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Review

Carotenoids in the treatment of diabetes mellitus and its complications: A mechanistic review

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ABSTRACT

Carotenoids are a large class of natural antioxidants that occur in many vegetables, foods and other natural sources. To date, a large number of biological properties have been reported from carotenoids, particularly protective effects against diabetes mellitus (DM), cancer, and neurodegenerative, metabolic and cardiovascular diseases. However, recent studies including clinical evidences, have shown that carotenoids play a role in the treatment of diabetes via enhancing insulin sensitivity. They are also able to protect the body from long-term consequences of diabetes including infectious diseases, nephropathy, neuronal and eye abnormalities. In this review, we try to discuss the mechanisms behind the biological effects of carotenoids for the prevention and treatment of DM and its complications. The authors believe that carotenoids will have a prominent place in the treatment of DM and its complications in the future.

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Abbreviations: AChE, acetylcholinesterase; CAT, catalase; CCL2, CC-chemokine ligand 2; CXCL8, CXC-chemokine ligand 8; COX-2, cyclooxygenase2; DM, diabetes mellitus; DACD, diabetes-associated cognitive decline; FKN, fractalkine; GLUT4, glucose transporter 4; GPx, glutathione peroxidase; GR, glutathione reductase; HFFD, high fructose diet; iNOS, inducible nitric oxide; IKKβ, inhibitor κB kinase β; IRS-1, insulin receptor substrates; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1β; IL-6, interleukin-6; JNK, c-Jun NH2 – terminal kinase; LPS, lipopolysaccharide; MDA, malondialdehyde; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB; PGC-1α, peroxisome proliferator activated receptor γ coactivator-α; PPARγ, peroxisome proliferator-activated receptor gamma; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; STZ, streptozotocin; SOD, superoxide dismutase; TAC, total antioxidant capacity; TNF-α, tumor necrosis factor-α; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor.

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1. Introduction

Carotenoids are a class of natural antioxidants that occur in fruits, vegetables and marine sources as colorful pigments. Most carotenoids such as β-carotene, lycopene, lutein, zeaxanthin, astaxanthin and bixin are lipophilic tetraterpenoids (40-carbon skeleton) having isoprene as their biogenetic precursor (Fig. 1). A body of scientific evidence suggests that carotenoids have beneficial effects in prevention of a large number of diseases, particularly cardiovascular diseases and cancer. Versatile biological activities of these carotenoids have been attributed to their scavenging free radicals, quenching ROS, augmentation of self-defense systems and photo-protection. Therefore, carotenoids prevent cancer, cardiovascular diseases, diabetes, osteoporosis, age-related eye diseases, Alzheimer's disease, etc.

Recent advances on biological properties of carotenoids have shown that carotenoids are able to not only prevent but also treat or ameliorate diabetes and its subsequent complications. Beneficial effects of carotenoids in diabetes and metabolic syndrome are more than those expected from natural antioxidants. It has been shown that dietary carotenoids and plasma β-carotene concentrations were inversely associated with fasting plasma glucose concentrations and insulin resistance, respectively [1]. An inverse relation was also observed between serum carotenoid (lycopene, lutein, β-carotene) concentrations and fasting serum insulin concentrations and metabolic syndrome [1,2]. A large number of studies have revealed that carotenoids reduce type 2 diabetes risk in men and women [1,3]. It has also been observed that carotenoid intake has an inverse relation with HbA_{1c} level [4]. In addition, recent findings have confirmed the protective roles of carotenoids including lycopene, lutein and zeaxanthin against diabetic retinopathy [5].

It should be noted, however, the role of carotenoids in the pathogenesis of diabetes remains unclear. The beneficial effects of carotenoids in diabetes cannot be simply associated with their antioxidant properties. It seems that other mechanisms (except antioxidant activity) play roles in the pharmacological effects of carotenoids. In this article, we review the preventive and therapeutic effects of carotenoids in diabetes and molecular mechanisms that are behind these pharmacological activities. In addition, we highlight the gaps in our knowledge about the association of carotenoid intake and diabetes, deserving future research.

