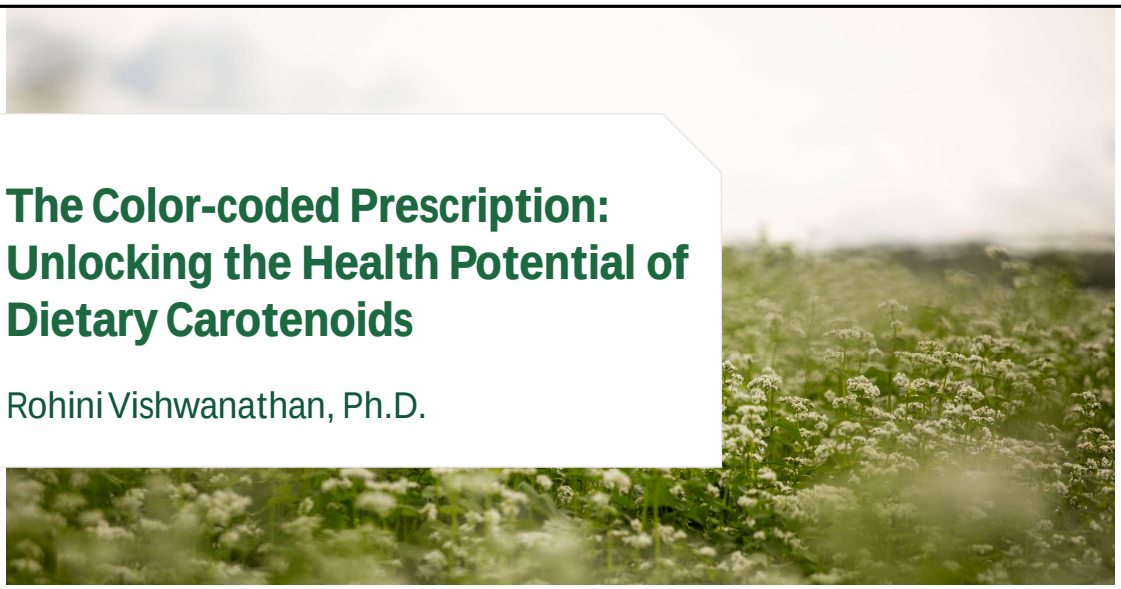

The Color-coded Prescription: Unlocking the Health Potential of Dietary Carotenoids

Rohini Vishwanathan, Ph.D.

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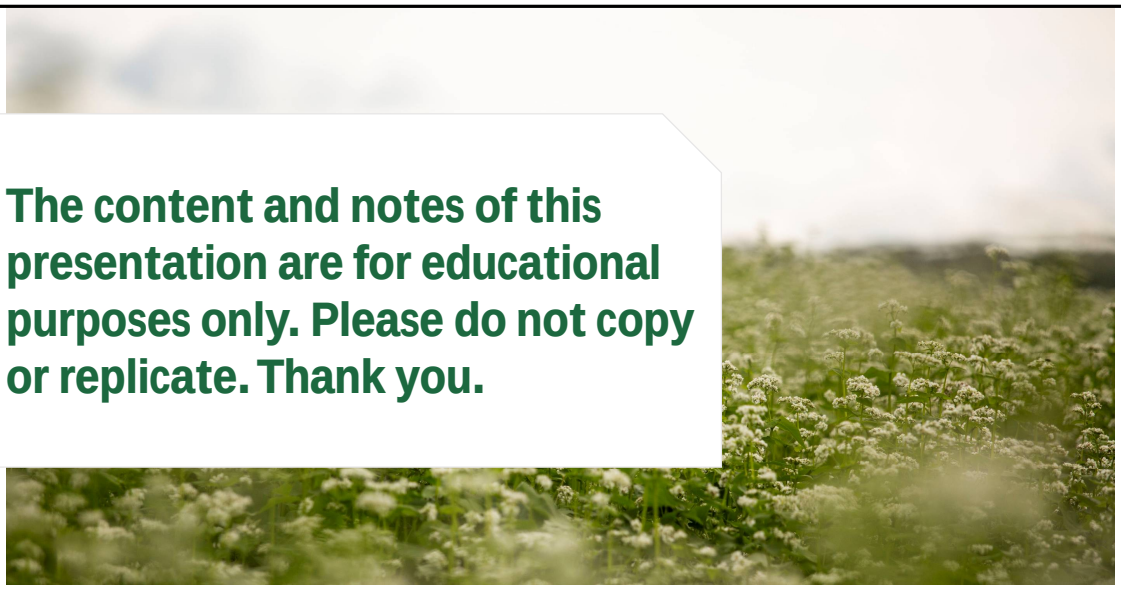

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Carotenoids are naturally occurring pigments that give the bright yellow, orange and red color to the foods we eat

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Carotenoids are a class of more than 750 naturally occurring pigments synthesized by plants, algae and photosynthetic bacteria. These pigments/colored compounds are responsible for the red, orange and yellow colors of many of the fruits and vegetables we eat. They are also present in dark green leafy vegetables, but we are unable to see them due to the green chlorophyll. Our body cannot make carotenoids – we rely on our diet – if we don't eat any, we don't have any in our body.

(images – plants, algae and bacteria…)

Carotenoids are all around us! Lessons from Nature...

Carotenoids are everywhere around us in nature! And nature is a constant reminder about how powerful these mighty pigments in our health. Grand prismatic spring at Yellowstone National park exhibits a range of colors due to diff bacterial species and their varying carotenoid production. These pigments act as sunscreen for the bacteria

Carotenoids are all around us! Lessons from Nature…

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Fall colors reveal carotenoid pigments in leaves – Carotenoids function as accessory pigments for photosynthesis. They absorb light in the blue green wavelengths that chlorophylls don't absorb efficiently and transfer it to chlorophyll. They also act as internal sunscreen protecting plants from light and reactive oxygen species

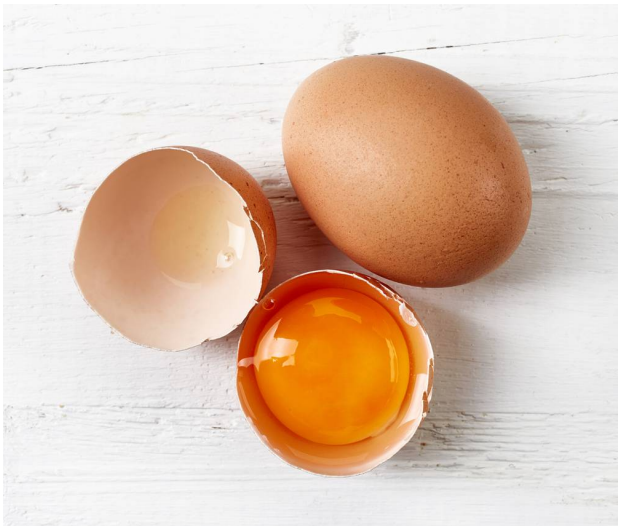
Carotenoids are all around us! Lessons from Nature…

Flamingoes have bright attractive pink color (which is astaxanthin) as the feed on algae and small crustaceans – they use their bight coloration to attract mates

Carotenoids are all around us! Lessons from Nature…

Salmon rely on astaxanthin (they obtain from feeding on algae, krill) to fuel their epic upstream migration from oceans back to freshwater for spawning – they swim for hundreds of miles battling strong currents and elevations jumping as high as 12 feet over rapids often for weeks without feeding. AX helps with endurance, protects from env stressors, sustained muscular activity.

Carotenoids are all around us! Lessons from Nature...



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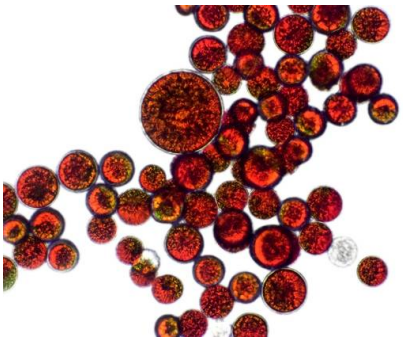
Carotenoids Lutein and Zeaxanthin in egg yolks – importance in early life

Colostrum – yellow due to accumulation of carotenoids

Carotenoids are all around us! Lesson from Nature...

Marigolds

Summer pheasant's eye



Green microalgae *Hematococcus pluvialis*

Carotenoids in marigold flowers – bright yellow and orange colors attract pollinating insects and animals, protect from sun damage

A few species of summer pheasant's eye only land plants that can make astaxanthin

Carotenoid astaxanthin is synthesized by green microalgae – turn red under high illumination

Carotenoids in our plate – How should they look like?

Or

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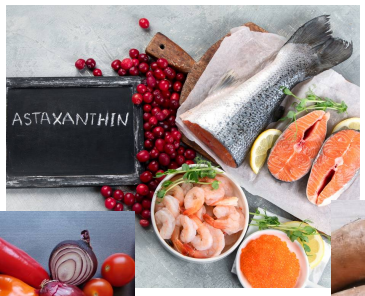
How does this translate to our plate? How should carotenoids look like in our plate?

A carotenoid-rich plate would include plenty of brightly colored fruits & vegetables! And eggs, salmon...



Are people getting enough carotenoids in the diet?

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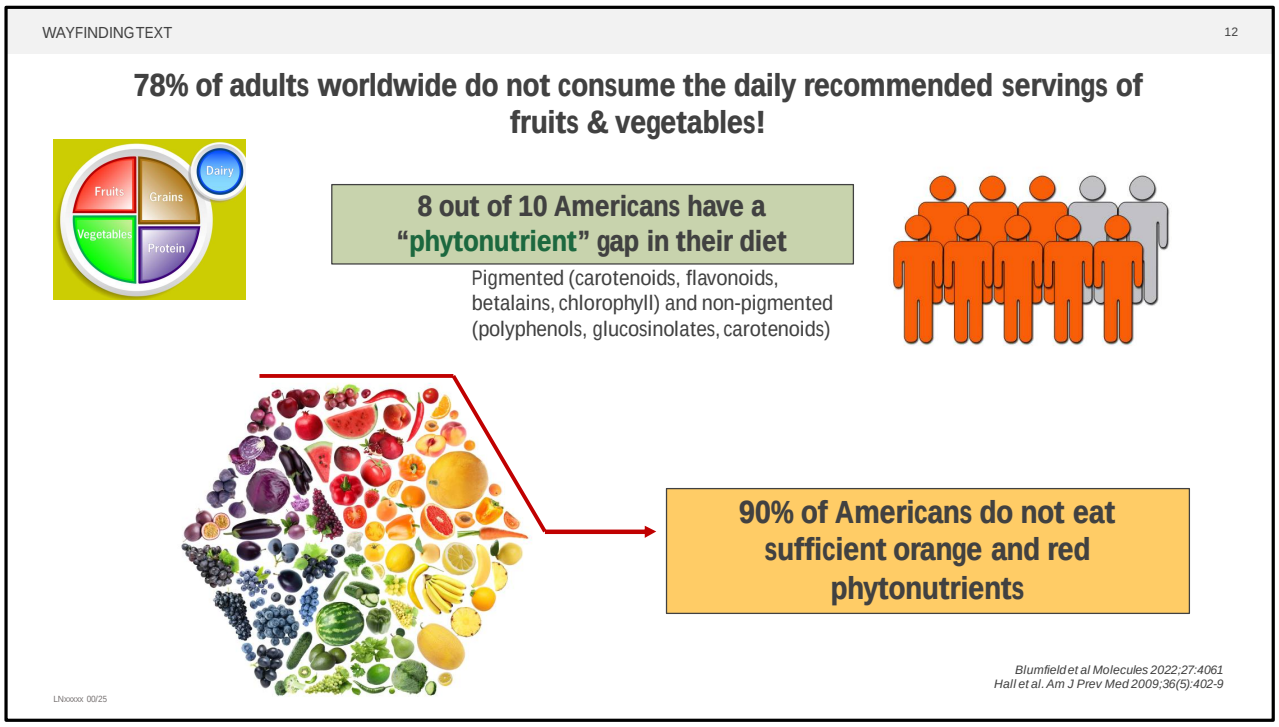
What do the numbers look like?



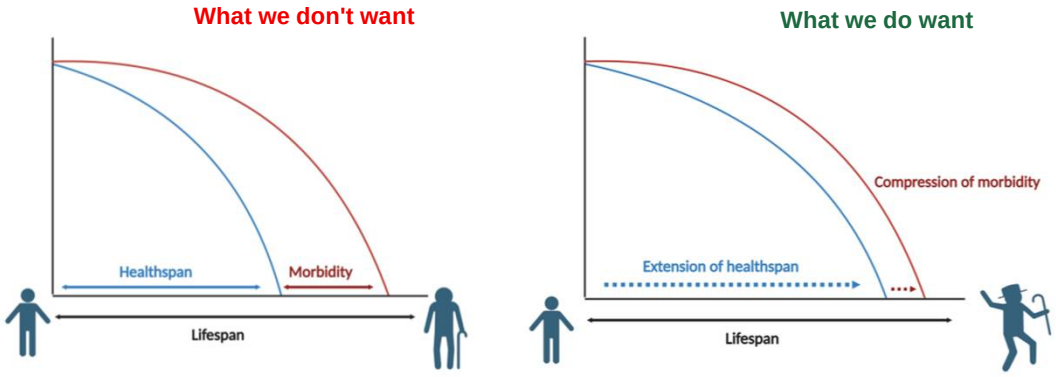
78% of adults….which is 1.5-2 cups of fruit and 2-3 cup equivalents of veg (half your plate)

Carotenoids fall in a bigger class of nutrients called Phytonutrients (phyto = plant, nutrients). Phytonutrients are natural bioactive compounds produced by plants that, although deemed non-essential, have been increasingly shown to have beneficial effects on health.

