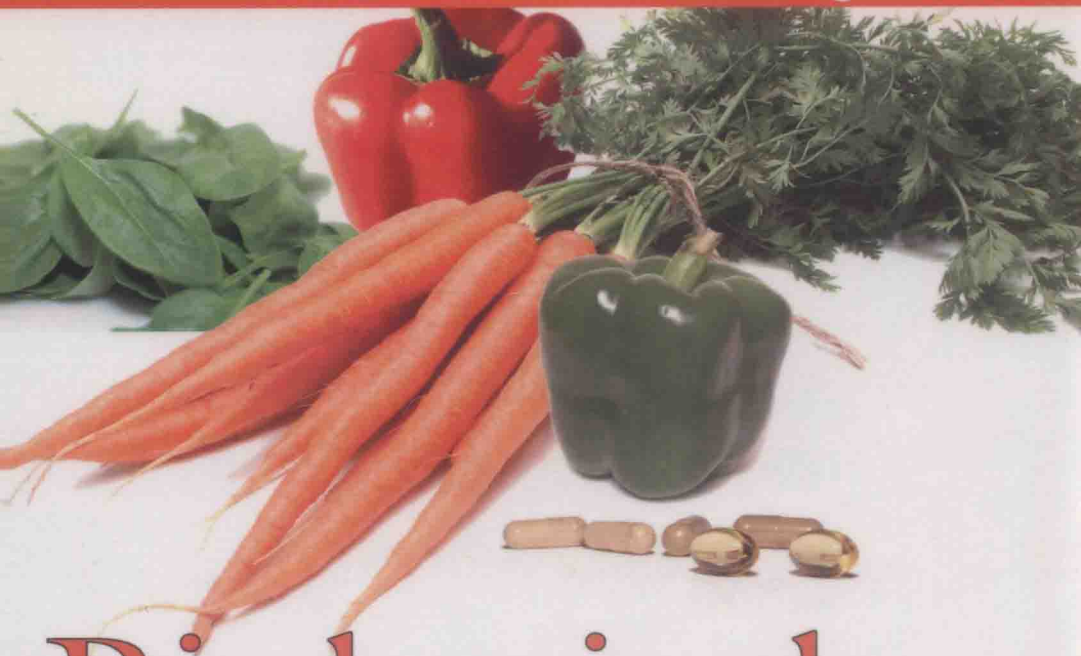
Nutrition and Diet Research Progress



Biological Effects of β–Carotene

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BIOLOGICAL EFFECTS OF β–CAROTENE

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PREFACE

Several carotenoids show enhancement of the immune response, inhibition of mutagenesis, reduction of induced nuclear damage, and protection from various neoplastic events in cells, tissues, and whole animals. Carotenoids protect also against photo-induced tissue damage. Some carotenoids, including β-carotene, quench highly reactive singlet oxygen under certain conditions and can block free radical-mediated reactions. There is a growing body of literature on the effects of β-carotene in human chronic diseases, including cancer. Evidence from observational epidemiological studies has shown that a high consumption of fruits and vegetables rich in carotenoids is associated with a low risk for cancer. However, some human intervention trials failed to demonstrate prevention of cancer by β-carotene supplements. Several studies have indicated that among subjects who neither smoked cigarettes nor drank alcohol, β-carotene was associated with a marked decrease in the risk of one or more recurrent adenomas but β-carotene supplementation conferred a modest increase in the risk of recurrence among those who smoked. An increase in the risk of lung cancer among smokers and asbestos workers who took β-carotene supplements is also reported. In fact this trial raises the possibility that these supplements may actually have harmful as well as beneficial effects. Alcohol intake and cigarette smoking appear to modify the effect of β-carotene supplementation at the risk of colorectal adenoma recurrence. Similarly, serum β-carotene levels have been associated with a decreased chance of developing cancer. These results show a remarkable consistency for the association of increased lung cancer risk with low amounts of dietary β-carotene or low plasma β-carotene concentrations. For stomach cancer, the evidence is also consistent, although the number of studies is more modest. For breast and prostate cancer, the studies indicate no

consistent association of plasma or dietary β-carotene and reduced cancer risk. For colorectal cancer, the effect will be moderate, if existent. Whatever the results of these trials, carotenoids clearly show biological actions in animals distinct from their function as precursors of vitamin A. This book is an up-to-date and comprehensive analysis of pharmacological, toxicological reports and clinical applications of the β-carotene.

