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Carotenoids

Properties, distribution, bioavailability, metabolism and health effects

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Summary

As colouring pigments in many fruits and vegetables like tomatoes, carrots, kale, mango or oranges, carotenoids are part of our daily diet. While the secondary plant compounds do not deliver essential nutrients to humans, numerous health-promoting effects are reported. One of the main functions is the provitamin A activity of some carotenoids. Due to their antioxidant potential, carotenoids are connected with a reduced risk of cardiovascular diseases, some kinds of cancer and age-related macular degeneration. Although the data published so far do not allow a recommended intake level, it is suggested to ensure a sufficient supply of carotenoids by eating high amounts of fruits and vegetables.

Keywords: secondary plant compounds, food additives, colouring compounds, antioxidant potential, bioavailability, isoprenoids, carotenoids

Chemistry and structure of carotenoids

Carotenoids are fat-soluble colouring compounds widely spread in nature, having various biological functions in plant and also animal organisms. This is mainly due to their chemical structure. Carotenoids belong to the natural poly-unsaturated isoprenoids. Often consisting of eight isoprene units, they form a basic structure of 40 carbon atoms. Thus, many carotenoids belong to the tetraterpenes. At the ends of the carbon chain various functional groups can be located, resulting in the enormous variety of more than 750 carotenoids known today [1]. According to their structure, they are distinguished in oxygen-free carotenes and oxygen-containing xanthophylls (◆ Figure 1).

The best known carotene is β-carotene, which had been first extracted from carrot juice in 1831 by the German pharmacist and chemist Heinrich Wilhelm Ferdinand WACKENRODER at Jena University [2].

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Properties

The long polyene structure of carotenoids is responsible for the characteristic colours and the antioxidant properties of this group of compounds. Due to the long chain of conjugated double bonds, blue and green parts of the visible light spectrum are absorbed. Carotenoids do not only give their colour to blossoms, fruits and vegetables, but are also responsible for the strong colours of bird feathers, tropical fishes and shellfishes [1]. By food intake, carotenoids are enriched in various tissues of the animal, like muscles, feathers or beak (◆ Figure 2).

Moreover, carotenoids protect other molecules from unwanted oxidation reactions, by acting as efficient radical quenchers. The electron-rich polyene chain which can easily be attacked by free radicals and oxidizing reagents donates electrons and hydrogen atoms to neutralise radicals. The resulting carotenoid radicals are relatively stable, thus less reactive, as their unpaired electron is delocalised along the conjugated polyene chain. The antioxidant properties are physiologically relevant, as carotenoids scavenge reactive oxygen species (ROS) in the human body. Thus, the carotenoids protect against oxidative damages of biological molecules, e.g. DNA, lipids or proteins [3].

As protein-bound pigments, carotenoids are part of the light-harvesting complex in photosynthesis. In the chloroplasts, they are involved in light absorbance in increasing the spectrum of absorbance and transferring light energy to chlorophyll molecules. The carotenoids also protect chlorophyll molecules against photo-oxidation [1].

The most important and most often investigated property of carotenoids is their provitamin A activity. For the conversion of carotenoids into vitamin A, the presence of an unsubstituted β-ionone ring is required. Around 50 carotenoids show this property. The most important provitamin A carotenoids are β-carotene, α-carotene and β-cryptoxanthin, contributing around 35 % to the actual vitamin A supply in human adults in industry nations [6].

Due to the double bonds, each carotenoid can have a large number of isomers. Each double bond can exist in two configurations – *trans* or *cis* or according to the IUPAC recommendation (*E*) or (*Z*). Most carotenoids exist in the more stable (*all-E*)-configuration. Food processing steps and endogenous metabolism reactions can lead to isomerisation of carotenoids, causing a changed stability and bioavailability. (*all-E*)-*β*-Carotene shows a higher bioavailability than the (*Z*)-isomers, whereas (*5Z*)-lycopene is more bioavailable than (*all-E*)-lycopene [4].

Distribution

Carotenoids can be synthesised by all higher plants, algae and bacteria as well as by some fungi and invertebrates [1]. In plant cells, carotenoids are located in lipid membranes and stored in plastids [7]..

The human organism is not able to synthesise carotenoids and is thus dependent on the supply via the food chain.

Around 80–90 % of the carotenoid intake originates from fruit and vegetables [7]. Yellow-orange coloured fruit and vegetables contain above all β-carotene and α-carotene, orange coloured fruit like mango and oranges high amounts of β-cryptoxanthin, dark green leafy vegetables lutein, and tomatoes and tomato products lycopene. By feeding animal food rich in carotenoids, they also accumulate in animal products. Milk, cheese and butter, for example, contain certain amounts of lutein and β-carotene. High amounts of lutein and zeaxanthin are present in egg yolk. Often, the amounts of lutein and zeaxanthin in food are stated as a sum of both carotenoids, as only recent developments enable a sufficient analytical separation (◆ Table 1).