Among phytonutrients, pigmented nutrients that give fruits and vegetables their characteristic yellow, orange, red, green, and purple color, have especially shown to be beneficial due to their antioxidant and anti-inflammatory activities.

More than 90% of Americans do not eat sufficient orange and red nutrients.

Diet (high phytonutrients) and lifestyle play a major role in extending healthspan!



Carotenoids are one class of phytonutrients that can make a significant impact on extending our healthspan

Jacquier EF et al. Front Nutr 2024;11:1409339

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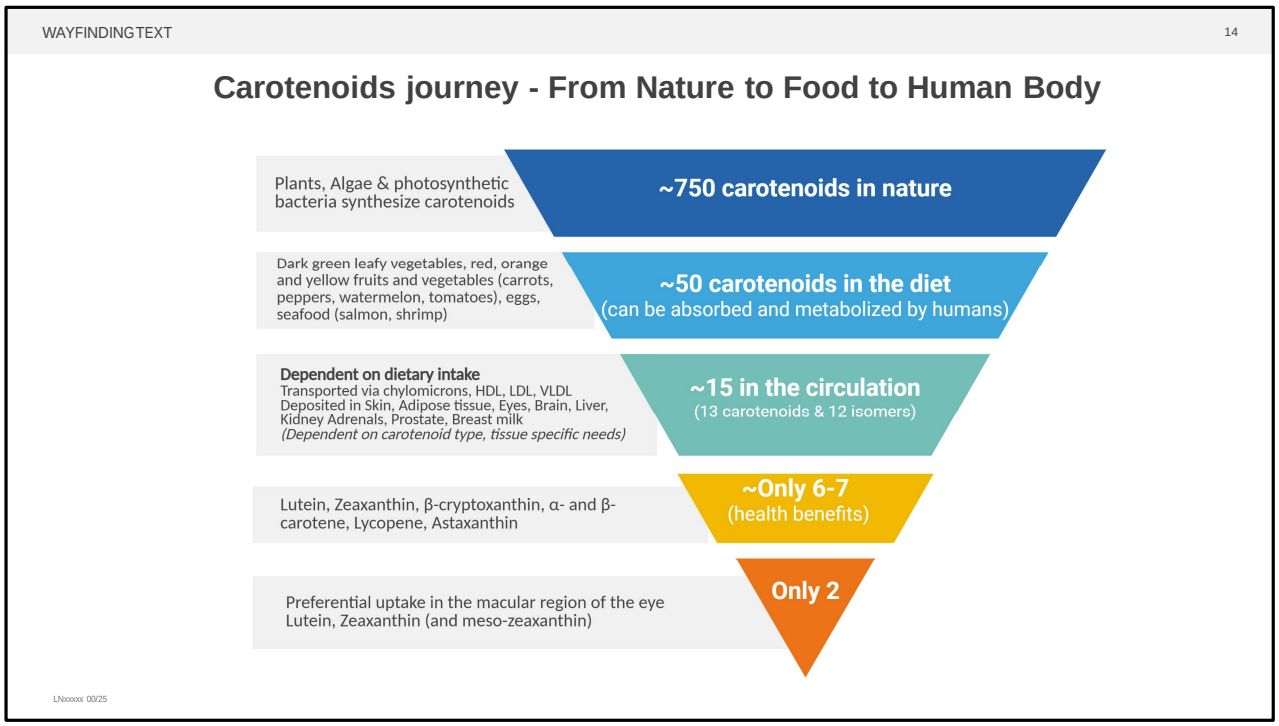
Why phytonutrients? higher consumption of fruits and vegetables was associated with a lower risk of all-cause mortality, particularly cardiovascular mortality.

Healthspan (healthy aging) is the number of years lived in good physical, cognitive and emotional health. Our lifespan has been increasing, but not necessarily healthspan – leading to number of age-related diseases. (What we don't want)

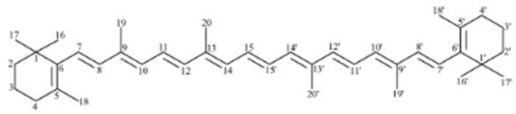
Key strategies to increase/extend healthspan include good quality plant-based diets which provide essential nutrients and bioactive phytonutrients that can combat multiple aging mechanisms in the body and extend healthspan.



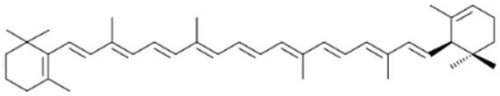
Of all the carotenoids identified in nature only 50 or so can be absorbed and metabolized by humans, and only 15 car (13 car and their isomers) can be identified in our serum. In the blood they are transported via chylomicrons and lipoprotein cholesterol HDL, LDL and VLDL. Of these only 6-7 carotenoids (which represent 95% of total blood carotenoids) have been studied in association with health benefits. In human tissue they are specifically concentrated in the adipose tissue, skin, liver, brain, kidneys, prostate, breast

Carotenoids relevant to human health – Structural categories

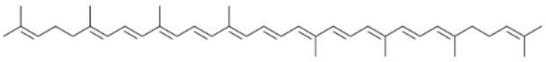
Carotenes



β-Carotene

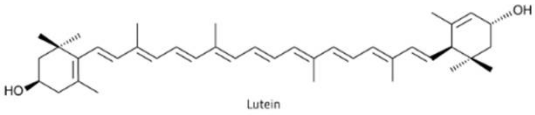


α-Carotene

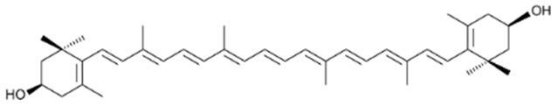


Lycopene

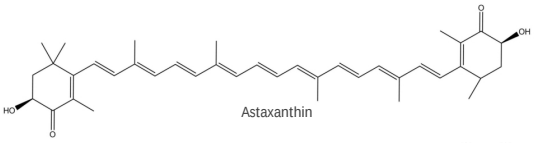
Xanthophylls



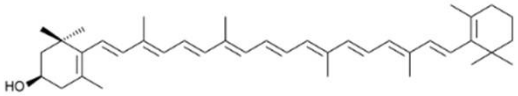
Lutein



Zeaxanthin



Astaxanthin



β-Cryptoxanthin

https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/carotenoids

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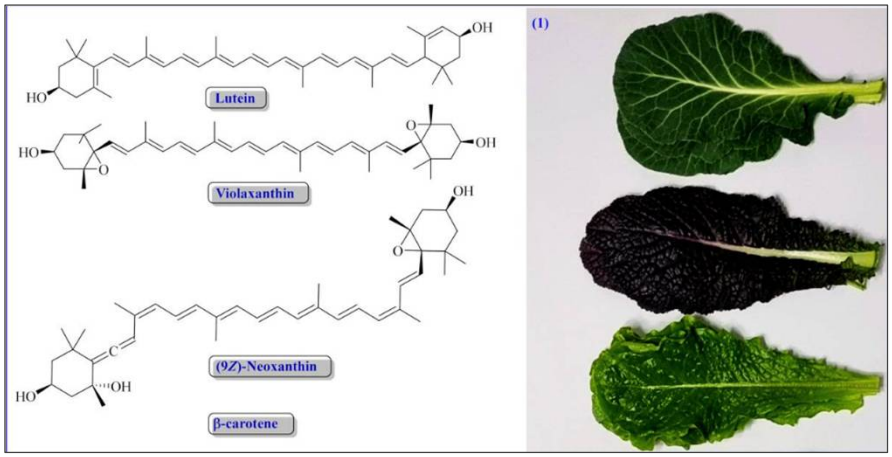
Structure of carotenoids- they are long 40 carbon molecules with long conjugated chain of alternating single and double bonds. Based on their structure they can be classified as carotenes and xanthophylls. Can anyone identify the diff betn..?

Carotenes are solely composed of carbon and hydrogen atoms, while xanthophylls contain oxygen as –OH (hydroxyl) or –O- (epoxy) groups. The oxygen groups makes xanthophylls slightly more polar than carotenes. Lycopene does not have a ring structure – open.

Beta-carotene, alpha-carotene and beta-cryptoxanthin have provitamin A activity – they can form vitamin A in the body

(which gives them their light absorbing property and distinct colors).

Dietary sources of carotenoids – Green leafy vegetables

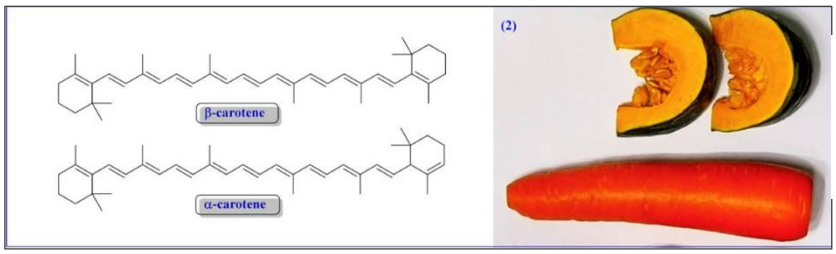


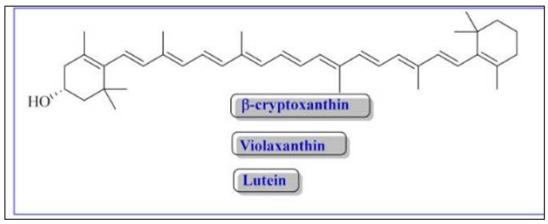
100g raw kale,
5-6 mg lutein
5-6 mg β-carotene
1.2-2.3 mg neoxanthin
2.0-3.4 mg violaxanthin

Saini et al. Antioxidants (Basel) 2022

Where and how much car can we get from diff dietary sources? Green leafy are the richest source of carotenoids! Lutein and b-carotene are the most dominant car in green leafy veg. 100 g raw kale chopped is roughly about 1.5 cups.

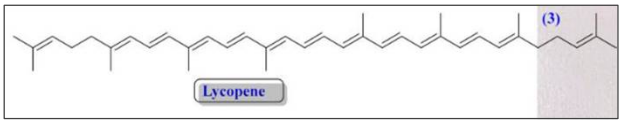
Dietary sources of carotenoids – Orange fruits & vegetables

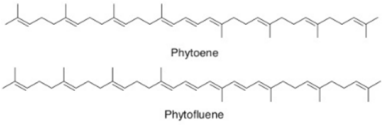




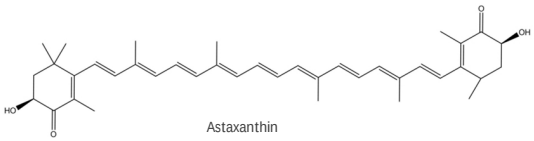
Saini et al. Antioxidants (Basel) 2022

Dietary sources of carotenoids – Red foods





Due to differences in lycopene bioavailability between raw tomatoes and tomato sauce/paste, tomato-based products such as ketchup and sauce are significant sources of lycopene in the US diet. One serving (120 g) tomato sauce provides ~ 7 mg lycopene.



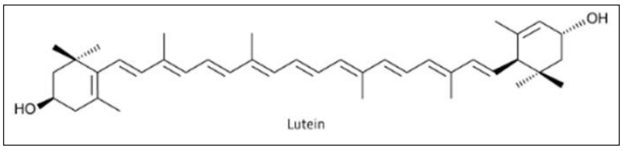
Astaxanthin

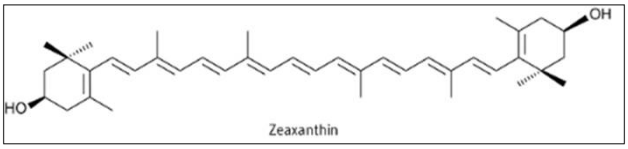
Saini et al. Antioxidants (Basel) 2022

Tomatoes, watermelon, red grapefruit - Lycopene, phytoene and phytofluene (colorless carotenoids). Tomato-based products contribute significantly to the American diet (think pasta sauce, ketchup) hence these tomato products are significant sources of lycopene in the US diet.

Salmon, shrimp, krill, - sources of astaxanthin

Dietary sources of carotenoids – Yellow foods

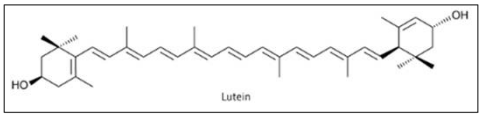


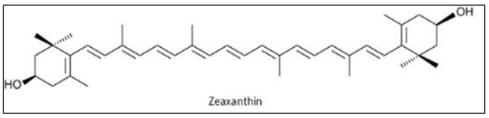


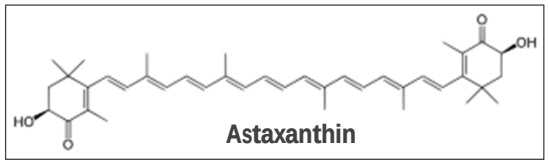
Saini et al. Antioxidants (Basel) 2022

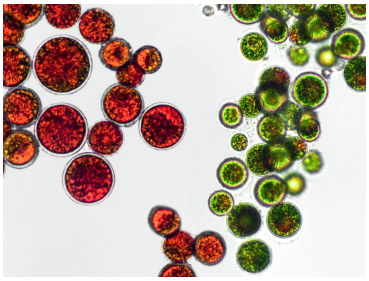
Corn (*Zea mays* L.) seeds and egg yolk are good sources of lutein and zeaxanthin [54]. As corn forms >50% of laying-hen diets [55], it supplies lutein and zeaxanthin, which are responsible for the intense yellow-orange color of egg yolk.

