

# Can Carotenoids Cure Or Protect Us?

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## SUMMARY

**Introduction:** Carotenoids are liposoluble plant pigments. The most common in the human diet are  $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin, lycopene, lutein, and zeaxanthin.

**Methods:** This article provides an overview of the findings on carotenoids to date, their depots in body, recommended daily doses and mechanisms of protective action. We searched PubMed, Google Scholar, SCIndex, Dimension, Scopus and Google for English and Serbian language abstracts, using the searching terms „carotenoids”, „provitamin A”, „antioxidants”, „cardiotoxicity”, „prevention” and „NADES”.

**Topic:** After being metabolised in intestinal mucosa (with the help of bile acids) and absorbed, carotenoids are mainly stored in the liver and adipose tissue. Major impact on carotenoids bioavailability is the nature of matrix/medium in which they are dissolved. The latest generation of non-toxic „green” solvents, the so-called NADES (natural deep eutectic solvents) are in special focus of research today. Lycopene has been confirmed to improve sperm efficiency, raising incidence of pregnancy. Regarding cardiovascular diseases, trans forms inhibit process of atherosclerosis, most likely by increasing HDL levels. Low serum  $\beta$ -carotene and  $\beta$ -cryptoxanthin concentrations is associated with increased mortality from heart diseases, but also stroke. Carotenoids also can cause apoptosis in TE1 cells of squamous cell carcinoma of the esophagus. The recommended daily doses are still not standardized, due to lack of studies performed. A group of provitamin A carotenoids, when converted to vitamin A, participate in the regulation of vision and prevention of eye diseases (xerophthalmia, macular degeneration, night blindness, ulcerations, scars). They are also associated with potential influences on reproduction, embryogenesis, immune system, intracellular connections as well as metabolic pathways. Studies indicate their influence in the prevention and treatment of cardiovascular diseases, but also various malignancies.

**Conclusion:** The literature data so far has indicated that carotenoids are a good choice in the prevention and treatment of various diseases, however, they are still insufficiently

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researched to define preventive and/or therapeutic doses.

**Keywords:** Carotenoids, Provitamin A, Antioxidants, Cardiotoxicity, Prevention, NADES

## INTRODUCTION

Carotenoids are liposoluble plant pigments present in dark yellow, red, orange and green fruits and vegetables. Over 700 carotenoids are known, and only about 40 are used in human nutrition and 12 can be measured in blood and human tissues. In the human organism, carotenoids are part of the antioxidant defense system. They interact synergistically with other antioxidants, and it has been noticed that a mixture of carotenoids are more effective than single compounds [1,2]. The most common are  $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin, lycopene, lutein and zeaxanthin (Figure 1). Although the chemistry of carotenoids has been studied extensively, their bioavailability, metabolism and biological functions are only now being brought to the focus of investigations. Recent interest in carotenoids has focused on their role in human health. Epidemiological evidence suggests that higher blood concentrations of  $\beta$ -carotene and other carotenoids obtained from foods are associated with a lower risk of several chronic diseases, other evidence suggests possible harm arising from very large doses in population subgroups, such as smokers and asbestos workers [2]. Existing recommendations calling for the increased consumption of carotenoid-rich fruits and vegetables for their health-promoting benefits are strongly supported [1].

## METHODS

This article provides an overview of the current findings on carotenoids, their depots in body, recommended daily doses and mechanisms of protective action. We searched PubMed, Google Scholar, SCIndex, Dimension, Scopus and Google for English and Serbian language abstracts, using the searching terms „carotenoids”, „provitamin A”, „antioxidants”, „cardiotoxicity”, „prevention” and „NADES”.