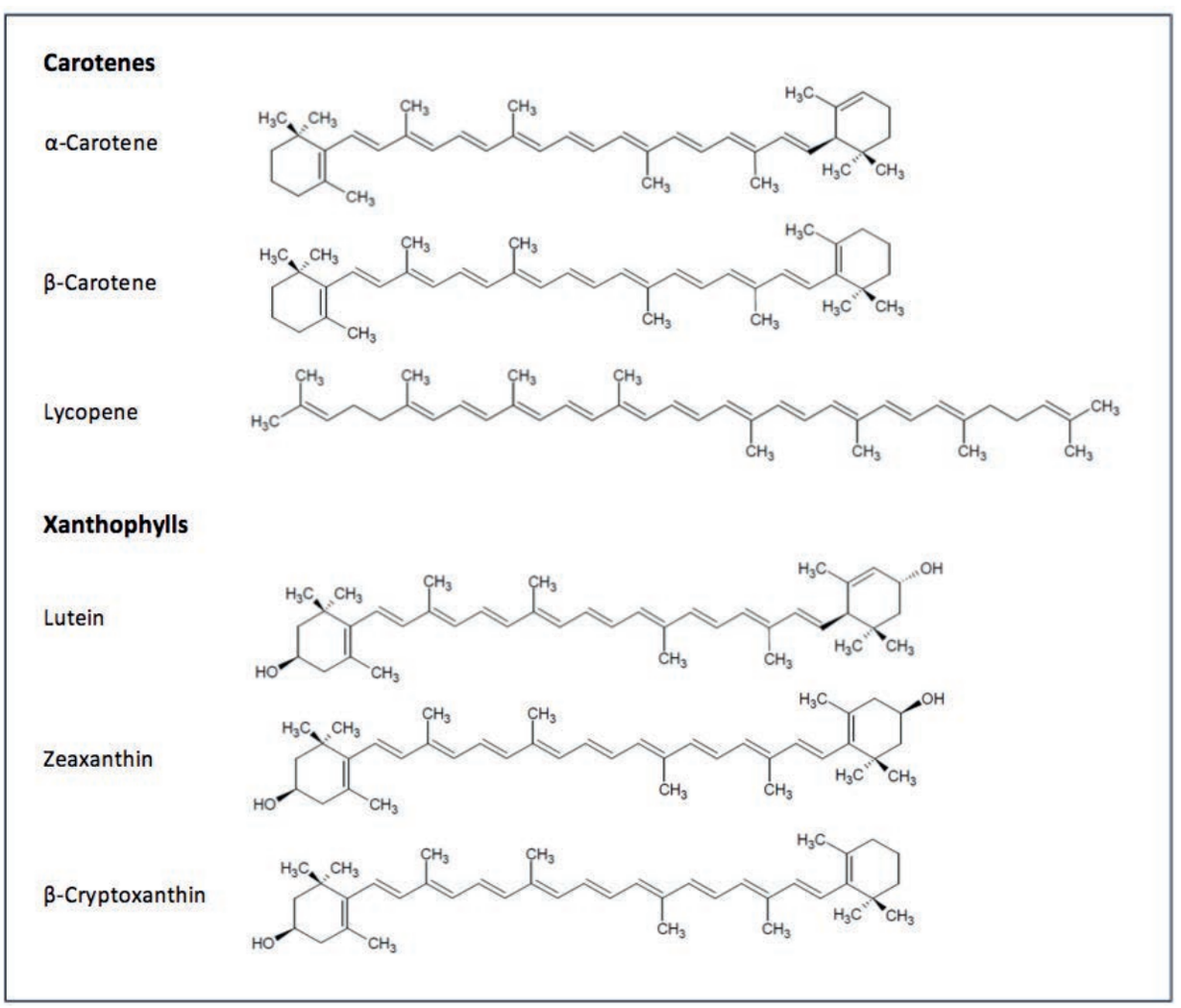

Fig. 1: **Classification of carotenoids (chemical structures): carotenes and xanthophylls**