2. Carotenoids intake and the incidence of diabetes mellitus

Previous studies revealed that dietary factors including antioxidants have important roles in the prevention of T2DM. Most of these studies show an inverse relation between dietary intake of vegetables and antioxidants and the risk of T2DM [6]. Considering the potent antioxidant effects of natural carotenoids, the role of carotenoids in the prevention and treatment of T2DM has been investigated in different studies. For example, Sugiura et al. in a recent study showed that in middle-aged and older Japanese subjects, serum levels of α-carotene and β-cryptoxanthin are associated with lower incidence of T2DM [7]. Another study evaluated the relation between serum concentrations of five carotenoids and T2DM incidence for 15 years [8]. The results revealed an inverse association between serum concentration of carotenoids and T2DM in non-smokers but not in smoker subjects. Such positive results were also reported by Ylonen et al. [1]. They showed that serum concentrations of lutein, zeaxanthin, lycopene, α-carotene and β-carotene were significantly lower in diabetic subjects. In agreement, there are more studies indicating the association of carotenoids intake and the reduced risk of T2DM [3,8,9]. However, there are inconsistencies among studies

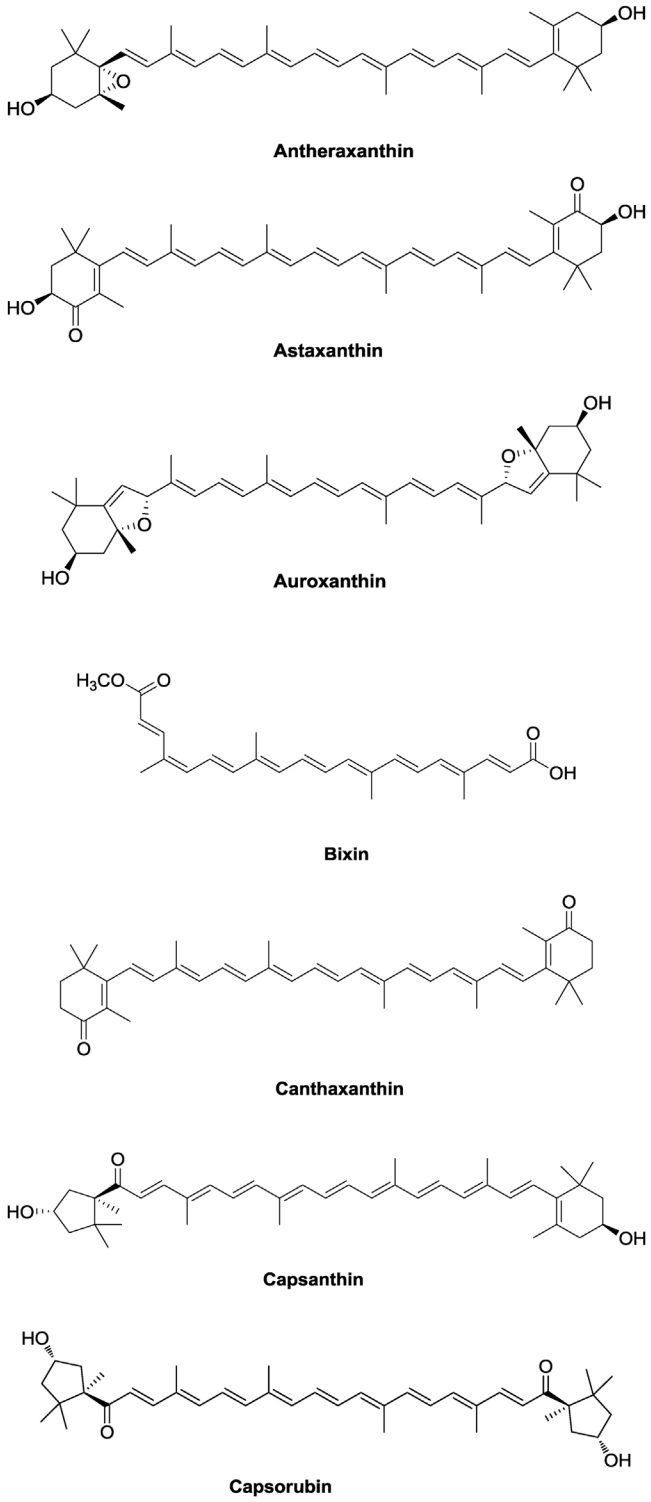

Fig. 1. Chemical structures of some carotenoids.