64
Total body fat mass,%	38.6±9.8	39.8±8.9**	0.05	35.5±10.6	35.8±10.4	0.67	0.25
Visceral body fat mass,%	11.15±3.6	11.85±3.8**	0.03	11.9±3.4	11.2±3.4*	0.08	0.03
Fasting blood glucose, mmol/l	8.4±2.7	9.4±3.2	0.18	9.1±2.9	8.3±2.7	0.09	0.057
Systolic blood pressure, mm Hg	130±19	133±19	0.34	143±27	132±18*,**	0.01	0.04
Diastolic blood pressure, mm Hg	81±11	84±11	0.123	85±15	83±13	0.25	0.10
Serum HDL cholesterol, mg/dl	36.6±7.9	36.1±7.2	0.66	37.4±5.2	38.1±5.7	0.09	0.06
Serum LDL cholesterol, mg/dl	89±29	92±26	0.64	85.7±27	88±27	0.54	0.71
Serum VLDL cholesterol, mg/dl	28±12	31±16	0.17	31±18	27±16*	0.09	0.05
Total cholesterol, mg/dl	153±34	159±37	0.56	153.8±35	146±30	0.06	0.12
Serum TG,mg/dl	140±57	150±85	0.37	156±90	128±52*,**	0.05	0.05
Serum fructosamine, µmol/l	6.02±3.79	7.32±4.31	0.12	7.36±4.2	5.8±3.8*,**	0.03	0.02
Serum adiponectin, µg/ml	46±15	45±13	0.82	36±15	47±14*,**	0.01	0.04

Values are means±SD.
*p<0.05 between groups.
**p<0.05 for change within group baseline to 8 weeks.

late fatty acid oxidation.[12,13] By contrast, we found that an increased adiponectin concentration was related to a decrease in the body fat mass induced by AST.

Our results demonstrated an inverse relationship between adiponectin and diabetes through a significant reduction in fructosamine concentrations and a marginal reduction in fasting plasma glucose concentrations, which has been reported in previous studies.[3,14] The upregulation of adiponectin is a partial cause of the insulin-sensitizing and antidiabetic properties of some drugs used in the treatment of diabetes.[15,16] Several studies have also reported that adiponectin increases fatty acid oxidation in muscles and reduces plasma glucose concentrations through molecular mechanisms that stimulate AMP-activated protein kinase and PPARα activation in the liver and muscles.[15,17,18]

Other proposed mechanisms may also be involved in the antidiabetic effects of AST. One study determined that AST supplementation in a diabetic db/db mice model protected pancreatic β-cells against glucose toxicity by reducing blood glucose concentrations and hyperglycemia-induced oxidative stress,[19] which can be related to adiponectin. However, animal studies have also demonstrated that AST may reduce hyperglycemia and improve insulin secretion and sensitivity through the improvement of glucose metabolism and β-cell dysfunction by GLUT4 regulation.[7,20]

In our study, AST reduced TG and VLDL cholesterol concentrations in the participants with diabetes. These data extend the results that have thus far been reported for participants with mild hypertriglycemia[21, 22] or in animal studies.[23] However, the affirmative effects of AST on the lipid profile of participants with diabetes remain unreported before our research. In this study, we observed an

inverse relation of adiponectin with TG and VLDL cholesterol, which is consistent with that reported in a previous study.[24] The enhanced catabolism of VLDL through increased lipoporotein lipase and VLDL receptor expression related to improved insulin resistance is considered as the mechanism underlying the reduction in the serum TG concentration.[21,25]

In this study, AST exerted a blood pressure lowering effect on participants with type 2 diabetes mellitus, this finding is consistent with that reported in a previous study.[26] Furthermore, reduction in SBP caused by AST was evaluated and linked to superoxide scavenging and vaso-relaxation properties, along with reductioning insulin resistance.[27]

Finally, we observed that AST exerted HDL-minor rising effects in our participants, which was positively correlated with a change in adiponectin concentration. Although the mechanisms underlying AST-mediated HDL elevation remain poorly understood, one study identified a significant association between serum adiponectin and HDL cholesterol.[28] Moreover, Yoshida et al reported that the administration of 12 mg of AST significantly increased the HDL cholesterol concentration in nonobese participants, and argued that changes in the adiponectin concentration were positively correlated with changes in the HDL cholesterol concentration.[21]

This study has some limitations that should be addressed. First, although we reported that AST supplementation improved insulin sensitivity, which is in contrast to the findings of previous animal studies, we could not determine molecular mechanisms underlying the effects of AST in human cells. Second, we could not compare hypolipidemic and hypoglycemic effects of AST with diabetic drugs in a dose-dependent manner. However, these findings may provide new insights into the potential role of AST in modulating several conditions in participants with type 2 diabetes mellitus.

In conclusion, we demonstrated that because participants with type 2 diabetes often have hypertriglycemia and uncontrolled glucose metabolism, our findings of dual beneficial effects are clinically valuable. Our results offer a novel complementary treatment with potential impacts on diabetic complications without adverse effects.

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AUTHOR DISCLOSURES

The author(s) declare that they have no competing interests.