Foods	α-Carotene	β-Carotene	Lycopene	Lutein + Zeaxanthin	β-Crypto-xanthin
Plant origin					
Apple	n. d.	27	-	29	11
Apricot	n. d.–44	585–3,800	54	123–188[a]/n. d.–39[b]	104
Banana	25–156	26–131	n. d.–247	22–192	n. d.–5
Grapes	1	39	n. d.	72	n. d.
Guava	n. d.	102–2,669	769–5,204	-	n. d.–118
Mango	n. d.–9	109–1,201	3–724	23	10–317
Orange	n. d.–11	71–476	n. d.	129	74–141
Papaya	n. d.–2	81–664	n. d.–7,564	89–318	n. d.–1,034
Peach	n. d.	162	-	91	67
Pear	1	14	n. d.	44	2
Pineapple	n. d.	35–347	265–605	-	n. d.–124
Plum	n. d.	190	-	73	35
Raspberry	16	12	n. d.	136	n. d.
Strawberry	n. d.	7	-	26	n. d.
Sour cherry	n. d.	770	-	85	n. d.
Water melon, red	n. d.	303–777	4,532–13,523	8	n. d.–78
Avocado	19–30	48–81	n. d.	213–361[a]/8–18[b]	21–32
Broccoli	n. d.–25	291–1,750	n. d.	707–3,300	n. d.–1
Cabbage/kale	54	1,020–7,380	n. d.	4,800–11,470	81
Carrots	2,840–4,960	4,350–8,840	n. d.–1	254–510	n. d.
Cucumber	n. d.–11	45–270	n. d.	23–840	n. d.–26
Leek	n. d.	1,000–3,190	n. d.	1,900–3,680	n. d.
Parsley	n. d.	4,440–5,054	n. d.	5,561–10,650	n. d.
Pepper, green	n. d.–139	2–335	n. d.	92–911[a]/n. d.–42[b]	n. d.–139
Pepper, red	n. d.–287	1,441–2,390	n. d.	248–8,506[a]/ 593–1,250[b]	248–490
Potatoes	n. d.	1	-	8	
Pumpkin	4,016	490–3,100	n. d.–500	630–1,500	n. d.–60
Spinach	n. d.	3,100–5,626	n. d.	5,930–12,198	n. d.
Tomato	n. d.–101	320–1,500	850–12,700	46–213	n. d.
Tomato, concentrate	29	901	49,300 - 94,000	-	n. d.
Tomato sauce, instant	n. d.	259	5,600–39,400	24	3
Animal origin					
Butter	n. d.–2	158–431	-	15–26[a]/n. d.–2[b]	n. d.–8
Cheese, ripened (Gouda)	n. d.	10–48	-	3[a]/0.2[b]	n. d.–0.2
Egg, yolk	n. d.–38	n. d.–88	n. d.	384–1,320/n. d.	n. d.–33
Egg	n. d.	n. d.	n. d.	182–503/n. d.	n. d.–9
Milk, full fat	n. d.–0.1	7–19	-	0.8–1.4[a]/n. d.–0.1[b]	n. d.–0.4
Milk, semi-skimmed	n. d.	0.2–9	-	0.5–0.8[a]/n. d.–0.1[b]	n. d.–0.1

Tab. 1: **Carotenoid contents of selected food of plant and animal origin (µg/100 g)**
(summary of data from [7, 89])
n. d. not detected or quantified
– not stated
a lutein content
b zeaxanthin content

Fig. 2: **Carotenoids are not only yellow! Currently, we can see carotenoids in coloured autumn leafs: Plants metabolise the "more valuable" (as containing nitrogen) green chlorophyll, making the before masked red-yellow leaf colours visible. Micro algae produce the carotenoids astaxanthin and canthaxanthin, being ingested by shellfishes and birds, thus colouring their shells or feathers.**

More than 750 carotenoids are known. Around 60 of them present in food have an effect on human nutrition. In human plasma, mainly α-carotene (0.03–0.22 μmol/L), β-carotene (0.13–0.53 μmol/L), β-cryptoxanthin (0.15–0.37 μmol/L), lycopene (0.61–1.38 μmol/L), lutein (0.14–0.34 μmol/L), and zeaxanthin (0.03–0.05 μmol/L) [7–9] are found. Other carotenoids and their metabolites like phytoene and phytofluene are contained in lower concentrations [10].

Contents and composition of carotenoids in food are influenced by a number of factors – starting from the plants' growing conditions and ripening status when harvested as well as processing and storage in industry and at home. When present in plant tissue, carotenoids are more stable than in an isolated form. Destroying the tissue by cutting, cooking or storing for too long outweighs this protection. Increased temperature, light, oxygen and acids can facilitate carotenoid degradation and isomerisation of (*all-E*)-carotenoids to (*Z*)-isomers. Cutting or extracting juice from fruit can liberate organic acids which promote isomerisation. Thermal treatment often has the highest impact. During thermal processes, (*all-E*)-lycopene is much more stable with regard to degradation and isomerisation than β-carotene or lutein. On the other hand, due to destroying cellular structures, thermal and mechanical treatment increases the bioavailability of carotenoids [11].