INTRODUCTION

Carotenoids are found almost everywhere in nature, but particularly among organisms that bask in the sun. These interesting compounds, most of which reveal a yellow to red color, have attracted the attention of biologists at least since the early 1800s. Colored compounds in plants, animals, and microorganisms were extracted and purified, and in time their structures were determined. Many treatises have been devoted to these compounds, the most comprehensive of which was edited by Isler in 1971.

Straub in 1971 listed the 273 compounds sufficiently characterized at that time to be clearly distinct from all others. An update of this key in 1987 expanded the list to 563 distinct compounds (Straub, 1987). Because *cis-trans* isomers of a given carotenoid are not listed separately, the actual number of naturally occurring carotenoids is significantly larger. Thus, carotenoids represent a very large group of substances with various structural characteristics and biological activities.

600 carotenoids from natural sources have been characterized, fewer than 10% serve as precursor's of vitamin A. Many dietary carotenoids, both with and without provitamin A activity, are found in the blood and tissues of humans. β-Carotene, the most nutritionally active carotenoid, comprises 15-30% of total serum carotenoids (Bendich and Olson, 1989).

β-carotene is a member of the carotenoids, which are highly pigmented (red, orange, yellow), fat-soluble compounds naturally present in many fruits, grains, oils, and vegetables (green plants, carrots, sweet potatoes, squash, spinach, apricots, and green peppers). α, β, and γ carotene are considered provitamins because they can be converted to active vitamin A, which is a nutrient that is vital to growth and development. It is obtained in the diet from animal sources and is also derived from β-carotene in plant foods. It is broken

down in the mucosa of the small intestine by β-carotene dioxygenase to retinal, a form of vitamin A and this is mainly stored in the liver in the form of retinol esters. β-carotene can also be absorbed and stored in the fatty tissue without being modified, producing a slightly yellow or orange color on the palms of the hands. Vitamin A and closely related molecules are also known as retinoids (Kennedy et al., 1996).

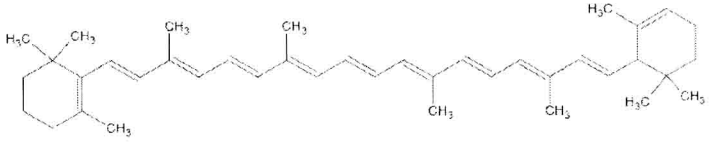
In humans, absorbed β-carotene is converted into retinal in enterocytes and the liver by a specific enzyme (15,15′-dioxygenase), which generates retinal by central cleavage (Roos et al., 1998). Another metabolic pathway is eccentric cleavage of β-carotene via β-apocarotenals to retinal (Blomhoff et al., 1992). Retinal is then converted into retinol by dehydrogenases, and retinol is transported by retinol-binding protein, a specific plasma protein, to target tissues. Human epidermis contains two major retinoids (retinol and retinyl esters) and carotenoids (mainly β-carotene) (Vahlquist, 1982). Vitamin A can be stored in keratinocytes through esterification of retinol into retinyl esters. This step is catalyzed by two enzymes, acyl-CoA: retinol acyltransferase (ARAT) and lecithin: retinol acyltransferase (LRAT); their expression is modulated by the differentiation state of the keratinocytes (Torma et al., 1988). Hydrolysis of retinyl esters into retinol is catalyzed by retinyl ester hydrolases. Retinol, via its oxidation into retinal, is a pro-hormone of retinoic acid (Siegenthaler et al., 1990), the biologically active form of vitamin A that modulates gene expression following its binding to nuclear receptors. Thus retinal, retinol, and its esters are endogenous precursors of the biologically active form of vitamin

A (Antille et al., 2004). Carotene is an orange photosynthetic important for photosynthesis. It contributes to photosynthesis by transmitting the light energy it absorbs to chlorophyll. Chemically, carotene is a terpene, synthesized biochemically from eight isoprene units. β-carotene is composed of two retinyl groups.The two primary isomers of carotene, α-carotene and β-carotene, differ in the position of double bonds in the cyclic group at the end (Pitchford, 2002).