REFERENCES

1. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344: 1343-50. doi: 10.1056/nejm200105033441801.
2. Ceriello A. Oxidative stress and glycemic regulation. Metabolism. 2000;49:27-9. doi: 10.1016/S0026-0495(00)80082-7.
3. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86: 1930-5. doi: 10.1210/jcem.86.5.7463.
4. Rafraf M, Malekiyan M, Asghari-Jafarabadi M, Aliasgarzadeh A. Effect of fenugreek seeds on serum metabolic factors and adiponectin levels in type 2 diabetic patients. Int J Vitamin Nutr Res. 2014;86:196-205. doi: 10.1024/0300-9831/a000206.
5. Ceriello A, Testa R, Genovese S. Clinical implications of oxidative stress and potential role of natural antioxidants in diabetic vascular complications. Nutr Metab Cardiovasc Dis. 2016;26:285-92. doi: 10.1016/j.numecd.2016.01.006.
6. Ambati RR, Phang S-M, Ravi S, Aswathanarayana RG. Astaxanthin: sources, extraction, stability, biological activities and its commercial applications—a review. Mar Drugs. 2014;12:128-52. doi: 10.3390/md12010128.
7. Ishiki M, Nishida Y, Ishibashi H, Wada T, Fujisaka S, Takikawa A et al. Impact of divergent effects of astaxanthin on insulin signaling in L6 cells. Endocrinology. 2013;154: 2600-12. doi: 10.1210/en.2012-2198.
8. Kishimoto Y, Yoshida H, Kondo K. Potential anti-atherosclerotic properties of astaxanthin. Mar Drugs. 2016; 14:35. doi: 10.3390/md14020035.
9. Kimura M, Iida M, Yamauchi H, Suzuki M, Shibasaki T, Saito Y, Saito H. Astaxanthin supplementation effects on adipocyte size and lipid profile in OLETF rats with hyperphagia and visceral fat accumulation. J Funct Foods. 2014;11:114-20. doi: 10.1016/j.jff.2014.08.001.
10. Yang Y, Seo JM, Nguyen A, Pham TX, Park HJ, Park Y, Kim B, Bruno RS, Lee J. Astaxanthin-rich extract from the green alga Haematococcuspluvialis lowers plasma lipid concentrations and enhances antioxidant defense in apolipoprotein E knockout mice. J Nutr. 2011;141:1611-7. doi: 10.3945/jn.111.142109.
11. Park JS, Chyun JH, Kim YK, Line LL, Chew BP. Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans. Nutr Metab. 2010;7:18. doi: 10.1186/1743-7075-7-18.
12. Asayama K, Hayashibe H, Dobashi K, Uchida N, Nakane T, Kodera K, Shirahata A, Taniyama M. Decrease in serum adiponectin level due to obesity and visceral fat accumulation in children. Obesity. 2003;11:1072-9. doi: 10.1038/oby.2003.147.
13. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11:11-8. doi: 10.1111/j.1467-789X.2009.00623.
14. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444:840-6. doi: 10.1038/nature05482.
15. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116:1784-92. doi: 10.1172/JCI29126.
16. Dibello JR, Baylin A, Viali S, Tuitele J, Bausserman L, McGarvey ST. Adiponectin and type 2 diabetes in Samoan adults. Am J Hum Biol . 2009;21:389-91. doi: 10.1002/ajhb.20858.
17. Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M et al. A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. Endocrinology. 2004;145:367-83. doi: 10.1210/en.2003-1068.
18. Goldberg RB, Temprosa M, Mele L, Orchard T, Mather K, Bray G et al. Change in adiponectin explains most of the

change in HDL particles induced by lifestyle intervention but not metformin treatment in the Diabetes Prevention Program. Metabolism. 2016;65:764-75. doi: 10.1016/j. metabol.2015.11.011.
19. Nakajima Y, Inokuchi Y, Shimazawa M, Otsubo K, Ishibashi T, Hara H. Astaxanthin, a dietary carotenoid, protects retinal cells against oxidative stress in-vitro and in mice in-vivo. J Pharm Pharmacol. 2008;60:1365-74. doi: 10. 1211/jpp/60.10.0013.
20. Bhuvaneswari S, Anuradha CV. Astaxanthin prevents loss of insulin signaling and improves glucose metabolism in liver of insulin resistant mice. Can J Physiol Pharmacol. 2012;90:1544-52. doi: 10.1139/y2012-119.
21. Yoshida H, Yanai H, Ito K, Tomono Y, Koikeda T, Tsukahara H, Tada N. Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. Atherosclerosis. 2010; 209:520-23. doi: 10.1016/j.atherosclerosis.2009.10. 012.
22. Hussein G, Nakagawa T, Goto H, Shimada Y, Matsumoto K, Sankawa U, Watanabe H. Astaxanthin ameliorates features of metabolic syndrome in SHR/NDmcr-cp. Life Sci. 2007; 80:522-9. doi: 10.1016/j.lfs.2006.09.041.
23. Karppi J, Rissanen TH, Nyyssönen K, Kaikkonen J, Olsson AG, Voutilainen S, Salonen JT. Effects of astaxanthin supplementation on lipid peroxidation. Int J VitamNutr Res. 2007;77:3-11. doi: 10.1024/0300-9831.77.1.3.
24. Cnop M, Havel PJ, Utzschneider K, Carr D, Sinha M, Boyko E et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia. 2003;46:459-69. doi: 10.1007/s00125-003-1074-z.
25. Christou G, Kiortsis D. Adiponectin and lipoprotein metabolism. Obes Rev. 2013;14:939-49. doi: 10.1111/obr. 12064.
26. Monroy-Ruiz J, Sevilla M-Á, Carrón R, Montero M-J. Astaxanthin-enriched-diet reduces blood pressure and improves cardiovascular parameters in spontaneously hypertensive rats. Pharmacol Res. 2011;63:44-50. doi: 10. 1016/j.phrs.2010.09.003.
27. Yanai H, Ito K, Yoshida H, Tada N. Antihypertensive effects of astaxanthin. Integr Blood Press Control. 2008;1: 1-3.
28. Belalcazar LM, Lang W, Haffner SM, Hoogeveen RC, Pi-Sunyer FX, Schwenke DC et al. Adiponectin and the mediation of HDL-cholesterol change with improved lifestyle: the Look AHEAD Study. J Lipid Res. 2012;53: 2726-33. doi: 10.1194/jlr.M030213.