Dietary sources of carotenoids – emerging novel sources with significant health benefits









Hematococcus pluvialis

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New research on carotenoids lutein and zeaxanthin use avocadoes and pistachios as bioavailable sources – shown to have imp visual and cognitive benefits.

AX a non provit A carotenoid is found predominantly in marine organisms such as krill, shrimp and salmon, and in unicellular algae *Hematococcus pluvialis*. We don't eat algae in our regular diet, but AX status in the body would depend on the intake of seafoods such as salmon, lobster, shrimp, crab, krill/krill oil or from AX supplements. Esp AX from this species of algae is widely used in supplements. More on these in subsequent sections…

Dietary sources of carotenoids – supplements containing carotenoids and chlorophyll contribute to dietary intake

Astaxanthin

Lutein, zeaxanthin, beta-carotene

Chlorophyll

Nutritional supplements contain carotenoids like lutein, zeaxanthin, beta-carotene, astaxanthin and chlorophyll – and can significantly contribute to dietary intake

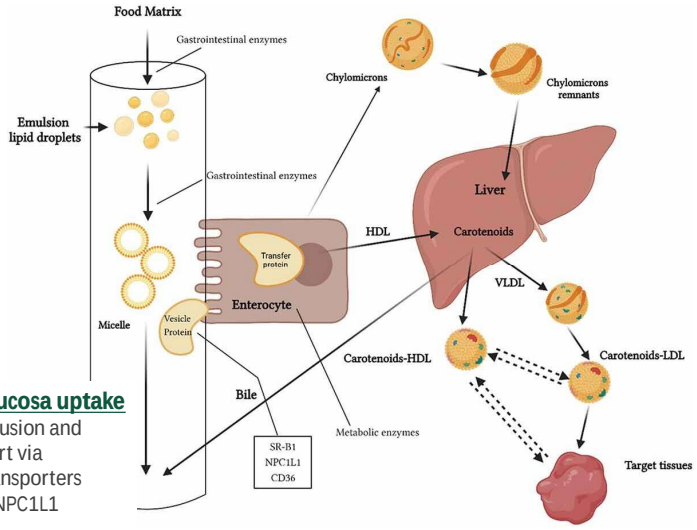
Carotenoid digestion and absorption pathway

Stomach
Carotenoids are solubilized into lipid globules

Duodenum of small intestine
Presence of fat triggers bile acids, pancreatic lipase breaks down TG into free fatty acids, mono- di- glycerides. Carotenoids + hydrolysis products

Mixed micelles

Intestinal Mucosa uptake
By passive diffusion and active transport via membrane transporters SR-B1, CD36, NPC1L1

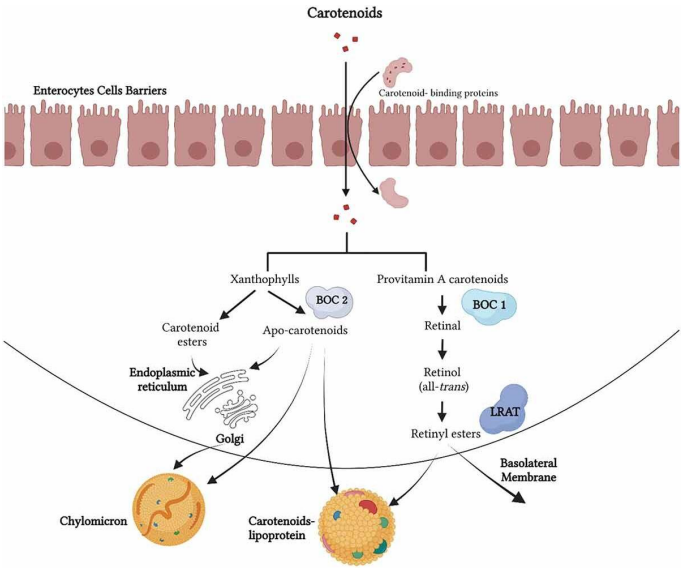


Duan et al. Food Reviews International 2024
Deming & Erdman. Pure Appl Chem 1999, 71(12): 2213-2223.

Carotenoids digestion and absorption pathway is similar to other fat-soluble compounds. No absorption happens in the mouth, but it is imp to chew and breakdown your food to make it easy for the stomach. In the stomach carotenoids are solubilized into lipid globules. In the duodenum of the small intestine – fat triggers the release of bile acids – enzyme pancreatic lipase breaks down the fat globules – free fatty acids, car, mono – di glycerides …which then reassemble into mixed micelles.

These mixed micelles containing carotenoids are absorbed into intestinal cells via passive diffusion and actively via membrane transporters SR-B1, CD36, NPC1L1

Carotenoid digestion and absorption pathway



Inside enterocytes

- Provitamin A carotenoids may be cleaved by enzymes BCO1 into retinal, retinol and retinyl esters which are incorporated in chylomicrons
- Non-provitamin A carotenoids may be cleaved by enzyme BCO2, but many remain intact and are incorporated into chylomicrons
- If cleaved by BCO2, apo-carotenoids are secreted via lipoproteins like HDL

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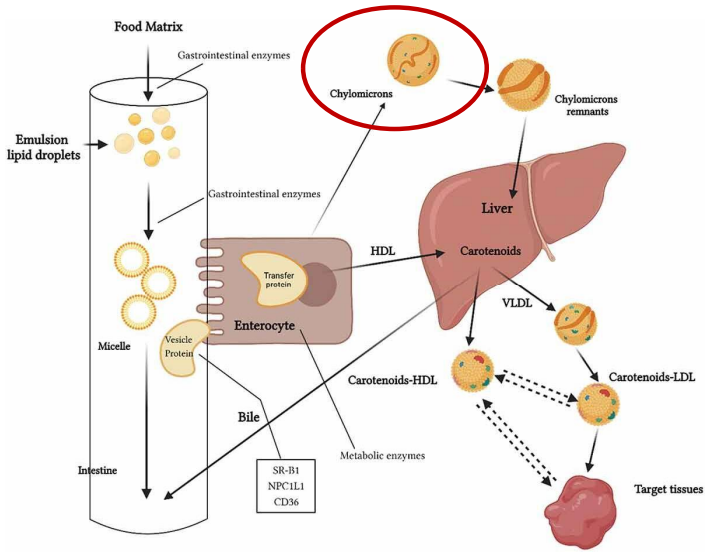
Duan et al. Food Reviews International 2024

Inside enterocytes (intestinal cells) Provitamin A carotenoids may be cleaved by enzymes BCO1 and BCO2 into retinal and retinol (vitamin A).

20 to 75% of b-car is estimated to be cleaved within mucosal cell – dose dependent and influenced by vit A

Uncleaved carotenoids are incorporated into TG rich chylomicrons, secreted into lymphatic vessels and released into the bloodstream.

Carotenoid digestion and absorption pathway



Chylomicrons (in circulation) are rapidly degraded by lipoprotein lipase and transformed into chylomicron remnants

Liver Uptake

Chylomicron remnants are taken up by the liver where they can be cleaved by BCO1/BCO2 or incorporated into lipoproteins and secreted back into circulation for delivery to extrahepatic tissues

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Deming & Erdman. Pure Appl Chem 1999, 71(12): 2213-2223

TG are removed from circulating chylomicrons by enzyme lipoprotein lipase resulting in formation of chylomicron remnants.

Chylomicron remnants are taken up by the liver where they can be cleaved by BCO1/BCO2 or incorporated into lipoproteins and secreted back into circulation for delivery to extrahepatic tissues – this is how carotenoids reach their target tissues – eyes, skin, brain, liver, prostate, adipose tissue

Bioavailability of Carotenoids

Bioavailability of carotenoids is highly variable and typically low from foods ranging from 5% to 30%

- **S**pecies of carotenoids – xanthophylls vs carotenes
- Molecular **L**inkage – cis and trans isomers (shape of the molecules)
- **A**mount of carotenoid consumed in a meal
- **M**atrix of delivery – plants vs animal, green leafy vs fruits and vegetables
- **A**bsorption modifiers – fat helps absorption, fiber can interfere with absorption
- **N**utrient status of the host
- **G**enetic Factors
- **H**ost-related factors and **I**nteractions

Karin van het Hof et al. J Nutr 2000

We looked at dietary sources and how car are absorbed – but there are several factors that control how much of what we eat actually makes it to the targeted tissues/organs of the body. And that is “bioavailability”

Bioavailability can be defined as the proportion of ingested nutrient that can utilized by the body for various metabolic activities. For carotenoids it is the proportion of car that is released from the food matrix, solubilized into lipid particles, forms the mixed micelles, which are then taken up enterocytes, form chylomicrons, and finally resecreted as lipoproteins in the blood that is taken up tissues. Thus bioavailability would depend on any factor that could affect this process of digestion and absorption. The mnemonic “SLAMENGHI” was put together by authors of this publication….to describe factors that affect bioavailability

Species & Form of Carotenoids

- Xanthophyll carotenoids tend to be more bioavailable compared to carotenes. They are more polar (oxygenated) and thus are more easily incorporated into the outer portions of micelles in the intestinal lumen and thus more easily taken up by enterocytes

  Bioavailability of lutein from vegetables was shown to be 5 times higher than that of β-carotene

	Relative plasma carotenoid response		
	High-vegetable diet	Carotenoid supplement	Relative bioavailability from vegetables
	$nmol \cdot L^{-1} \cdot mg^{-1}$		%
β-Carotene	55 ± 3.3	394 ± 2.2	14 ± 1.1
Lutein	41 ± 3.5	62 ± 5.2	67 ± 8

[1] $\bar{x}$ ± SE. *See* Results for calculations.

- **Isomeric form** – in plants they are typically found in all *trans* isomer form which is less bioavailable than the *cis* form, which can be created by heating and processing techniques which cause isomerization. *Cis* isomers are less rigid, preventing them from aggregating, in turn increasing their solubility and incorporation into micelles

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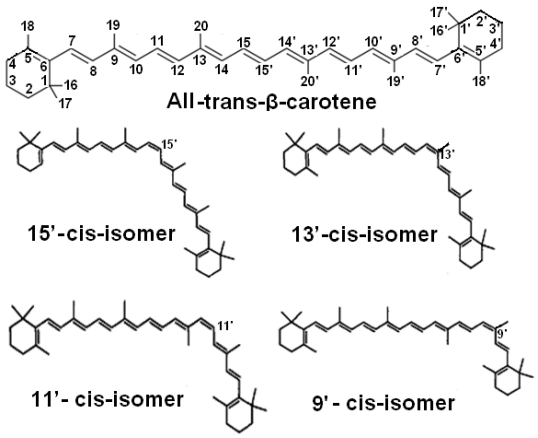
Van het Hof. AJCN 1999

One line about the study – this was a study done in healthy adults who consumed a high veg diet or low veg diet or low veg diet with car supp with 6 mg/d b-car and 9 mg/d lutein. Supp had increased plasma response. Lutein was 5 times higher than b-car. Some b-car could also have been converted to vitamin A.

Isomeric form – shape of the molecule -

trans and *cis* isomers of carotenoids (shown here β-carotene isomers)



- All *trans* **β-carotene** is more bioavailable than cis forms. *Cis* β-carotene from food micellarizes more efficiently than all *trans*, but cellular uptake of both forms was similar.
- **For lycopene**, *cis* isomers are more predominant in human tissue. Tomato products with greater proportion of *cis* lycopene results in great lycopene absorption (raw tomatoes are mostly all *trans* lycopene)

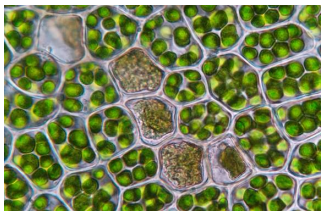
Chen et al.

Trans form – long chains

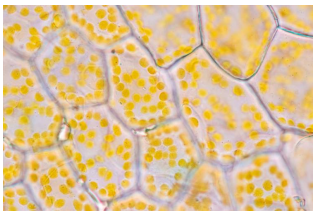
Cis forms more bendy and flexible. These are isomers of b-car. For b-car trans form more bioavailable.

Molecular Linkage and Matrix of delivery

- **Molecular Linkage** – Ester vs non-ester form of carotenoids that have –OH group (lutein, zeaxanthin). A study showed bioavailability of lutein esters was significantly lower when consumed as part of a low-fat meal compared to a high-fat meal
- **Food matrix** – Plant vs animal, and in plants matrix structure (carotenoids in green leafy vs in fruits and vegetables)



Chlorophyll



Chromoplasts

Van het Hof. AJCN 1999. Schweiggert et al. Br J Nutr 2014.

Some hydroxy carotenoids exist as esters (fatty acid attached to the –OH group) and need to be hydrolyzed before being absorbed. Higher amount of fat is required for optimum deesterification of lutein esters and absorption of lutein.'

Release of carotenoids from the food matrix is the first step in digestion and absorption – and the type of matrix in the which carotenoids are present in food affects their release. Data indicate that chloroplasts may be less efficiently disrupted in the intestinal tract than chromoplasts. Broccoli and green peas induced a larger b-carotene response in plasma than whole leaf and chopped spinach, even though the amt of b-car in peas and broccoli is 10 times lower.