More and more, carotenoids play a role in food industry as natural and nature identical colouring compounds. They are especially suitable for yellow to orange coloured soft drinks and are also used to colour various other foods. Due to improved carotenoid formulation processes, e.g. insertion in emulsions or nanoparticles, carotenoid colourings show a high stability with regard to light, acids and heat. Due to the antioxidant properties of carotenoids, the product gets an additional health benefit for the consumer. Carotenoids are also used as animal food additives and as supplements.

Bioavailability

Bioavailability of carotenoids depends on several factors and can be increased by specific measures. The most important and also limiting factor for resorption is the liberation of carotenoids from the food matrix. Especially for vegetables, the relatively stable cell walls have to be destroyed. Chewing raw vegetables thoroughly is a first step [12]. In green leafy vegetables, carotenoids are often bound to proteins and have to be liberated by hydrolysis. In carrots and tomatoes, they are present in a semi-crystalline structure, making them less bioavailable. In mangos and peppers, they are dissolved in lipids, increasing the bioavailability [7, 13].

Food processing mostly has a positive effect on the bioavailability of carotenoids. Thermal treatment and mechanical crushing break the cell walls, carotenoids are liberated from intracellular organelles, carotenoid-protein complexes are split and the particle size becomes smaller [14]. With 3 %, the bioavailability of carotenoids from non-heated food is very small, whereas heating increases it to more than 15 % [15].

Thus, carotenoid intake from tomato sauce or cooked, mashed carrots is higher than that of raw tomatoes or carrots [7, 16]. Nonetheless, the food should be cooked carefully, as extreme temperatures above 100 °C can lead to degradation and isomerisation of carotenoids [7].

Lipids stimulate the secretion of bile salts which are needed for emulsification of carotenoids. From salad with fat-free or reduced-fat dressing, carotenoid resorption was lower than from salad with full-fat dressing [17]. Adding oil to carrots during cooking increases the carotenoid bioavailability considerably [16].

For an optimal carotenoid absorption, it is recommended to consume 3–5 g fat per meal [7].

Fibres reduce the resorption of carotenoids, as they build hardly soluble complexes with carotenoids which the body cannot absorb. They also bind bile acids and thus excrete lipids and fat-soluble substances like carotenoids [10]. Also fat replacing compounds, statins, and plant sterols can decrease the carotenoid intake [14]. When consuming several carotenoids at the same time, occurring interactions inhibit but also promote resorption of the single compounds. This takes places e. g. on the level of incorporation in the mixed micelles or when entering the enterocytes [7].

Often, a better bioavailability of carotenoids from supplements compared to plant food is found. This is mainly due to the missing plant matrix and the presence of oil in the supplements. The bioavailability of lutein from lutein-enriched egg yolk is comparable to that of food supplements as it is present in a lipid matrix, too [18]. Also the isomeric form influences the bioavailability. (*Z*)-Isomers mostly are better bioavailable than (*all-E*)-isomers as they are more soluble in the bile acid micelles, enabling the incorporation in chylomicrons [1].

Bioavailability is also influenced by the nutritional status and diseases like dysfunctions of lipid absorption or infections with parasites, as well as gender and age [19]. Moreover, some people are considered as so-called high responder or low responder. Due to their genetic status, they can absorb carotenoids better or *poorer*. This is caused by polymorphisms in the genes coding for specific carotenoid transporters [20].

Resorption and metabolism

Due to the lipophilic character of carotenoids, their resorption is closely connected to the digestion of lipids. Liberation of carotenoids from the food matrix starts in the mouth and continues in the stomach and in the small intestine. In the stomach, the low pH-value and digestive enzymes have a positive effect on carotenoid liberation before they are transferred to the lipid phase [14]. The following resorption takes place in the upper small intestine. Only free non-esterified carotenoids are taken up in the enterocytes. Stomach lipase and carboxyl ester lipase are, among others, part of the hydrolysis of carotenoid esters [20, 21].

Together with lipids from food, carotenoids are emulsified with the help of bile acids and phospholipids and stored in mixed micelles.

When carotenoids are taken up in high, pharmacological doses – far above the usual intake of about 5 mg β-carotene – absorption takes place by passive diffusion [22]. Taken up with food in normal concentrations, carotenoids are absorbed by protein induced transport [20]. Studies confirm the participation of SR-B1 (scavenger receptor class B type 1 protein), an ABC transporter protein which plays a role in the reverse cholesterol transport. The importance of further transporter proteins like CD36 (cluster of differentiation 36, fatty acid translocase) or NPC1L1 (Niemann Pick C1-like 1 protein) is currently discussed [10, 20, 21]. After carotenoid absorption in the epithelium cells of the small intestine, they are stored in the Golgi apparatus in chylomicrons, passed on to the lymphatic system and reach the blood circulation. After degradation to chylomicron remnants, they are absorbed in the liver parenchyma cells by receptor induced endocytosis.