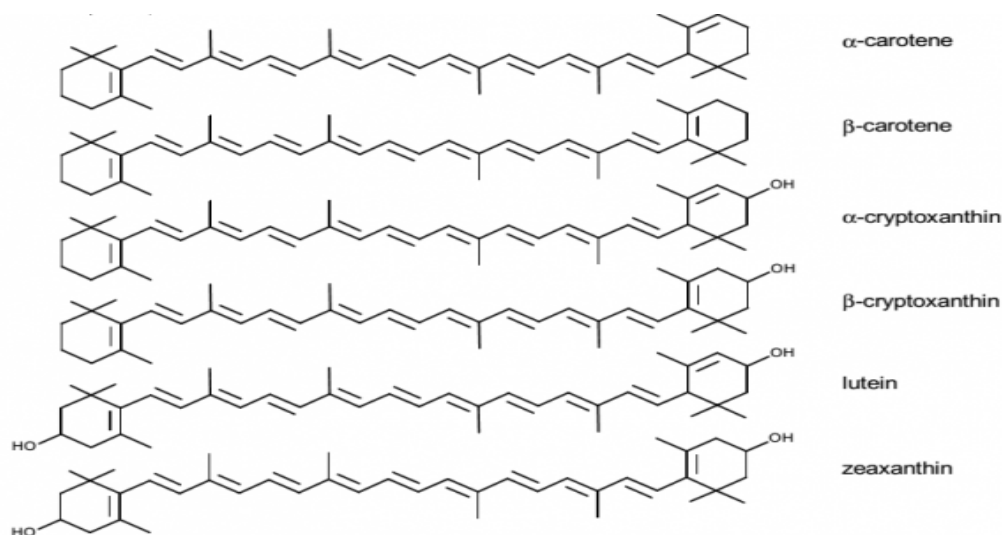
Based on expert selection review, we chose both open and blinded studies, reviews and meta analysis, and available comments and editorials, related to the MESH terms.

## TOPIC

### Depots in the human body, bioavailability and recommended daily intake

**The main depots** of carotenoids in the body are the liver and adipose tissue. Some representatives show affinity for certain tissues and organs, thus  $\beta$ -cryptoxanthin is deposited in the liver, lycopene in the testes, while in the adrenal glands they are all found in high concentrations [2]. Also, they can accumulate in the skin, mostly on the forehead and palms, and after the cessation of supplementation, they stay here longer than in the blood [3]. Their concentration in the body is determined from

**Figure 1.** Molecular structure of carotenoids



a blood sample, but it does not always correlate with the real concentration in the tissues [1].

**Absorption** of carotenoids takes place mostly in the intestinal mucosa through passive diffusion with the help of bile acids, from where the intact ones are mostly absorbed. Also, those converted into vitamin A or its metabolites can be absorbed. The lungs, liver and kidneys convert  $\beta$ -carotene to retinoic acid. The extent of absorption varies between 10% and 90%. Cigarettes and alcohol reduce circulating serum levels. Increased carotenoid intake in smokers increases the risk of lung cancer. Absorption is considered to be linear up to an intake of 20-30 mg, but becomes limited at higher intakes. Limited absorption allows the intake of large amounts without the risk of toxic effects.

There are several factors, which determine their bioavailability, and in the first place it is the matrix /medium in which they are dissolved. Effective transfer of carotenoids from food to target tissues where they can perform various biological functions includes several phases, namely: release from food matrix and formation of mixed micelles during intestinal digestion, then enterocyte uptake through passive diffusion, incorporation into chylomicrons rich in triacylglycerol and secretion into lymphatic system. In this whole process, the stability of the food matrix in this case of solvent, and the dissolution of carotenoids within the mixed micelle is a critical step for intestinal absorption of carotenoids [1].

Dissolved in an adequate solvent and protected by antioxidants, they are absorbed up to 70% or more. Regarding the solvents, it is necessary to use those that can dissolve natural or synthetic chemicals that are poorly soluble in water. The latest generation of „green” solvents, the so-called NADES (natural deep eutectic solvents) are in a special focus of research because, unlike conventional solvents, they are not toxic [4]. NADES solvents use only natural, non-toxic, biodegradable solids at room temperature to prepare liquid solvents. The great advantage of modern extraction techniques is the possibility of more efficient separation and preservation of sensitive bioactive compounds. The most important characteristics are their simple preparation, without the need for purification and simple creation of their properties by careful selection of appropriate starting compounds [4]. The use of NADES in solid-liquid extraction processes

also depends on their thermophysical properties, such as viscosity, density, mixing ability, polarity, and pH value [5]. Since NADES are specific solvents, it is possible to adjust their properties in order to achieve high solubility capacity, high extraction power and high stabilization ability of some natural products [6]. All these characteristics of NADES make them promising solvents for carotenoid extraction. As important as solvent is in extracts, so important is the method of preparation for food, where cooking in oil improves absorption, while too long exposure to high temperatures (until boiling) significantly reduces bioavailability. Studies show that consuming fat in the same meal with carotenoids increases absorption. Other factors important for the bioavailability of carotenoids are genetic, individual characteristics of humans, structure of molecules, as well as interaction with other nutrients and drugs [1,2,7].