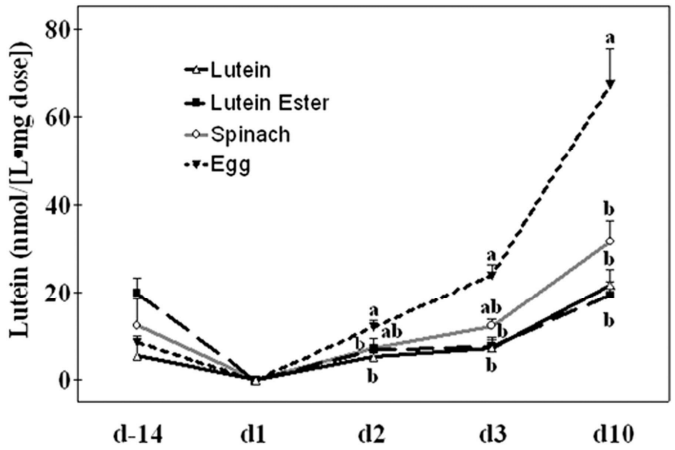
Differences in bioavailability between plant matrices

- **RCTs have shown different plant matrices affect bioavailability of carotenoids** – fruits vs vegetables vs green leafy vegetables
  - Compared to purified β-carotene, relative bioavailability of β-carotene ranges between 3% and 6% for green leafy vegetables, 19 and 35% for carrots and 22 and 24% for broccoli
  - Broccoli and green peas induced significantly greater plasma β-carotene responses compared to spinach despite the β-carotene content being 10 times lower

Carotenoids stored in plant chromoplasts are more bioaccessible than in chlorophyll of green leafy vegetables.

Van het Hof. AJCN 1999

Differences in bioavailability between plant and animal matrix (Lutein)



In a randomized crossover study in healthy men (n=10) bioavailability of lutein (6 mg) from eggs (high lutein eggs) was significantly greater than spinach, lutein and lutein ester supplements.

>

Egg borne lutein bioavailability ~3 times greater than spinach

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Chung et al. J Nutr 2004

This is data from a RCT - where the goal was to compare bioav lutein from eggs, spinach and supplements

(*all interventions were consumed as a test meal frittata made with egg whites*)

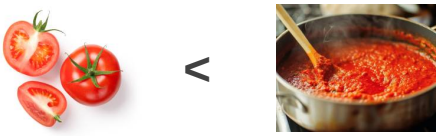
D-14 to d 1 – low car diet -

the meals for the various treatments were designed to contain similar amounts of fat (18.8–20.4 g), carbohydrate (6.7–8.0 g), and protein (22.9–26.4 g). The only appreciable difference in nutrient composition was that the egg frittata contained 643.1 mg cholesterol, whereas the spinach and plain frittata provided only 17–18 mg of cholesterol. Additionally, the spinach treatment contained 6.9 g fiber compared with 2.0 g in the other treatments.

Matrix of delivery and Absorption modifiers

- **Food matrix** – chopping, pureeing, juicing, cooking can disrupt plant cell walls and protein-carotenoid complexed increasing release and absorption of carotenoids
  - Whole leaf vs chopped spinach (plasma response of lutein increased ~14%)

  - Raw tomatoes vs tomato paste (plasma lycopene response 22-380% greater after consumption of tomato paste compared to raw tomatoes that delivered same amount of lycopene)



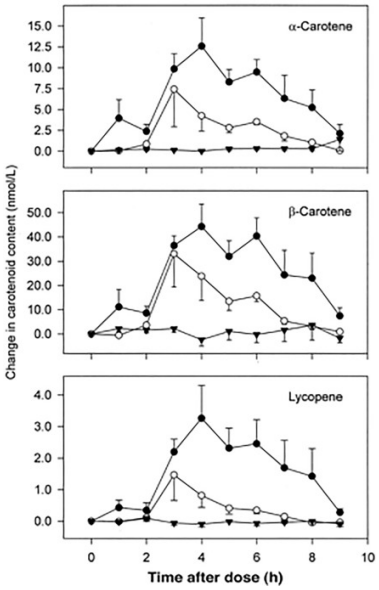
Van het Hof. AJCN 1999. Schweiggert et al. Br J Nutr 2014.

The second step in the absorption process of carotenoids involves the incorporation of released carotenoids into mixed micelles. Among other factors, formation of these micelles is dependent on the presence of fat in the intestine.

Dietary Fat - Ingestion of fat is crucial for carotenoid absorption!

Several RCTs have shown carotenoids to have significantly improved bioavailability when co-consumed with different forms of dietary fat

- Appearance of carotenoids in chylomicron fraction was negligible when salad was consumed with fat-free salad dressing (0 g fat, *shown as triangles*) and **progressively increased with reduced fat** (6 g fat, *shown as clear circles*) and **full fat dressings** (28 g fat, *shown as black circles*).



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Brown et al. AJCN 2004.

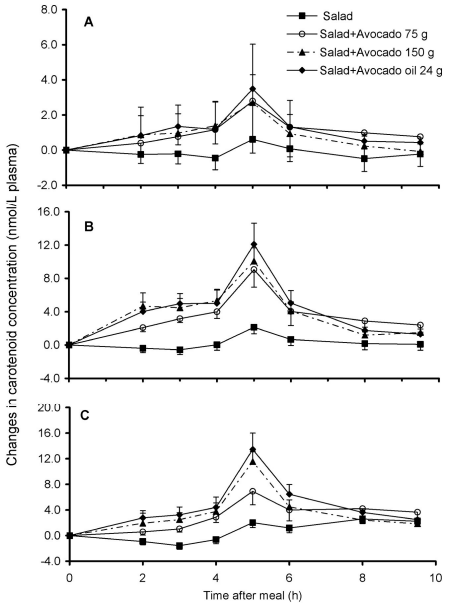
In this cross over study – participants ate 3 salads contg same amt of spinach, cherry tomatoes, romaine lettuce and carrots but with salad dressings contg 0, 6 and 28 g of fat – separated by 2 wk washout in betn the 3. shown here are carotenoids in chylmicron fraction of the blood.

For practical purposes – 1 tbsp of olive oil is about 13.5 g

Dietary Fat - Ingestion of fat is crucial for carotenoid absorption!

RCTs have also shown carotenoids to have significantly improved bioavailability when consumed with lipid-rich foods such as eggs and avocados

- Supplementing with avocado (75 g and 150 g) or 24 g avocado oil **significantly enhanced absorption** of **α-carotene** (7.2 times, graph A), **β-carotene** (15.3 times, graph B) and **lutein** (5.1 times, graph C) compared to avocado-free salad

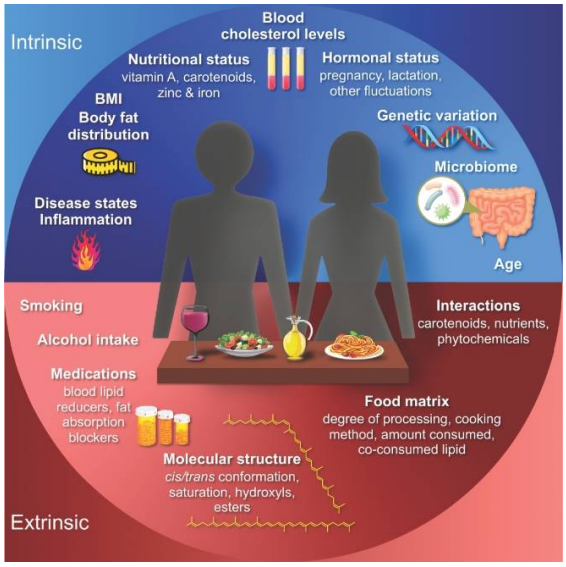


LNxxxxx 00/25 *Unlu et al. J Nutr 2005.*

What about adding a lipid rich food to carotenoid meal? This cross over study looked at whether adding lipid rich avocado enhances car absorption – subjects ate low car diet for 2 wk before the study – then ate study meals and car were measured in plasma TG fraction

Review of factors affecting Carotenoid Status

- BMI is inversely associated with carotenoid status



- SNPs in genes that code for enzymes involved in carotenoid metabolism, lipids and lipoprotein metabolism

- Drugs that block lipid absorption
- Smoking negatively affects carotenoid absorption
- Alcohol intake evidence is mixed

- Structure (cis vs trans, more polar better absorption)
- Green leafy vs fruits and veg
- Cooking techniques
- Presence of fat - 3 to 5 g of fat in a meal is sufficient to ensure carotenoid uptake

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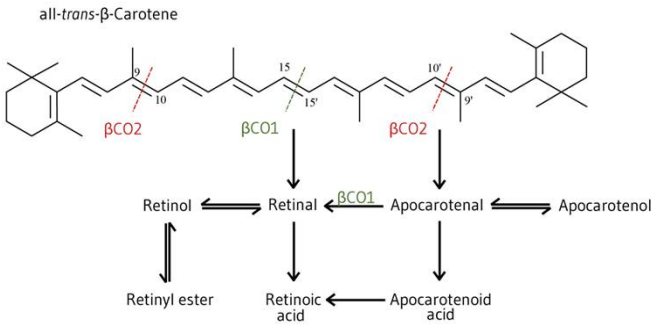
Moran et al. Adv Nutr 2018

Summarize bottom half right side first – We reviewed several extrinsic factors that control bioavailability carotenoids – structure (xanthophyll carotenoids more easily absorbed than carotenes, cis forms more bendy more bioavailable than trans remember lycopene tomato sauce/paste vs raw). The food matrix - 3 to 5 g of fat in a meal is sufficient to ensure carotenoid uptake. Vitamin A status improved to the same extent when 5 g or 10 g of dietary fat was added to spinach, whereas 0 g resulted in less improvement.

Cigarette smokers generally have lower serum carotenoid concentrations than nonsmokers, as a result of lower fruit and vegetable consumption and possibly because tobacco smoke can directly degrade carotenoids. Several epidemiologic studies have shown that alcohol consumption is generally associated with lower serum Carotenoids. Moran NE et al. Adv in Nutrition 2018 paper has a good summary of all factors.

Provitamin A activity

Vitamin A is essential for normal growth and development, immune system function and vision. α-carotene, **β-carotene**, and β-cryptoxanthin serve as a source of vitamin A.



Retinal and Retinoic acid are the two main active vitamin A metabolites. Most of the body's vitamin A is stored in the liver as retinyl esters.

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https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/carotenoids

Vit A can be acquired from the diet as preformed vit A in animal sources (milk, eggs, fish, meats, liver) or from provitamin A carotenoids in plant foods. Explain how it is formed.

We will not get too deep into vit A studies today. Vit A deficiency is not a problem in the US. Up to 80% of vitamin A in the US diet comes from preformed vit A. But in low-income countries provit A carotenoids are the main source of vit A as they consume more plant based foods – and vit A deficiency is a problem in the developing countries and there is a lot of research and innovation around preventing vit A deficiency in these developing countries. Some examples include biofortification programs – breeding/genetic eng to increase b-car in staple crops – orange flesh sweet potato in Africa. Orange maize, golden rice.

Provitamin A activity

- The international standard of measure for vitamin A is now **RAE** (Retinal Activity Equivalent), which represents vitamin A activity as retinol. It used to be IUs.

Quantity Consumed	Quantity Bioconverted to Retinol	RAE Ratio
1 µg of dietary or supplemental preformed vitamin A	1 µg of retinol	1:1
2 µg of supplemental β-carotene	1 µg of retinol	2:1
12 µg of dietary β-carotene	1 µg of retinol	12:1
24 µg of dietary α-carotene	1 µg of retinol	24:1
24 µg of dietary β-cryptoxanthin	1 µg of retinol	24:1

- The **RDA for vitamin A for a female age 19 – 50 y is 700 mcg RAE**. To meet this number entirely from intake of β-carotene, they would have to consume **8.4 mg of β-carotene from food** or **1.4 mg from β-carotene supplement**.

https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/carotenoids
https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/

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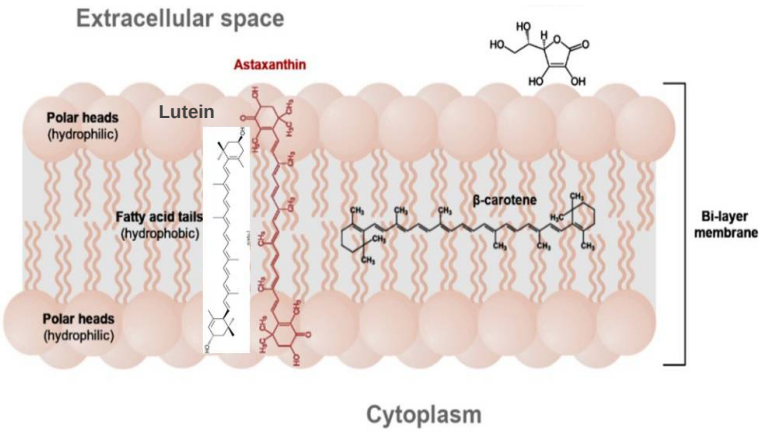
Lets look at the conversion efficiency – how much b-car do you need eat to make vit A in your body? When you eat vit A as vit A – it is a direct 1 to 1 ratio – you eat 1 ug and your body gets 1 ug. But Provitamin A carotenoids are less easily absorbed than preformed vitamin A and must be converted to retinol and other retinoids by the body. And we just saw there are a number of factors that affect bioavailability of carotenoids – bcos of this the efficiency of conversion of provitamin A carotenoids into retinol is highly variable. Of the 3 with provita A activity, b-car is the most potent. 12 ug of b-car can give your body 1 ug of retinol. So for example, RDA for Vit A……to meet this number…..they would have to consume 700 x 12 = 8400 ug/8.4 mg of b car

Bullet 2 – hypothetical example -

Other biological activities that give them unique health benefits

- Antioxidant Activity - Quenching free radicals generated during normal metabolic processes thus reducing oxidative burden, also inhibit lipid peroxidation. Upregulate expression of antioxidant and detoxifying enzymes



LNxxxx 00/25 https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/carotenoids Riaz et al. Carotenoids Structure and Function in human body. Springer 2021.