In the enterocytes, a large part of the provitamin A acting carotenoids are cleaved to retinol by the β-carotene 15,15'-monooxygenase (BCMO1) [23]. Another part is converted to vitamin A in the liver. Around 20–90 % of the resorbed β-carotene is converted to vitamin A. 60 % is cleaved in the enterocytes to vitamin A, 40 % in the liver [5]. Besides the symmetrical cleavage of the carotenoids to vitamin A by BCMO1, an asymmetrical cleavage by the β-carotene 9,9'-dioxygenase (BCDO2) can take place, forming various apo-carotenoids [21].

The non-cleaved, intact carotenoids are incorporated in lipoproteins and reach the blood circulation. Hydrophobic carotenoids like β-carotene and lycopene are preferably transported in the blood via VLDL und LDL, whereas xanthophylls like zeaxanthin and lutein reach it via HDL and LDL [10].

All carotenoids present in the blood are enriched in specific organs and tissues, but in different concentrations. The selective intake depends on the expression of membrane receptors like SR-B1, CD36, or LDL-receptors [10]. In tissues with a high LDL receptor density, e. g. liver and adrenal gland, carotenoids are enriched to a higher degree.

The selective intake of carotenoids in the retina cells is influenced by SR-B1. CD36 seems to have a vital importance on the selective absorption of lycopene and lutein in adipose tissues [10]. In humans, the main part of carotenoids is stored in the lipid tissue, with highest concentrations in the lipid tissue of the abdomen [10]. Another destination carotenoids reach is the skin.

The isomeric structure of carotenoids in tissue does not necessarily reflect the isomeric structure in food. In tomatoes and tomato products, lycopene is present to more than 90 % in (*all-E*)-form, whereas (*Z*)-isomers represent more than 50 % of the plasma lycopene and more than 75 % of

the tissue lycopene [14]. So far there is no conclusive explanation whether this is caused by a preferred resorption of the (*Z*)-isomers or an isomerisation in the organism [24].

Provitamin A activity

Vitamin A is supplied to the body by 33 % from retinol, by 48 % from β-carotene and by 19 % from mixed carotenoids [5]. In Germany, supply of provitamin A carotenoids averages to 3.7 mg/d [7].
The provitamin A activity of the single carotenoids is stated as retinol equivalents (RE), as the carotenoids have different provitamin A activities. So far, 6 mg β-carotene and 12 mg mixed carotenoids have equalled 1 RE. Now, the conversion factors have been corrected, as the bioavailability of the provitamin A carotenoids and the transformation to retinol had been considerably overestimated [23].

New equivalent values are:
1 RE = 12 mg β-carotene and 24 mg mixed carotenoids [25].

These values, however, also only give guidance, as the transformation of carotenoids to vitamin A depends on several factors. The transformation from β-carotene to vitamin A from different food matrices can vary eightfold, from 3.6:1 with the so-called Golden Rice (rice enriched with β-carotene by genetic engineering) to 28:1 with leafy vegetables [23]. Supplemented β-carotene in oil capsules, in contrast to that from vegetables, is absorbed very well, resulting in a conversion factor of 2:1 [26]. In the status of a poor vitamin A supply, more β-carotene is converted to vitamin A, compared to a sufficient supply status [5, 26]. Genetic factors also cause different conversion efficiencies in humans. Polymorphisms in the gene which codes for the enzyme BCMO1 are discussed [5].

An over-dosage of vitamin A by too high doses of β-carotene is not possible, as the cleavage of β-carotene is regulated by a feedback mechanism [5].

Antioxidant properties

As part of the antioxidant network in our body, carotenoids can counteract damages caused by reactive oxygen species (ROS) [3]. If oxidants and antioxidants are imbalanced, increased ROS production leads to oxidative stress which is involved in the development of a number of diseases. Recent studies, however, also show that ROS are important signal molecules mediating an adaptive answer of the human body. A complete elimination of ROS therefore prevents the body from reacting to outer stressors [27].
Due to their lipophilic properties, carotenoids develop their antioxidant activity mainly in cell membranes and lipoproteins. In many epidemiological, clinical and intervention studies data regarding the carotenoids β-carotene, lycopene, lutein and zeaxanthin have been collected which confirms that a nutrition high in carotenoids from fruit and vegetables can decrease the risk of chronic diseases like atherosclerosis, coronary heart diseases, diabetes type 2 or asthma [3]. Various *in vitro* test systems for determining the antioxidant capacity show that carotenoids (concentration: 10 μM) have a distinct antioxidant activity against a number of radical species [28]. The importance of the antioxidant effects *in vivo*, however, is controversial: interactions of various antioxidants during resorption and metabolism can cause changes in the antioxidant *in vivo* mechanisms. Synergistic interactions between carotenoids and tocopherols, ascorbic acid and flavonoids are equally important in the antioxidant network of the body [29]. Under certain circumstances, carotenoids are also able to develop pro-oxidant effects. When taken up in physiologically relevant doses and in the status of low oxygen partial pressure, they are antioxidants. At high doses and in the status of high oxygen partial pressure, e. g. in the lung, or at strong oxidative stress, carotenoids show pro-oxidant properties [29–31].