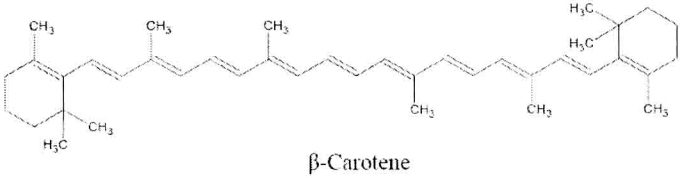
β-Carotene is the most abundant carotenoid in nature and most important for the human diet, so muc so that it gives its name to a whole group of biochemical compounds. Its structure was determined in 1930 by a Paul Karrer work that earned him the Nobel prize in chemistry. This was the first time in history in which the structure of a vitamin or pro-vitamin was identified. The absorption spectrum of β-carotene shows two absorption peaks between 400 and 500 nm, corresponding to blue and green, so that the red-orange-yellow reflecting gives its characteristic color (Karrer, 1928).

The main properties of the β-carotene are:

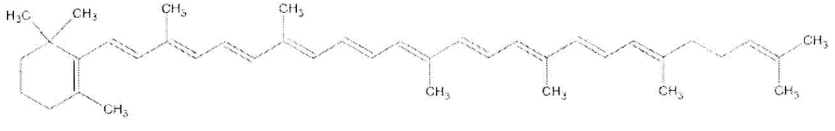
- Antioxidant function: quenching the action of oxygen free radicals, inhibiting the peroxidation of lipids of the membranes.
- Protection from solar radiation (photoprotectors), encouraging the production of melanin and therefore a tan uniform and intense.
- Immune function: improved resistance to infection.
- Restoration and maintenance of the epithelial cells which are the cavities of the body (skin, glands, membranes, gastrointestinal mucosal).



α-carotene



β-Carotene



γ-Carotene

CONTENTS

Chapter 1

B-CAROTENE AND CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is a major cause of mortality and morbidity in the Western world. In recent years its importance has expanded internationally and it is believed that by 2020 it will be the biggest cause of mortality in the world, emphasizing the importance on preventing or minimizing this increase. Studies have indicated that beta-carotene mediates pro-oxidant effects and it has been suggested that its negative effects may diminish the beneficial effects mediated by the other vitamins in the supplementation cocktail. Trials that used a combination of vitamins that include β-carotene have been disappointing (Honarbakhsh and Schachter, 2008).

In middle-aged and older women free of CVD and cancer, plasma carotenoids were associated with smoking, obesity, LDL cholesterol, HDL cholesterol, Hb A(1c), and CRP. Associations differ among individual carotenoids, possibly reflecting metabolic effects of lifestyle and physiologic factors on plasma carotenoids, and may partially explain the inverse association of plasma carotenoids with CVD outcomes observed in epidemiologic studies.

The possible protective effect of antioxidants on coronary heart disease (CHD) has been under intensive investigation during the last two decades. The major hypothesis behind this interest is the role of oxidized low-density lipoprotein (LDL)-cholesterol in atherogenesis and the *in vitro* evidence that antioxidants inhibit oxidative modification of LDL-cholesterol (Esterbauer et al., 1989). Oxidised LDL cholesterol stimulates differentiation of monocytes into macrophages and accumulates in macrophages by a nonregulated

scavenger receptor pathway. Oxidised LDL induces proliferation of smooth muscle cells, is chemotactic and cytotoxic, and impairs endothelial function (Kaplan and Aviram, 1999).