Carotenoids orient differently across the cell membrane lipid bilayer which causes differences in their antioxidant potential. Astaxanthin's superior antioxidant activity can be attributed to its transmembrane orientation cross the bilayer of cell membranes, specifically mitochondrial membrane.

Cell membranes are particularly vulnerable to oxidative stress due to their high PUFA composition. Lutein and zeaxanthin also have similar transmembrane orientation, but b-carotene and non-polar carotenoids are embedded horizontally inside the lipid membranes.

Astaxanthin's lipid peroxidation is 100 times more potent than vitamin E

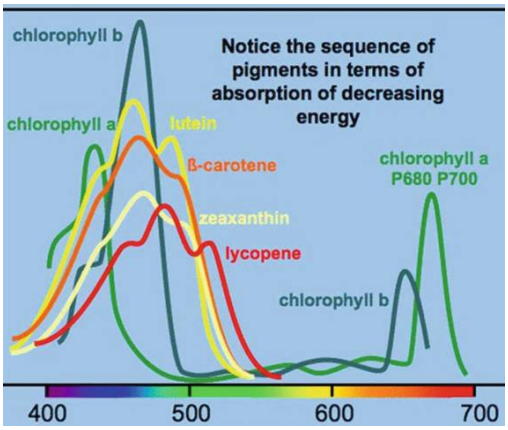
Astaxanthin's singlet oxygen quenching activity is 40 times more potent than beta-carotene

Other biological activities that give them unique health benefits

- Light Absorbing property

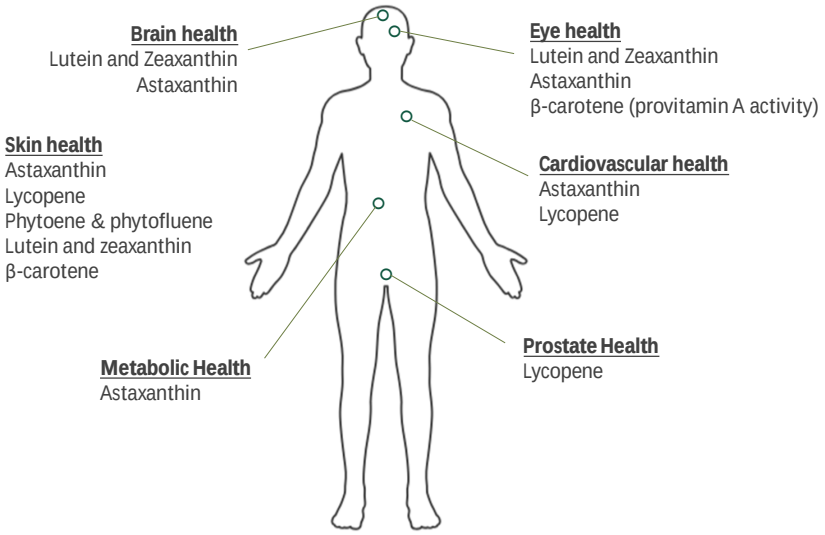
  The long chain of alternating double bonds allows them to absorb blue-green wavelength of visible light.

  In plants, carotenoids act as accessory pigments extending light absorption range for photosynthesis.



https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/carotenoids
Riaz et al. Carotenoids Structure and Function in human body. Springer 2021.

Carotenoids and Whole-body Health



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Adapted from Honda, M. (2020). Nutraceutical and Pharmaceutical Applications of Carotenoids. In: Jacob-Lopes, E., Queiroz, M., Zepka, L. (eds) Pigments from Microalgae Handbook. Springer, Cham.

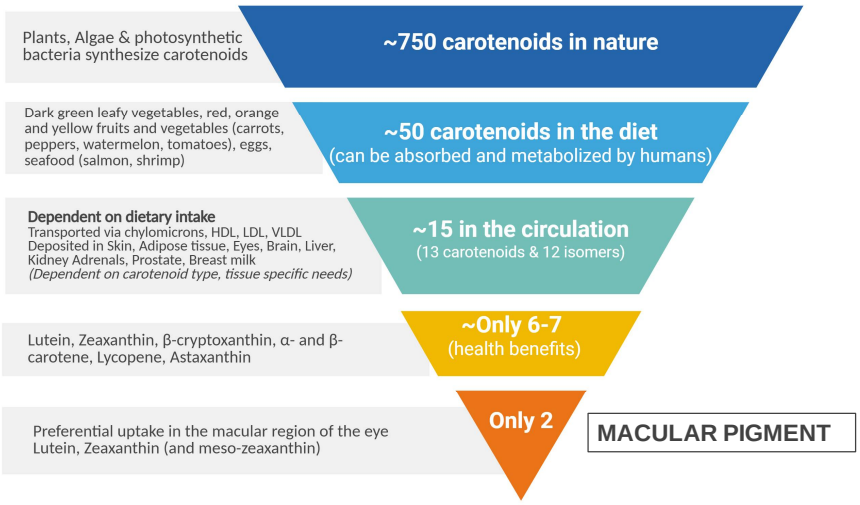
we looked at what car are? Where we can find them? How they are digested absorbed – and their special properties that make them valuable for our health.

Next section we will look at bigger picture – how these colorful pigment can make a big impact on our health.

In dept review of literature on the carotenoids that are (i) prevalent in the diet and have substantial evidence behind their benefits (2) carotenoids are emerging in the nutraceutical industry

Start with Eye

Carotenoids journey - From Nature to Food to Human Body



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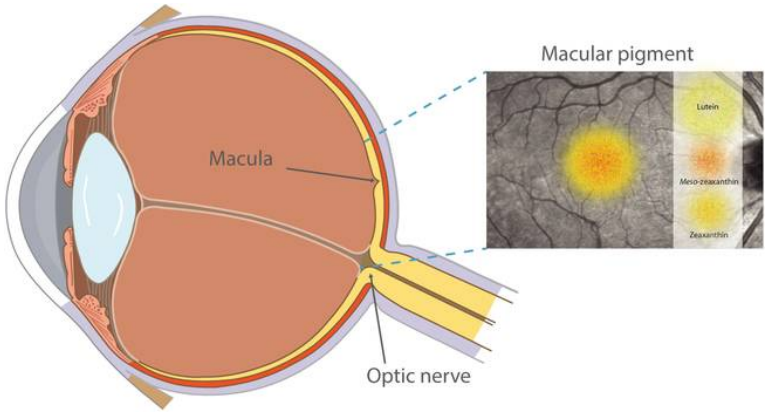
Let's go back to that carotenoid funnel – of the major carotenoids that are absorbed in our body and found in our circulation – it so cool that the retina selectively accumulates only two car – L and Z in the back of the eye to form MP

Lutein and Zeaxanthin – carotenoids that preferentially accumulate in the macular region of the retina. Lutein, zeaxanthin and meso-zeaxanthin (a lutein isomer formed in the retina) are referred to as macular pigment (MP).



Scanlon et al. Nutrition Research Reviews 2019.

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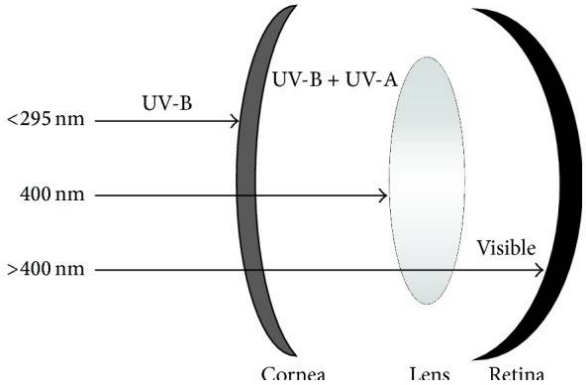
This is a picture of the eye, front lens, in the back of the eye is retina – the centermost region of the retina is the macula – responsible for sharp, central vision. L & Z are the only 2 carotenoids in the diet that preferentially accumulate in the macula (form a visible yellow spot, because of its color it is called macula lutea) to form macular pigment.

(The first report that the yellow spot in the macula of human retinas might be a carotenoid was in 1945. In 1985 MP components were identified as L &Z and then 1993, meso zeaxanthin was identified – HPLC)

Exclusive location of MP is clue to its function!

Most of the UV light is absorbed by the cornea and lens in adults. Visible blue light reaches the retina causing photodamage to the retina. MP (yellow) can absorb blue visible light.



Light induced damage can occur through,

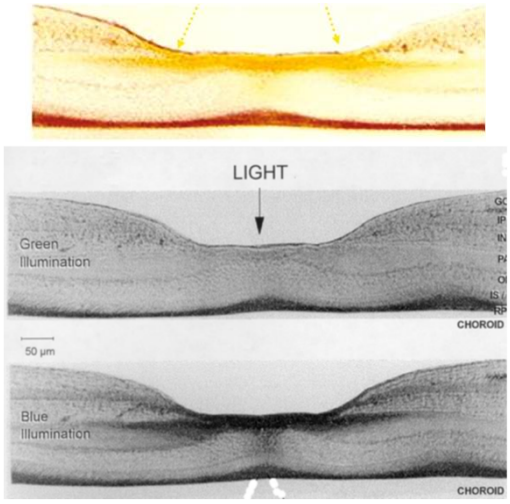
- Inflammatory response or
- Photooxidation reaction (free radical generation, oxidative stress)

Scanlon et al. Nutrition Research Reviews 2019.

Most UV light is absorbed by the adult cornea and lens, In adults, the lens absorbs UV-B and all the UV-A (295–400 nm); therefore only visible light (>400 nm) reaches the retina.

The very young human lens transmits UV radiation to the retina, while the elderly lens filters out much of the short blue visible light (400–500 nm) before it reaches the retina.

Cross section of a human macula photographed in either a green or blue light, showing absorption of blue light by macular pigment



Deep yellow color of MP and its ideal location in the retina,

- Blue light filters
- Protection from photooxidative damage (antioxidant activity)

Krinsky NT, Bone RA & Landrum JT. Ann Rev Nutr 2003;23:171-201

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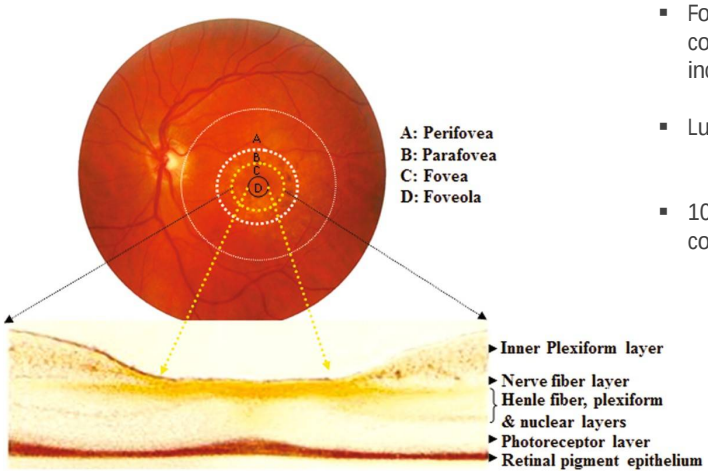
Cross section – macula is characterized here by both depression in the retinal and also presence of blue light absorbing carotenoids.

Macular pigment distribution in the retina - relevant to understanding its measurement as MPOD



- Fovea (centermost) has the highest concentration of MP, declines rapidly with increasing eccentricity
- Lutein: zeaxanthin = 1:2.4 (center 0- 0.25 mm)
  = 2:1 (increasing eccentricity)
- 100-fold drop in MP in peripheral retina compared to the fovea

Arunkumar et al. Eye 2018.

MP has a unique distribution in the retina with high concentrations in the fovea and inner plexiform layer of the retina. The ratio of lutein:zeaxanthin is 1:2.4 in the center (0–0.25 mm) to over 2:1 in the periphery (8.7–12.2 mm) of the human retina. There is a 100-fold drop in the macular pigment concentration in the peripheral retina compared to the fovea,

MP can be measured non-invasively as MPOD (Macular Pigment Optical Density)

- Psychophysical Techniques - **Heterochromatic Flicker Photometry** (HFP) is the most commonly used method in clinical practice (examples – QuantifEye, MacuScope). Gives you a number ranging from 0 to 1.0, which is MPOD.

Densitometer

Portable Zx Pro

- **Objective Techniques** - Fundus Reflectometry or Autofluorescence are more complex, require expensive and high-end equipment and not practical for clinical use

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https://eyepromise.com/blog/mpod-measurement-approved-for-category-iii-cpt-code
https://eyepromise.com/zxpro-product/
Christaras et al. Biomed Opt Express 2019;10(7):3572-3583

What is really cool?! Macular pigment can be measured non-invasively by various techniques. And these devices have significantly contributed to the research and understanding of how diet and supplementation can influence MP. Most common in clinical practice is Heterochromatic flicker photometry-based devices – this uses flickering light stimulus (alternating blue and green light) – patients are adjusting the amount of blue and green light to stop the flicker. MP is yellow and absorbs blue light, MP can be quantified based on the amount of blue light needed to stop the flicker (https://iovs.arvojournals.org/article.aspx?articleid=2163179 – more details)

Objective techniques are accurate – but require expensive and bulky instruments – making it impractical for clinical use.