**The recommended daily doses** of carotenoids are not yet standardized, and differ depending on the type of carotenoids, but also on whether they are used for preventive or therapeutic purposes [7]. Studies have examined the effect of preventive intake of 2-3 mg of various carotenoids per day, each of which shows the potential for a beneficial effect on a particular organ system. On the other hand, therapeutic doses should be several times higher than prophylactic ones. Some human studies have examined therapeutic doses for eye disease where doses up to 180 mg per day have been shown not to have adverse effects on the body and to inhibit disease progression [2].

### Mechanism of protective action

They are powerful **antioxidants** that can neutralize free radicals such as hydroxyl radicals and superoxide anions [8]. Iron (Fe) is considered to be one of the leading mediators in causing oxidative stress. Iron chelate, iron-nitrotriacetate (Fe-NTA), has been shown to cause lipid peroxidation of cells. Previous studies indicate that lycopene has a protective effect on Fe-NTA-treated breast cells, as well as preventing DNA damage and histopathological changes at the level of liver treated with the same iron chelate [9,10].

Certain carotenoids ( $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin) can be converted to vitamin A, and are called **provitamin A**

**carotenoids**, the effects of which have been largely investigated so far. Vitamin A has an antioxidant effect, and is important in the regulation of vision, being that its deficiency can cause xerophthalmia, night blindness, as well as ulcerations and scars [1]. Lutein and 2-5 mg of zexanthin per day can prevent the progression of some eye diseases, macular degeneration e.g. [7].

Also, carotenoids are associated with potential influences on **reproduction, embryogenesis, immune system, intracellular connections as well as metabolic pathways** [1]. A recent study investigated the effects of lycopene in men with infertility. A dose of 8 mg per day for 12 months has been shown to raise plasma lycopene levels, but also to improve sperm efficiency, resulting in pregnancy in 36% of male partners in the study [7].

Recent studies indicate that they may have a protective effect against **cardiovascular disease** [1,11]. Animal studies show that all trans forms of beta carotene can inhibit the process of atherosclerosis, most likely affecting the increase in HDL levels, which has a protective effect. Low serum  $\beta$ -carotene concentrations have been associated with increased mortality from heart disease, proving its protective role [12]. In addition, low concentrations of  $\alpha$ -carotene are associated with an increased risk of carotid and femoral atherosclerosis [13]. Ceilings et al. have shown that  $\beta$ -cryptoxanthin reduces the incidence of acute myocardial infarction [14]. Increased intake of tomatoes and its products rich in lycopene reduces the risk of atherosclerosis, acute coronary events, but also stroke, which could be associated with atherosclerotic plaques in carotid arteries [13]. Low plasma lycopene concentrations have been found in people with hypertension, indicating its protective potential in relation to arterial hypertension [7].

Carotenoids have the ability to slow tumor growth and **induce apoptosis**. Increasing number of research is dealing with their anticancer effect on tumor cells and prevention of malignant tumors.  $\beta$ -carotenes is decreasing apoptosis of MCF-7 breast adenocarcinoma cells, by reducing the activity of various enzymes which consequently leads to DNA damage of the malignant cell. Also, in small concentrations, it can cause apoptosis in TE1 cells of squamous cell carcinoma of the esophagus. *Lycopene* acting on the mitochon-

drial system of cells slows down the growth of ovarian cancer, while by acting on DNA fragments it leads to apoptosis of pancreatic cancer cells [15]. It has been proven that lycopene originating from tomatoes induces apoptosis of prostate cancer cells [13]. *Lutein*, unlike  $\beta$ -carotene, leads to apoptosis and necrosis of MDA-MB-468 breast cancer cells, but not MCF-7 cells. Apoptosis is induced by caspases of the independent mitochondrial pathway. *B-cryptoxanthin* induces apoptosis in both in vivo and in vitro models of gastric cancer. Doses of 5 and 10 mg/kg have been shown to suppress tumor growth. *Astaxanthin* causes apoptosis, inhibits the growth and proliferation of LS-180 colorectal cancer cells. The effect of astaxanthin is to reduce malonyldehyde levels and increase the concentration/activity of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase [16].