Abdominal aortic aneurysm (AAA) is a common and often a fatal condition of the human aorta with a clear male predominance. In the scope of public health, the importance of AAA has been growing, because its mortality rate has not shown a decreasing trend during the last decades (Drott et al., 1992), as has that of other cardiovascular diseases. AAA is a degenerative disorder with a complex etiology. Atherosclerosis is considered the major cause, but lately evidence of the importance of other factors has emerged. There is evidence of familial clustering and involvement of hemodynamic factors (MacSweeney et al., 1992). In patients with aneurysm, histological studies have shown atherosclerosis, inflammation, and loss of elastin and collagen content in the aortic wall (Thompson, 1996).

According to Wang et al., (2008) CVD risk factors may potentially influence plasma concentrations of carotenoids. Baseline plasma carotenoids, (α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein-zeaxanthin), blood lipids, Hb A(1c), and CRP were available for studies in 2895 women. Results showed that women who were current smokers or obese had lower plasma concentrations of most carotenoids, expect for lycopene. An increase in LDL cholesterol was associated with a increase in α-carotene, β-carotene, and lycopene.

Tornwall et al., (2004) evaluate the 6-year post-trial effects of α-tocopherol and β-carotene supplementation on coronary heart disease (CHD). 29,133 male smokers, aged 50–69 years were randomised to receive α-tocopherol 50 mg, or β-carotene 20 mg, or both, or a placebo daily for 5–8 years. At the beginning of the post-trial follow-up, 23,144 men were still at risk for a first-ever major coronary event (MCE), and 1,255 men with pre-trial history of myocardial infarction (MI) were at risk for MCE. β-Carotene seemed to increase the post-trial risk of first-ever non-fatal MI but there is no plausible mechanism to support it. Reports do not advocate the use of α-tocopherol or β-carotene supplements in prevention of CHD among male smokers.

In a nested case-control study of 513 women with cancer; 130 with cardiovascular disease and equal numbers of controls, we found no effect of randomised β-carotene on risk of cancer or cardiovascular disease within any quartile of baseline plasma β-carotene, nor was there a trend across quartiles (Lee et al., 2002).

A 12-year followup of cardiovascular mortality was also reported by Gey et al., (1993) and reveals a significantly increased relative risk of ischemic heart disease and stroke at initially low plasma levels of β-carotene (< 0.23 μmol/l) and/or vitamin C (< 22.7 μmol/l), independently of vitamin E and of the classical cardiovascular risk factors. Low levels of both carotene and vitamin C increase the risk further, in the case of stroke even with significance for overmultiplicative interaction. In conclusion, in cardiovascular disease an independent inverse correlation may exist for every major essential antioxidant although the latter can also interact synergistically.

It is also reported by data of 6-year post-trial effects of α-tocopherol and β-carotene supplementation on coronary heart disease (CHD) in the α-tocopherol, β-carotene cancer prevention (ATBC) study on 29,133 male smokers, aged 50-69 years were randomised to receive α-tocopherol 50 mg, or β-carotene 20 mg, or both, or placebo daily for 5-8 years. Results supported that α-tocopherol supplementation had no significant post-trial effect on first-ever MCEs during the 6-year followup, a result similar to that observed during the trial period. In contrast, β-carotene supplementation increased the post-trial risk of MCE (major coronary event) and non-fatal MI by 14% and 16%, respectively.

Post-trial risk for fatal CHD increased by 11%, but did not reach statistical significance. These findings of β-carotene were unexpected since no increased risk was observed during the trial period when the corresponding relative risks were 1% for MCE, 0% for non-fatal MI (myocardial infarction) and 2% for fatal CHD. The late effects of α-tocopherol and β-carotene on MCEs in men with pre-trial MI. α-Tocopherol supplementation had no significant effect on MCEs in these men either during or after the intervention. During the intervention the risk of fatal CHD was significantly increased by 44% among those who received β-carotene compared with those who did not, whereas β-carotene had no post-trial effect on fatal CHD or non-fatal recurrent MI (Tornwall et al., 2001).