MPOD (Macular Pigment Optical Density) clinical significance

There is substantial evidence that indicates,

- MPOD measures positively correlate with dietary lutein and zeaxanthin and serum lutein and zeaxanthin – **Biomarker of retinal lutein and zeaxanthin**
- MPOD significantly correlated with **visual function measures** – contrast sensitivity, photostress recovery, glare disability (indicate importance for everyday activities)
- MPOD significantly correlated with **cognitive function** measures – along with data that carotenoids, specifically high lutein in brain tissue + correlation between MPOD and brain lutein and zeaxanthin (study in rhesus monkeys)

MPOD offers potential clinical biomarker of visual & cognitive health

Celentano et al. Am J Clin Nutr 2001;74:796–802., Johnson EJ et al. Eye 2021;35:1620-1628, Kelly et al. J of Alzheimer's disease 2015;48:261-277

There is a ton of research on macular pigment measurements in clinical studies and its correlations that is relevant to clinical practice.

(bullet 2) - Given that MPOD can be augmented through increased dietary intakes, these findings have meaningful significance for day-to-day activities and functions. In terms of photostress recovery and glare disability, short-wave light filtration would appear to be a reasonable explanation for performance enhancement. However, for CS, light filtration cannot explain a significant enhancement. These effects are more likely due to more efficient communication among visual neurons.

MPOD is a biomarker of estimating brain L & Z, retinal/visual health & cognitive health

Photostress recovery – how quickly your eye can recover from being bleached by a bright light, glare disability – temporary impairment in vision caused by bright light sources – headlights

MPOD (Macular Pigment Optical Density) clinical significance

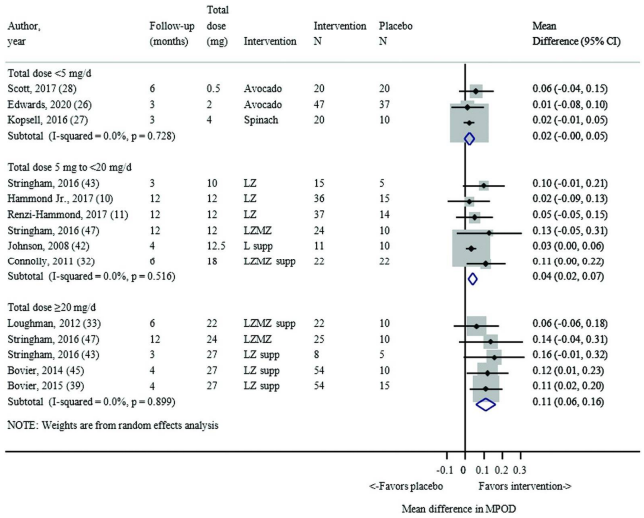
- Evidence suggests that low macular pigment levels are associated with higher risk of AMD (Age-related macular degeneration)
- AMD is the leading cause of vision loss in older adults causing loss of sharp central vision caused by age-related damage to the macula

Normal vision (left) and a scene viewed by a person with AMD (right)

Scanlon et al. Nutrition Research Reviews 2019.

Age-related macular degeneration (AMD) – is the leading cause of vision loss in older adults causing loss of sharp central vision caused by age-related damage to the macula

MPOD can be augmented through interventions with foods & supplements!



Meta-analysis of 46 RCTs

- Lutein and zeaxanthin intake at doses over 5 mg/d for ≥3 mo can increase MPOD concentrations among adults with healthy eyes by 0.04 to 0.11 units
- Daily doses 5 – 20 mg/d may increase MPOD by 0.04 units
- Daily doses >20 mg/d may increase MPOD by 0.11 units
- A different study also showed lutein supplementation was effective in improving MPOD in individuals with AMD and those at risk

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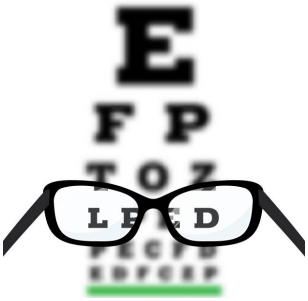
Wilson LM et al. Advances in Nutrition 2021;12(6):2244-2254

There are several studies that have evaluated supplementation with L&Z (dietary sources and supplements) that show MPOD can be increased with diet and that this increase translates to improved clinical/functional measures –

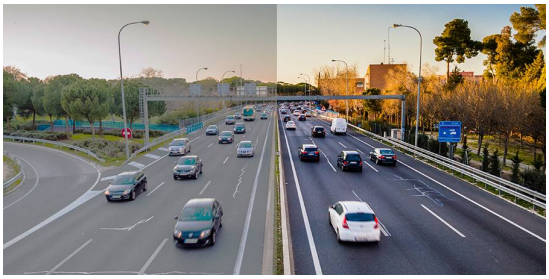
This is a meta-analysis of 46 studies objective was to determine a minimum concentration of lutein/zeaxanthin intake that is associated with a statistically significant and/or clinically important change in macular pigment optical density (MPOD) among adults with healthy eyes.

Lutein supplementation can improve Visual Function Measures in AMD patients

- Several clinical studies have shown beneficial effects of lutein supplementation on visual function measures in AMD patients
- A meta-analysis of 9 RCTs (2019) showed lutein supplementation (10 and 20 mg/d) was associated with improved visual acuity & contrast sensitivity in AMD patients



Visual acuity



Contrast sensitivity

Richer et al Optometry 2004;75(4):
Feng et al. PLOS One 2019;14(12):e0227048

We saw that intervention can increase your MPOD – but does that translate to functional improvement – YES

Lutein supplementation has shown to improve visual function in healthy eyes & diseased eyes. Data here is meta-analysis of 9 RCTs in AMD patients that showed lutein supp with 10 and 20 mg/d improved visual acuity and contrast sensitivity.

Contrast sensitivity is the ability to distinguish between an object and its background

WAYFINDING TEXT 51

AREDS/AREDS 2 Clinical Trials

The National Eye Institute (NIH) conducted two large scale studies to test whether nutritional supplements could prevent or slow the progression of cataracts and AMD

Nutrient	AREDS formula*	AREDS2 formula
Vitamin C	500 mg	500 mg
Vitamin E	400 IU	400 IU
Beta-carotene	15 mg	-
Copper (cupric oxide)**	2 mg	2 mg
Lutein	-	10 mg
Zeaxanthin	-	2 mg
Zinc	80 mg	80 mg

*Not recommended for current or former smokers
**Added to avoid zinc-related copper deficiency
mg = milligrams
IU = international units

- Taking AREDS or AREDS-2 supplements reduced the risk of progression from intermediate to advanced AMD by about 25%
- AREDS 2 10 y follow up – lutein and zeaxanthin formula reduced AMD progression by an incremental 15% compared to β-carotene
- CAUTION: β-carotene nearly doubled the risk of lung cancer among former smokers but not lutein & zeaxanthin

https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/about-areds-and-areds2

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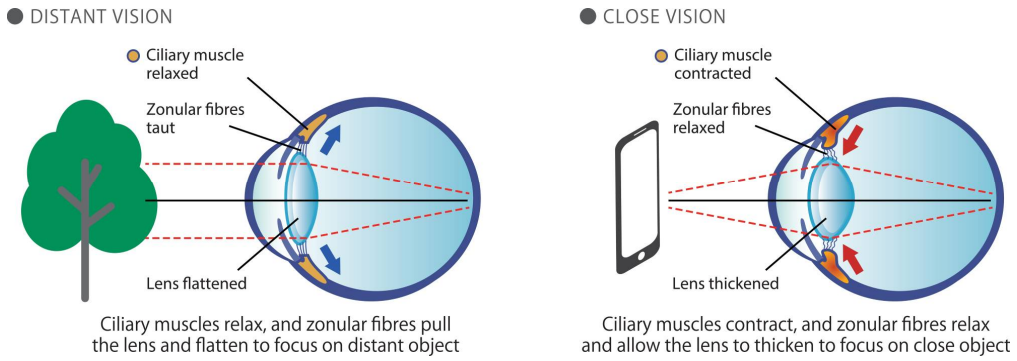
those with intermediate AMD, and those with advanced AMD in one eye only—reduced their risk of developing advanced by about 25 percent when treated with the combination of antioxidants and zinc + copper (final AREDS formula). The AREDS formula also reduced the risk of central vision loss by 19% in the same group.

B-car at doses of up to 50 mg/d is safe in non-smoking populations, and in heavy smokers a dose of under 15 mg is not expected to increase risk of lung cancer

Accommodative Dysfunction & Digital Eye Strain

- **Accommodative function** is the ability of the eye to automatically change its focus from distant to near objects and vice versa
- Age & **prolonged near work** (reading or **screen use**) affect accommodative ability



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When you look at something close, the ciliary muscles contract. This contraction relaxes the tension on the suspensory ligaments, allowing the flexible lens to become thicker and rounder. The increased curvature of the lens increases its refractive power, focusing light from the nearby object onto the retina. When you shift your gaze to a distant object, the ciliary muscles relax. This action increases tension on the suspensory ligaments, which pull on the lens, causing it to become thinner and flatter. This reduced curvature decreases the lens's refractive power, enabling clear focus on distant objects.

Accommodative ability weakens with age – lens looses elasticity (presbyopia), prolonged near work (reading, screen use) can fatigue muscles

Accommodative Dysfunction & Digital Eye Strain

- The average American spends 7.5 h every day focused on screens. This overworks the ciliary muscles contributing to digital eye strain, which is experienced by 65% of Americans who use screens
- Prolonged exposure to blue light emitted from screens also contribute to eye strain and fatigue (CVS, computer vision syndrome)
- Symptoms include, inability to look from near to far quickly without any blur, transient blurred vision, Eye strain/fatigue, headaches, difficulty concentrating
- Studies show that **Astaxanthin helps support ciliary muscle endurance and recovery, helping alleviate eye fatigue and promoting focus**

https://www.aoa.org/healthy-eyes/eye-and-vision-conditions/accommodative-dysfunction
https://astarealusa.com/health-benefits/eye-health/

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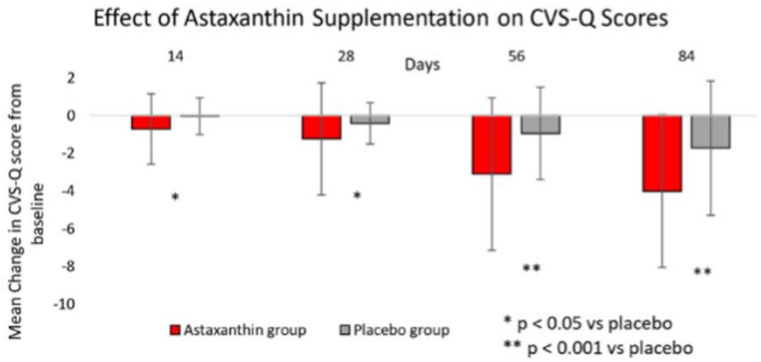
The constant contracting of ciliary muscles contributes to eye strain.

High energy blue light reduces contrast therefore causing eyes to constantly have to re-adjust focus and overwork ciliary muscles. Tired ciliary muscles directly cause eyes to feel strained and fatigued.

Daily 4 mg of astaxanthin for 84 days reduced digital eye strain symptom scores by 29% in school-aged children whose daily screen time was ≥4 h



29% reduction compared to baseline

20% reduction compared to placebo

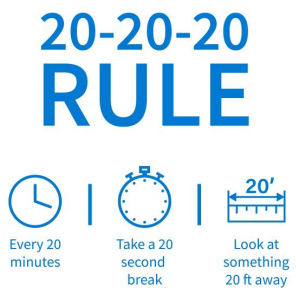
CVS-Q = computer vision syndrome questionnaire, assess frequency and intensity of 16 eye strain-related symptoms

Hecht KA et al. Astaxanthin (AstaReal®)) Improved Acute and Chronic Digital Eye Strain in Children: A Randomized Double-Blind Placebo-Controlled Trial. Adv Ther. 2025;42(4):1811-33.

Astaxanthin supplement studies showing positive eye health benefits

Visual health outcomes that has significant beneficial effects with astaxanthin supplementation

- **Improved accommodation power** in RCTs in subjects who work on computers and complain of eye strain
- **Alleviated eye strain** – these included subjective symptoms such as "bleary-eye feeling", "tendency of irritation", "heavy head", "tired eyes"
  (5 studies, doses 5 mg, 6 mg, 9 mg and 12 mg/d)
- **Increased retinal capillary blood flow** (6 mg/d) explains the improvement in accommodation
- **Improved symptoms of dry eye** in middle to older adults with mild to moderate dry eye disease (12 mg/d)
- **Improved accuracy of depth perception (55.4%)** in university hand ball players (n=18) who took 6 mg/d astaxanthin for 4 weeks



Nagaki 2011, Iwabayashi 2009, Nagaki 2006, Shiratori 2005, Nitta 2005, Nagaki 2002
Tian 2022, Nagaki 2005, Sawaki 2002

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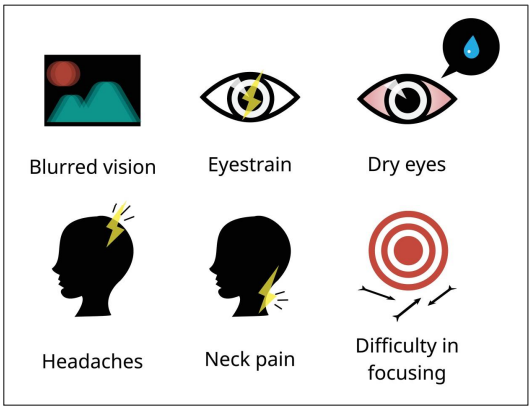
AX supplementation was shown to improve accommodative function and eye fatigue associated with screen use at doses that ranged from 4 mg/d to 12 mg/d. Several of these clinical studies were done in healthy volunteers who complained of tired eyes and/or were regularly working on screens

The accommodation mechanism of the eye involves the contraction and relaxation of ciliary muscles. The increased retinal blood flow also probably increases blood flow to the ciliary muscles that could result in improvement in amplitude of accommodation.