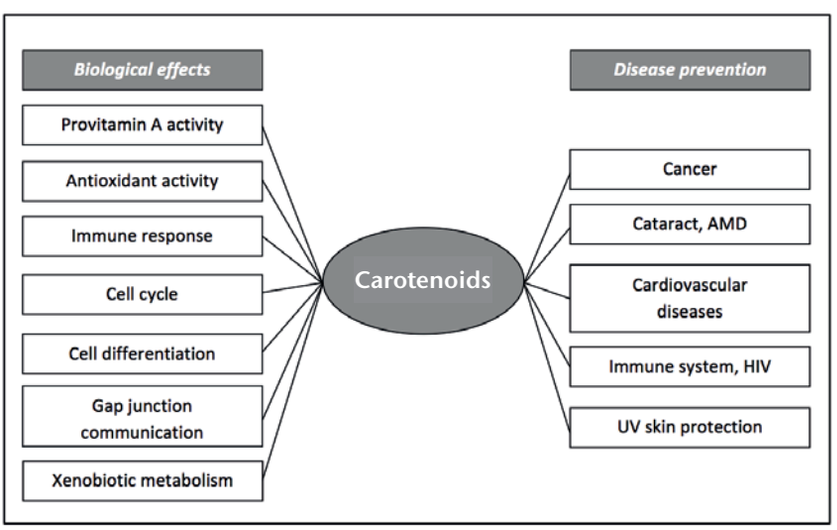

Fig. 3: **Role of carotenoids in the prevention of chronic diseases**
(own illustration following [30])

Discussed effects

Even after many years of research, scientists still discuss various health effects of carotenoids controversially. Many epidemiological and clinical studies indicate the preventive effects of an adequate carotenoid supply on the development of certain diseases caused by ROS [3]. The connection between a nutrition rich in fruit and vegetables and a decreased risk of cancer and other chronic diseases like atherosclerosis or diabetes type 2 has been proofed in many epidemiological studies [11, 32]. The same number of studies however shows only a small or no connection [1].

In addition to the antioxidant effects, carotenoids are involved in a number of other mechanisms which assist in preventing certain diseases (♦ Figure 3). Carotenoids are able to stimulate the immune system, and they influence the cell differentiation and the intracellular signalling paths via gap junctions.

Furthermore, lycopene seems to participate in the regulation of the cell cycle by influencing the intracellular cyclin D level. By changing apoptosis proteins like proteins of the Bcl-2 or caspase family, carotenoids also participate in the regulation of the programmed cell death. Also growth factors and several receptors or adhesion molecules can be influenced by them [3, 33].

Cancer

Current meta-analyses of randomised, controlled human intervention studies with β-carotene supplementation did not reveal a general preventive effect on the risk of pancreas, colon, prostate, breast or skin cancer. Therefore, primary or secondary cancer prevention by supplementation of β-carotene is not recommended [34, 35].

Especially for smokers, intake of β-carotene is contraindicated with lung cancer, as shown in the ATBC study (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) and the CARET study (Carotene and Retinol Efficacy Trial) in the 1990ies. In specific population groups, e. g. heavy smokers or asbestos workers, daily supplementation with 20–30 mg β-carotene resulted in increased rates of lung or stomach cancer [34]. It is assumed that the metabolism of smokers plays a decisive role, converting the antioxidative effect of β-carotene to a pro-oxidative effect (e. g. due to the high oxygen partial pressure in the lung) [1, 36]. Analysing a sub-group revealed a significant increase of the risk for bladder, renal pelvis and ureter cancer [35].

Meta-analyses of prospective cohort studies showed that intake of α- and β-carotene, lycopene, lutein, and zeaxanthin as well as total carotenoids or their contents in serum is associated with a lower risk for ER (oestrogen receptor)-negative breast cancer in women, but not with ER-positive breast cancer [37, 38]. A higher uptake of these carotenoids also lowered the risk of oesophagus cancer in men and women [39].