Also reported was the relation between the intakes of dietary carotene, vitamin C, and vitamin E and the subsequent coronary mortality which was studied in a cohort of 5,133 Finnish men and women aged 30-69 years and initially free from heart disease. Food consumption was estimated by the dietary history method covering the total habitual diet during the previous year. Altogether, 244 new fatal coronary heart disease cases occurred during a mean follow-up of 14 years beginning in 1966-1972. An inverse association was observed between dietary vitamin E intake and coronary mortality in both

men and women with relative risks between the highest and lowest tertiles of the intake (Knekt et al., 1994).

Other double-blind studies were randomised to receive an antioxidant cocktail including 600 mg of α-tocopherol, 250 mg of vitamin C and 20 mg of β-carotene was supplemented for five years without any benefit on major coronary events among over 20,000 high-risk subjects (Heart Protection Study Collaborative Group, 2002). In contrast, the Cambridge Heart Antioxidant Study among 2000 patients with angiographically proven coronary atherosclerosis found a significant decrease in risk for non-fatal MI, but this surprisingly high risk-reduction was not reflected in cardiovascular mortality (Stephens et al., 1996).

Furthermore, β-carotene trials have not provided evidence of favourable effects on CHD, although the opposite was expected based on the observational studies (Pandey et al., 1995). In a Physicians' Health Study, no effect on cardiovascular mortality or risk for MI was observed among over 22,000 male physicians randomised to receive 50 mg of β-carotene or placebo every other day for 12 years (Hennekens et al., 1996). In nearly 40,000 US women randomised to receive 50 mg of β-carotene, or 600 IU of α-tocopherol, or 100 mg of aspirin, or placebo every other day no early effect of β-carotene was observed on cardiovascular endpoints (Lee et al., 1999). In these two studies, only 11% and 13% of the participants, respectively, were smokers.

In the beta-carotene and retinol efficacy trial (CARET), the effect of the combination of 30 mg of β-carotene and 25,000 IU of vitamin A supplementation on lung cancer and cardiovascular diseases was assessed among 18,000 current or former smokers or workers exposed to asbestos. A suggestion of increased risk for cardiovascular mortality was observed among those who received combination supplementation compared with those who received placebo group after an average follow-up of 4 years (Omenn et al., 1996b).

In another study, meta analysis of 6 randomised trials was observed that the risk of cardiovascular death with β-carotene treatment was slightly increased (Vivekananthan et al., 2003).

Another trial show the evaluation of the effects of α-tocopherol and β-carotene supplementation on incidence of large abdominal aortic aneurysm (AAA) in a randomised, double-blind, placebo-controlled trial. Subjects 29,133 were 50–69-years-old male smokers, participants in the Finnish α-tocopherol, β-carotene Cancer Prevention (ATBC) Study. They were randomised to receive either 50 mg/day of α-tocopherol, or 20 mg/day of β-

carotene, or both, or a placebo. Incidence of AAA was evaluated from mortality and hospital registers. During 5.8 years of follow-up, 181 male were diagnosed with either ruptured AAA or nonruptured large AAA treated with aneurysmectomy. A modest though nonsignificant decrease in risk for nonruptured AAA was observed among α-tocopherol and β-carotene, supplemented male compared with male not receiving these antioxidants. Neither affected risk for ruptured AAA. In conclusion, long-term supplementation with α-tocopherol or β-carotene had no preventive effect on large AAA among male smokers (Tornwall et al., 2001).

The treatment during five year period of 20,536 UK adults (aged 40-80) with coronary disease, other occlusive arterial disease or diabetes with antoxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg of β-carotene daily). Although this regimen increased blood vitamin concentration substantially, it did not produced any significant reductions in five years mortality from, or incidence of, any type of vascular disease, cancer or other major outcome (UK Medical Research Concil, 2002).