AX is working in a similar fashion in the eye, improving ciliary muscle endurance and recovery helping alleviate eye fatigue.

Depth perception is important in sports performance – when a baseball player is going to catch a ball, a tennis player is going to smash – player has to have a sense of distance to goal and be able to understand the position of moving ball

Lutein supplementation also provides visual health benefits in regular screen users!



Several studies have shown **supplementation with lutein (and zeaxanthin) to improve symptoms of digital eye strain in regular screen users**

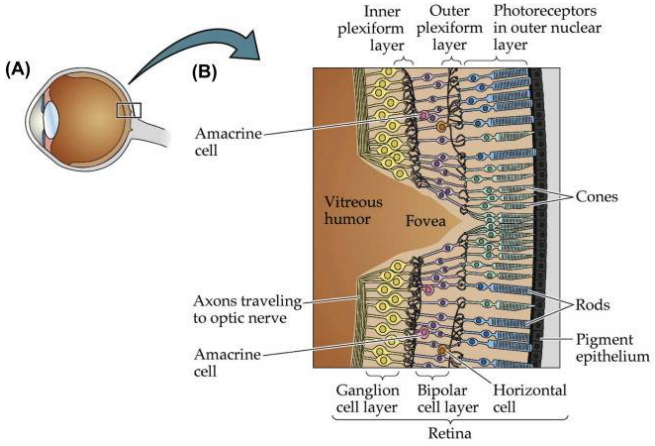
- Age 18 to 65 y, >6 hours screen use, supplemented with 10 mg lutein and 2 mg zeaxanthin for 6 months – increased tear production (dry eyes), shortened photo stress recovery time
- Age 22 to 30 y, healthy subjects with long-term computer use supplemented with 6 mg and 12 mg lutein for 12 weeks – contrast sensitivity increased with both doses, higher dose showed a trend towards increase in visual acuity

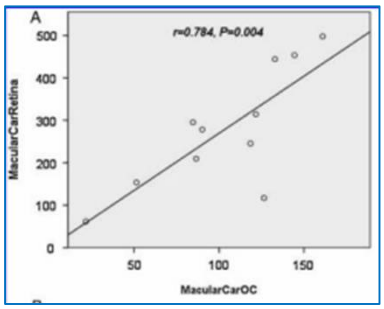
Ma et al. British J of Nut 2009
Lopresti et al Frontiers in Nutrition 2025

Photostress recovery is the time it takes your vision to return to normal after a bright light has temporarily “bleached” the photoreceptor cells in your retina.


Brain Health

Retina is Neural Tissue – Macular carotenoids correlate with brain carotenoids





Macular carotenoids (in retinal tissues) positively correlated with lutein and zeaxanthin in occipital cortex.

MPOD can potentially be a biomarker for estimating brain lutein and zeaxanthin

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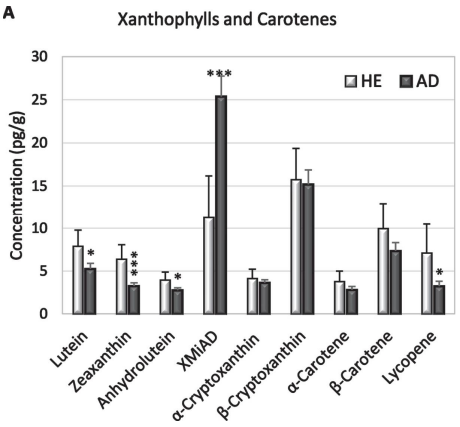
Vishwanathan R et al. Nutr Neuroscience 2015
Moran Furman,Chapter 19 - Visual Network., Neuronal Networks in Brain Function, CNS Disorders, and Therapeutics, Academic Press 2014: 247-259,

Data obtained from donated brain and retina tissue National Disease Research Interchange, a national human tissue resource center which adheres to strict consent and confidentiality procedures. Decedents were men and women aged >50 years who either had normal cognitive function or Alzheimer's disease.

Observational studies show carotenoids correlate with cognitive Function

- Alzheimer's disease brains had significantly lower (almost half) levels of lutein, zeaxanthin, anhydrolutein, retinol, lycopene, and alpha-tocopherol compared to Healthy Elderly (HE) brains
- A nutrient pattern **rich in carotenoids (in brain tissue) was positively associated with better performance in cognitive measures** – memory, language, lower depression in subjects with no dementia

Plate to brain to cognitive functioning



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Dorey KC et al. J of Alzheimer's disease 2022;94(1)
Tanprasertsuk J et al. Front Nutr 2021

Clues that indicate carotenoids (specifically lutein and zeaxanthin) play a role in cognition

Lutein supplementation improves Cognitive Function – data from several RCTs

Meta-analysis of RCTs
(several diff authors/diff publications) – similar conclusions

Lutein 10 mg/d
Zeaxanthin 2 mg/d
(treatment period ranging 4 months – 1 year)

- **Cognitive function benefits** – either improvement or suggested maintenance.
- Domains – Memory, attention, learning, cognitive flexibility
- Effect is more pronounced in healthy older adults, those with self-reported cognitive complains,

Lopresti AL et al. Front Nutr 2022, Hammond BR et al. Fron in Aging Neuroscience 2017
Li J et al. Moelcules 2021, Davinelli S et al. Antioxidants 2021

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From correlations to randomized clinical trials – there is evidence that supplementation with L and Z (most commonly used dose in clinical studies is 10 and 2 mg/d) – at treatment periods ranging from 4 to 12 months (12 months most studies)

To take 10 mg lutein from vegetables and fruits, people need about 200 g every day. For astaxanthin, if people take 4 mg astaxanthin in daily consumption, they need to eat about 600 to 2000 g salmon or seafood every day


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Skin Health
LNxxxxx 00/21
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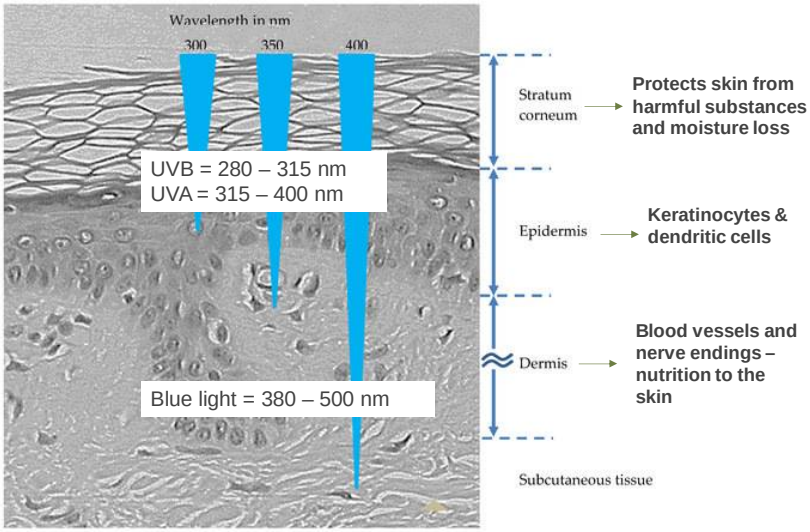
Carotenoids & Skin Health

Everyday challenges,

- External – sunlight (UV), blue light (reaches dermis), air pollution, other environmental stressors
- Internal – Age, nutritional & mechanical factors, internal stressors

Photoaging accounts for 80% of age-related changes in skin appearance, which is caused by chronic UV-induced deteriorations in addition to the intrinsic aging process



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The skin is the largest multifunctional organ on the surface of the human body and consists of three layers: the epidermis (outer), dermis (inner), and subcutaneous tissue (innermost). The epidermis is composed of keratinocytes and dendritic cells, and the stratum corneum (outermost layer of the epidermis) protects the skin from harmful substances and moisture loss. The dermis provides nutrition for the skin and is rich in blood vessels and nerve endings. Diet and nutrition play an important role in maintaining skin health.

Skin is exposed to challenges everyday….

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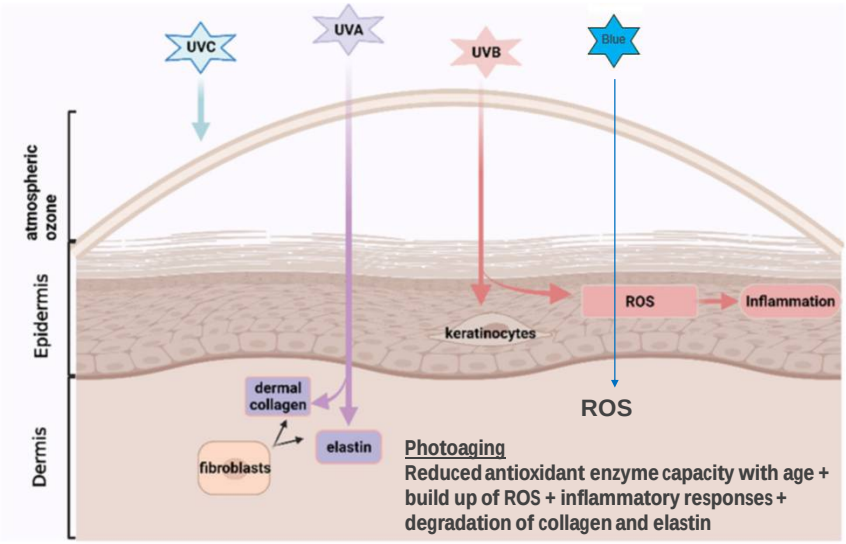
Mechanisms by which UV radiation (and blue light) cause photodamage



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Zhou et al. Nutrients 2021, 13:2917.
Tominaga et al. J Clin Biochem Nutr 2017;61(1):33-9.

UVA, which contributes up to 95% of the total UV exposure, penetrates the skin dermis and degrades the dermal collagen and elastin which are produced by the fibroblasts and are responsible for skin strength and elasticity, respectively.

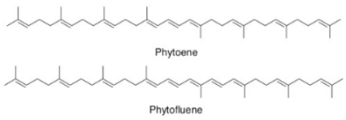
UVB mainly affects the epidermis causing DNA damage in keratinocytes. UVB could also damage cellular macromolecules (nucleic acids, protein and lipids) and induce generations of high-level ROS, stimulating chronic inflammation

Blue light penetrates the skin reaching the dermis where it can lead to oxidative stress, inflammation, leading to the degradation of collagen and elastin.

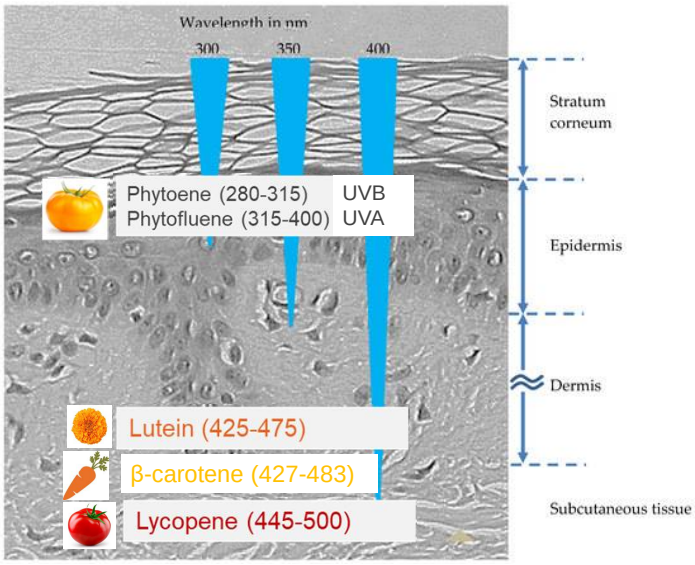
Clinically these effects translate to – wrinkling, loss of elasticity/firmness, moisture/hydration, redness,

Mechanisms by which Carotenoids protect the skin

- **Phytoene** and **phytofluene** are colorless carotenoids that absorb maximum light in the UV range (protect against UV-induced erythema)

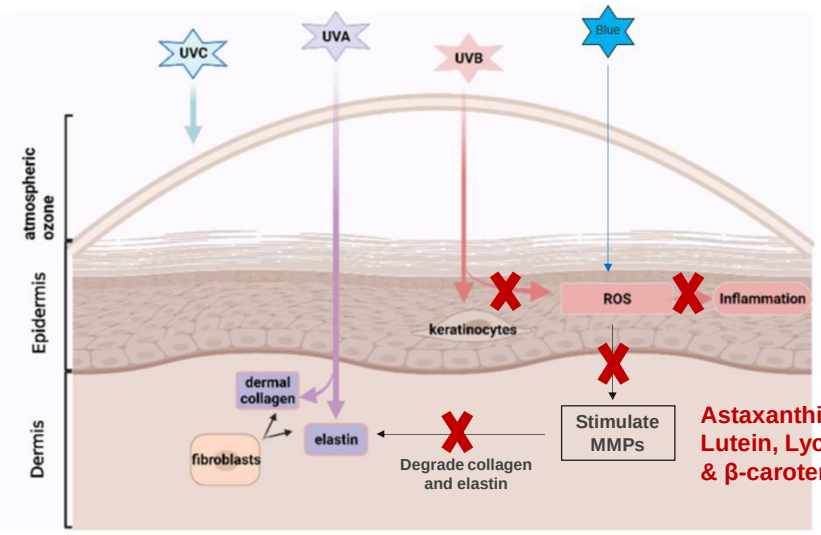


- **Lutein, β-carotene, lycopene** absorb maximum light absorption abilities in the blue wavelength range. They also have strong antioxidant activity and anti-inflammatory activity.
- **Astaxanthin** has the most potent antioxidant activity – protects UV and blue light-induced downstream reactions



Phytoene and phytofluene are found in lycopene sources like tomatoes, watermelon, red grapefruit, apricots, very similar in structure to lycopene (lycopene is formed from phytoene and phytofluene in plants).