In addition to the antioxidative effects of lycopene, many *in vitro* and *in vivo* studies demonstrated that this carotenoid acts antiproliferatively, induces apoptosis and minimises the metastatic capacity of prostate carcinoma cells [40]. In vitro treatment of human prostate adeno carcinoma cells with 10 μM lycopene for 24–96 h indicated antiproliferative effects [41]. In a study with mice, supplementation of lycopene (4 and 16 mg/kg body weight) and β-carotene (16 mg/kg body weight) twice a week for seven weeks led to a reduction of tumour volume and weight [42]. Current meta-analyses of a supplementation with lycopene or intake of tomatoes (raw and cooked) did not reveal a decreased risk for prostate cancer or a benign prostate hyperplasia [43, 44]. A meta-analysis of two studies, however, showed lower PSA (prostate specific antigen) level in men with prostate cancer who supplemented 30 mg lycopene/day [43]. Nonetheless, the prevailing data do not allow a general recommendation for lycopene intake for prevention or adjuvant treatment of prostate carcinoma [45].

> **The European Food Safety Authority (EFSA) also rejected a health claim which was applied for the interaction between lycopene intake and preservation of prostate health [46].**

Some apocarotenoids possess multifunctional biological properties which play a role in cancer prevention. They block the proliferation of cancer cells (HL-60 leukaemia cells, MCF-7 and T47D breast cancer cells and LN-CaP prostate cancer cells) and can influence the activity of various transcription systems involved in cancer development [47].

Cardiovascular diseases

A protective effect against cardiovascular diseases is attributed to carotenoids. Due to their radical-scavenging, antioxidant properties they are able to protect lipoproteins and vessel cells from oxidation. Data prevalence for prevention of atherosclerosis and other cardiovascular diseases, however, is not unequivocal. Epidemiological studies indicated a correlation between carotenoid-rich nutrition and reduced risks for developing cardiovascular diseases [3]. However, results of clinical human studies were inconsistent [3, 31].

Epidemiological studies showed that increased concentrations of the carotenoids lycopene, α-carotene and β-carotene in blood had a protective effect against atherosclerosis [48]. Lower β-carotene levels in serum, however, were associated with an increased risk for heart insufficiency and sudden cardiac death [49, 50].

A double-blind, placebo-controlled study indicated that an intake of 7 mg lycopene per day for two months had a significant effect on the endothelium dependent vasodilatation of patients with pre-existing cardiovascular diseases. In healthy patients, lycopene had no effect [51]. Furthermore, a prospective study showed that high concentrations of lycopene in serum were correlated with a minimised risk of stroke [52]. A daily dosage of ≥ 25 mg lycopene led to a significant reduction of total and LDL cholesterol values and to a significant decrease of the systolic blood pressure [53].

Applications for a health-connected indication (health claim) regarding the relation between lycopene and cardiovascular diseases, however, were declined by the EFSA [46].

Numerous animal studies proof a preventive effect of astaxanthin towards atherosclerotic cardiovascular incidents [54]. A randomised human study with adipose volunteers indicated a positive effect on the reduction of LDL cholesterol, apolipoprotein B and oxidative stress markers for supplemented astaxanthin [55]. A number of cross section studies indicated a reduced risk for the metabolic syndrome in case of a high total carotenoid supply with food or high carotenoid concentrations in blood [56–58].

AMD/Cataract

By selective accumulation of lutein, zeaxanthin and its stereo isomer meso-zeaxanthin in the human eye, these xanthophylls are directly connected to the protection from frequent eye diseases like age-related macular degeneration (AMD) and cataract [59]. They lend a slightly yellow colour to the macula lutea, the point of the sharpest vision in the retina. The pigments absorb energy-rich short-wavelength light. Thus, the retina is protected from damaging photochemical reactions. Among patients with an early-stage macular degeneration, supplementation with lutein and zeaxanthin improved the optical density of the macular pigment [60]. The LUTEGA study showed that daily supplementation with a combination of lutein, zeaxanthin, omega-3 fatty acids and several antioxidants for 12 months had protective effects with regard to AMD and seems to be suitable to stabilise dry AMD [61, 62].
The LUXEA study indicated that lutein is predominantly deposited in the fovea, the centre of the macula lutea, while zeaxanthin is found in a wider retinal area. Therefore, zeaxanthin may also play a role in diseases of the peripheral retina [63]. Studies with healthy volunteers could not observe a protective role of lutein and zeaxanthin [64, 65].
The large US American ARED (Age Related Eye Disease) study investigated the effects of a supplementation with zinc and a mix of antioxidants (β-carotene, vitamin C and E) and indicated a decreasing probability of AMD progression and loss of vision. The following ARED2 study led to the conclusion that additional doses of lutein and zeaxanthin as well as the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) do not lower the AMD risk any further [66, 67]. A diet rich in lutein and zeaxanthin and a supplementation with both carotenoids was associated with a lower risk for cataracts [68, 69].