Studies indicate a protective role of carotenoids in doxorubicin-induced toxicity. It is believed that the use of carotenoids reduces lipid peroxidation in the heart, meninges, liver and kidneys. The protective effect correlates with the ability to remove oxygen free radicals (ROS). The protective effect was proven histopathologically, and there was no increase in biochemical markers of damage in these organs [16,17]. The use of carotenoids prevented doxorubicin-induced damage to healthy (tumor-unaffected) organs without interfering with the antitumor action of doxorubicin [18].

## CONCLUSION

The literature data so far indicate that carotenoids are a good choice in the prevention and treatment of diseases. However, clear mechanisms of potentially beneficial effects are still insufficiently researched. Recent studies should focus on several issues, namely: a) to improve extraction techniques in order to increase the oral bioavailability of carotenoids; b) investigate side effects and interactions with drugs and food; c) determine and standardize safe doses for various diseases; e) identify carotenoids that can prevent side effects and increase the effectiveness of drugs for the treatment of malignant diseases, the toxic effect of antitumor drugs, and at the same time accelerate their effect.

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## CONFLICT OF INTEREST

All authors declare no conflict of interest.

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## Mogu li nas karotenoidi zaštititi ili izlečiti?

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### KRATAK SADRŽAJ

**Uvod:** Karotenoidi su liposolubilni biljni pigmenti. Najčešće zastupljeni u ljudskoj ishrani su  $\alpha$ -karoten,  $\beta$ -karoten,  $\beta$ -kriptoksantin, likopen, lutein i zeksantin.

**Materijal i metode:** Ovaj članak daje pregled dosadašnjih saznanja o karotenoidima, njihovim depozitima u telu, preporučenim dnevnim dozama i mehanizmima zaštitnog delovanja. Pretraživali smo PubMed, Google Scholar, SCIndex, Dimension, Scopus i Google na srpskom i engleskom jeziku, koristeći ključne reči za pretragu „karotenoidi”, „provitamin A”, „antioksidansi”, „kardiotoksičnost”, „prevencija” i „NADES”.

**Tema:** Nakon što se metabolišu u crevnoj sluznici (uz pomoć žučnih kiselina) u apsorbuju, karotenoidi se uglavnom skladište u jetri i masnom tkivu. Glavni uticaj na bioraspoloživost karotenoida je priroda matriksa/medijuma u kome su rastvoreni. Najnovija generacija netoksičnih „zelenih” rastvarača, takozvani NADES (natural deep eutectic solvents) danas su u posebnom fokusu istraživanja. Potvrđeno je da likopen poboljšava efikasnost sperme, te povećava učestalost trudnoća. Kada su u pitanju kardiovaskularne bolesti, trans forme inhibiraju proces ateroskleroze, najverovatnije povećavanjem nivoa HDL-a. Niske koncentracije  $\beta$ -karotena i  $\beta$ -kriptoksantina u serumu su povezane sa povećanom smrtošću od srčanih oboljenja, ali i moždanog udara. Karotenoidi, takođe, mogu izazvati apoptozu u TE1 ćelijama karcinoma skvamoznih ćelija jednjaka. Preporučene dnevne doze još uvek nisu standardizovane, zbog nedostatka sprovedenih studija. Grupa provitamin A karotenoida, kada se pretvori u vitamin A, učestvuju u regulaciji vida i prevenciji očnih bolesti (kserofthalmija, makularna degeneracija, noćno slepilo, ulceracije, ožiljci). Takođe, povezani su sa potencijalnim uticajem na reprodukciju, embriogenezu, imuni sistem, intracelularne veze kao i metaboličke puteve. Studije ukazuju na njihov uticaj u prevenciji i lečenju kako kardiovaskularnih bolesti tako i različitih maligniteta.

**Zaključak:** Dosadašnji literarni podaci ukazuju da su karotenoidi dobar izbor u prevenciji i lečenju različitih oboljenja, međutim, još uvek su nedovoljno istraženi. Zbog toga se sve više studija usmerava ka ovom polju.

**Ključne reči:** karotenoidi, provitamin A, antioksidanti, kardiotoksičnost, prevencija, NADES

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