In spite of the scientifically unquestioned fact that lutein and zeaxanthin increase the macular pigment density and improve eyesight, the present scientific proofs are not sufficient for issuing a health claim at the EFSA [70]. Nonetheless, β-carotene as provitamin A can be claimed as contributing to maintain normal vision [71].

UV protection in skin

On the one hand, carotenoids can accumulate in the skin by diffusion from adipose tissue, blood or lymph flows. On the other hand, they are secreted via perspiratory or sebaceous glands onto the skin surface and penetrate the epidermis.
Dietary habits and stress situations are reflected by the concentration of carotenoids in the skin. Smoking or a simple cold can lower the concentration of the dermal carotenoids [72]. Accumulation of carotenoids in the skin can increase basal dermal defence against UV induced light damages and contributes to maintenance of skin health [73]. With a daily supplementation and alimentary intake of β-carotene and lycopene, a protective effect against sunburn was ascertained [74, 75]. In the studies of a meta-analysis, the daily dosage of β-carotene was between 15 and 180 mg. In addition, β-carotene should be supplemented for a minimum of 10 weeks to provide a protective effect [75]. Lycopene intake was between 8.2 mg (from 2 x 250 mL lycopene drink from tomato extract) and 16 mg lycopene (from 40 g tomato puree) per day [74].

The UV protection effect of carotenoids, however, is much less than that of sun screens, so that carotenoids are only regarded as an additional UV protection [73].

Possible effects of carotenoids to minimise the risk for white skin cancer and light induced skin aging could not be proofed clearly [3].

There is a proofed health claim for β-carotene as provitamin A, indicating that it contributes to maintain normal skin and mucosa [71].

Immune system

An immune stimulating effect for inflammatory diseases like rheumatoid arthritis or asthma and immune deficiencies has been attributed to carotenoids [3, 76, 77]. Some clinical studies showed that β-carotene supplementation led to a stimulation of the immune response in healthy adults and older subjects, whereas other studies did not reveal any effect [78].

According to EFSA, there is a proof that β-carotene as provitamin A contributes to a normal function of the immune system [79].

Recommendation and status of supply

Even if the scientific data now allow claiming a preventive effect of carotenoids, there are no studies so far to confirm the relation of cause and effect [80]. Up to now, no recommendations for the daily uptake of carotenoids exist. The D-A-CH recommendation for vitamin A supply for women and men aged 19 and above is 0.8 mg or 1.0 mg/day. A consensus conference in July 2009 disproved the current estimated value for a desired intake of β-carotene of 2–4 mg/day.

In order to guarantee a sufficient vitamin A supply for at least 95 % of the US population, β-carotene uptake should be at 7 mg/day [5]. For pregnant and breast feeding women, a vitamin A uptake of 1.1 mg or 1.5 mg/day is recommended. Taking a factor of 6, this corresponds to 6.6 mg or 9 mg β-carotene. Total estimated carotenoid supply is 5–6 mg/day [15, 81]. The food report 2008 states that recent data indicate a higher intake which might be due to changed food habits.

Carotenoid uptake also differs depending on the nutrition in some European countries. In Greece or Italy, uptake is higher than in Sweden or England, as the Mediterranean nutrition with its high proportion of fresh and processed fruit and vegetables, and vegetable oils, contains high amounts of carotenoids [82]. Average carotenoid supply per day is

- 9.4 mg in Germany,
- 21.0 mg in Greece,
- 15.8 mg in Italy,
- 7.5 mg in Sweden,
- 8.7 mg in England.

For the single carotenoids, the uptake in Germany was calculated as follows: lutein and zeaxanthin 4.9; β-carotene 3.1; lycopene 0.8; α-carotene 0.3; β-cryptoxanthin 0.3 mg/day [7].

As the intake of isolated β-carotene for heavy smokers increased the lung cancer incidence, and as in Germany around 30 % of adults smoke, there is a high risk especially for this group when taking in β-carotene via food supplements or enriched foods [83].

β-Carotene preparations containing more than 20 mg β-carotene/daily dosage should not be taken by heavy smokers. Preparations with a daily dosage of 2–20 mg β-carotene must bear a health warning that the product should not be taken on a regular basis by heavy smokers for a longer period of time [84].

Taking up larger amounts of carotenoids (≥ 30 mg/day) can result in carotenodermia/carotenemia (yellow pigmentation of the skin) [85]. This yellow pigmentation can be reversed within some weeks and is unproblematic for health.

Currently, there is no precise indication by EFSA with regard to a secure daily maximum intake of β-carotene [86]. The German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR) suggests 2 mg/daily dosage as maximum amount of β-carotene in food [83]. According to an EFSA statement, with a daily uptake of less than 15 mg β-carotene with enriched food or food supplements, no negative effects on the total population's health, including heavy smokers, are to be suspected [87, 88].

Conflict of Interest
The authors declare no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

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