Mechanisms by which Carotenoids protects the skin



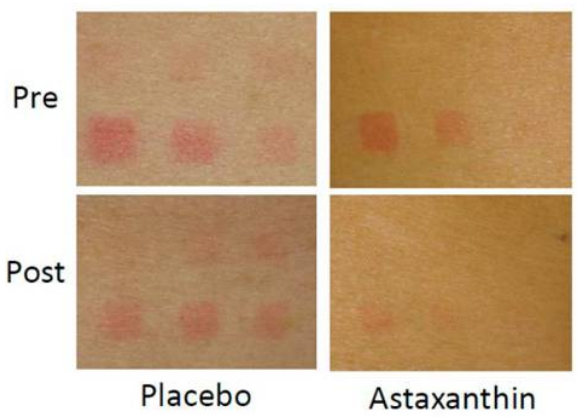
Zhou et al. Nutrients 2021, 13:2917.
Yoon HS et a. J of Med Foods 2014; 17(7):810-6.

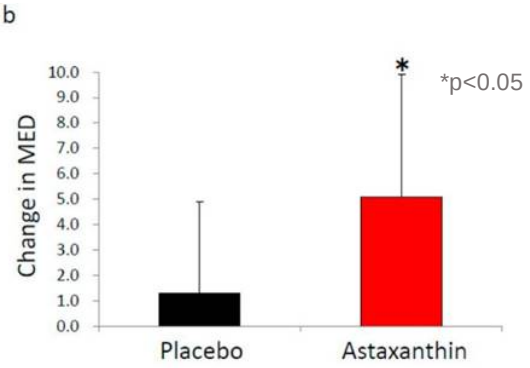
Carotenoids prevent the deleterious effects of UV by decreasing UV-induced reactive nitrogen species production, inflammatory cytokine expression, and apoptosis in keratinocytes (and similarly with blue light induced ROS…)

UV-induced (and blue light induced) ROS also stimulate synthesis of MMPs. MMPs are zinc-containing endopeptidases that degrade various components of extracellular matrix proteins, including collagen and elastin. In vitro studies have shown AX, lycopene, b-car to effectively inhibit the expression of MMPs and protect degradation of elastin and collagen

Clinical evidence on Astaxanthin supplementation and protection from photoaging

- Double-blind, randomized, placebo-controlled trial in healthy men & women aged 30 to 60 years (n=23)
- Increased MED, reduced loss of skin moisture in the irritated area, subjective improvement in rough skin and texture in non-irradiated areas





4 mg/d for 9 weeks

Ito et al. Nutrients. 2018;10(7):817.

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In the double blinded, placebo control randomized trial in healthy men & women aged 30 to 60 y - AX supplementation (4 mg/d for 9 weeks) increased UV-induced minimal erythema dose (MED). MED is amount of UV light that produces minimal redness of the skin, increase in amt of UV light indicates increased protection. AX group required 5 units more of UV radiation to cause redness after AX supp for 9 wk, while placebo required only 1 unit more compared to baseline.

In addition, the astaxanthin group had a reduced loss of skin moisture in the irradiated area compared with placebo. Subjective skin conditions for “improvement of rough skin” and “texture” in non-irradiated areas were significantly improved by astaxanthin. Astaxanthin seems protective against UV-induced skin deterioration and helps maintain healthy skin in healthy people.

Clinical evidence on Astaxanthin supplementation and protection from photoaging

- Single blind, placebo-controlled study in healthy middle-aged women (n=49)
- Astaxanthin at 4 mg/d for 9 weeks
- Significant improvements in fine lines/wrinkles & firmness
- Skin moisture content (hydration) also improved

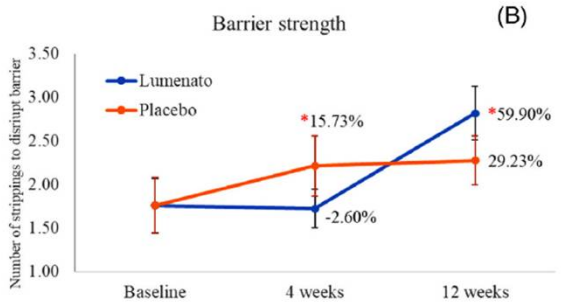
Yamashita E. Food Style 21. 2005;9(9):72

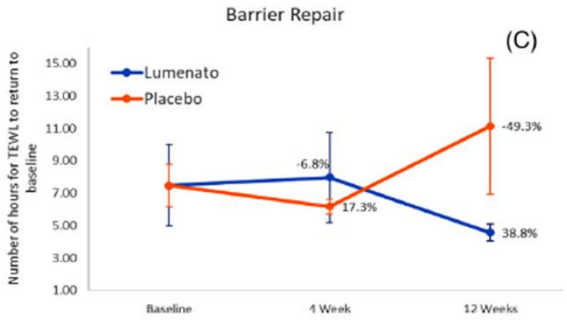
Significant improvements were observed with AX supp in,

- Fine lines/wrinkles and elasticity (visual assessment by dermatologist)
- Moisture content, indicative of skin hydration (instrumental assessment)
- Elasticity improved with AX but worsened with placebo (instrumental assessment)

Clinical evidence on Phytoene and Phytofluene supplementation and skin health

In a double-blind, randomized, placebo-controlled study supplementation with Lumenato (yellow tomato oleoresin, 10 mg/d total carotenoids, primarily phytoene and phytofluene) for 12 weeks significantly strengthened skin barrier (Figure B), shortened barrier repair time (Figure C), improved skin firmness and elasticity and reduced skin fatigue in healthy women aged 35 – 55 y (n=59).





Tarshish et al. Skin Res Technol 2023

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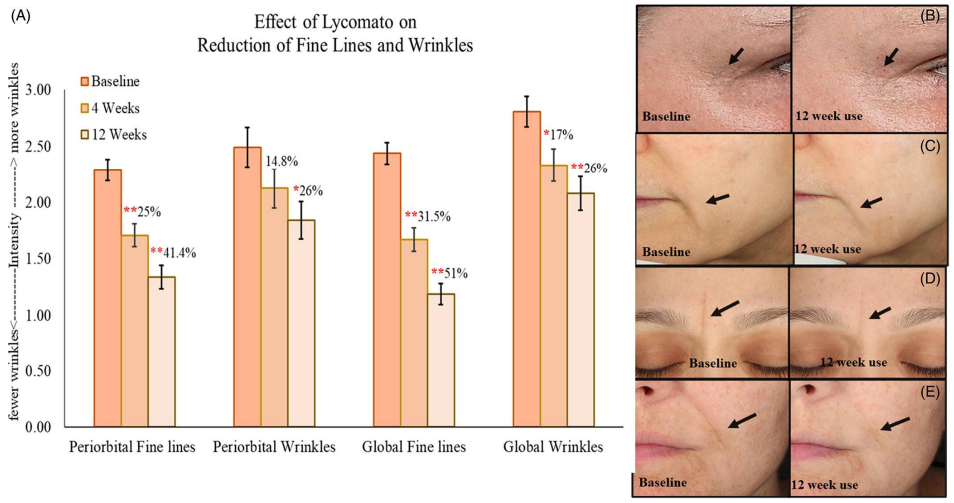
Results indicated a statistically significant improvement ($p < 0.05$) in skin barrier strength; barrier strength measured in terms of number of layers of stratum corneum removed with D-squam tape - a higher number of strippings were required to disrupt skin barrier after 12 weeks of supplement use.

Barrier repair measures in terms of calculated number of hours for repair to baseline. Lumenato treatment appeared to accelerate barrier repair from about 7 h at baseline to about 4 h after 12 weeks treatment.

There was also a significant improvement in skin firmness and elasticity as observed with a cutometer.

Clinical evidence on lycopene supplementation and skin health



Tarshish & Hermoni. J Cosmetic Dermatol 2023

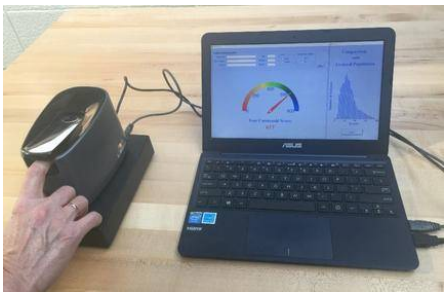
LNxxxxx 00/25

In an open label study in healthy women aged 35-55 y, 12 mg/d of lycopene for 12 weeks was shown to improve skin barrier function (measured as transepidermal water loss), skin visual attributes (tone, texture, wrinkles – measured by expert clinical grading & digital photographs)

Skin Carotenoids can be measured noninvasively in minutes!

- Skin carotenoids can be measured non-invasively by two validated optical instruments,
  (i) Resonance Raman spectroscopy (RRS) - Pharmanex S3 scanner
  (ii) Reflection spectroscopy (RS) – Veggie Meter®
- They can be used as screening tools in clinical setting to assess dietary interventions and study correlation between health outcomes

NuSkin BioPhotonic S3 scanner



Veggie Meter®

Ermakov IV et al. Archives of Biochemistry 2018
http://www.longevitylinkcorporation.com/products.html
https://www.nuskin.com/content/nuskin/en_US/products/pharmanex/scanner/s3_score.html

Both are optical methods applic. RRS is the older, more thoroughly validated method, whereas RS is newer and has several advantages uses pressure mediated reflection spectroscopy

Both able to the non-invasive detection of carotenoids in human skin

Skin carotenoids correlated significantly with serum carotenoid measures

Skin carotenoids can serve as a biomarker for fruit and vegetable intake!

- Skin carotenoids measured non-invasively correlate significantly with serum carotenoid measures (n=29 studies)
- Shown here are example outputs/results from both devices

Veggie Meter®

Pharmanex BioPhotonic S3 scanner

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Radtke MD et al. Adv Nutr 2020;11:1282-1299

29 studies found significant correlations or associations between spectroscopy-based skin carotenoids and plasma or serum carotenoids and/or dietary F/V intake. Majority of the studies evaluated carotenoid concentration in adults; however, 4 studies were conducted in infants and 6 studies evaluated children.

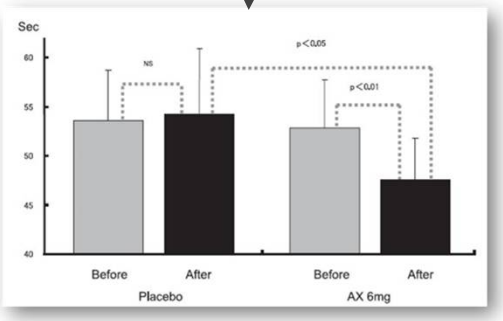
Veggie meter example output – gives you a carotenoid score and also a graph that compares your score to a reference population of all ages, races, sexes and ethnicities previously measured on this device

The S3 scanner results are higher numbers – but gives you an interpretation of what your score indicates with regard to carotenoid intake – low, moderate, high, extra high.

Obs studies indicate high blood carotenoids are associated with reduced risk of CVD – the antioxidant properties of carotenoids prevent oxidation of LDL cholesterol a key step in plaque formation

Astaxanthin has beneficial effects on blood flow and blood pressure

- Daily astaxanthin (6 mg/d for 10 days**) significantly decreased blood transit time by 10%**, **a measure of improved blood flow**, in a placebo-controlled single blind study in healthy men aged 50-60 years



- **Astaxanthin at 8 mg/d** for 8 weeks significantly lowered systolic blood pressure in patients with type 2 diabetes aged 30 – 60 y (n=44)
- **Astaxanthin at 12 mg/d** for 8 weeks lowered systolic and diastolic blood pressure in healthy postmenopausal women aged ≤65 y (n=35)

Miyawaki et al J Clin Biochem Nutr 2008
Mashhadi et al. Asia Pacific Journal of Clinical Nutr 2018
Iwabayashi et al Anti-ageing Medicine 2009

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In this study RCT – blood transit time was measured using by collected blood sample, heparinizing them and forcing it through a Microchannel array machine –

6 mg of AX dose – eating 16 oz/4-5 servings of salmon a day

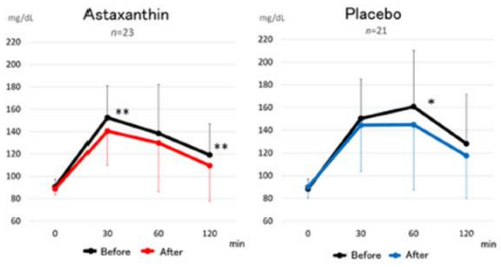
Astaxanthin has beneficial effects on blood glucose, lipids and cholesterol

Astaxanthin enhances insulin sensitivity and glucose uptake

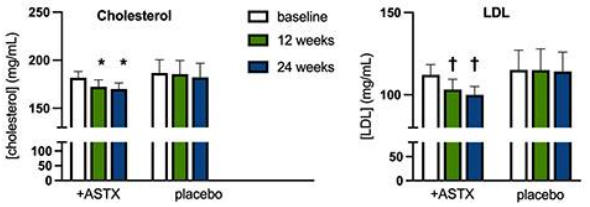
METABOLISM

Astaxanthin lowers lipid synthesis and enhances lipid turnover

- **Astaxanthin at 12 mg/d** for 12 weeks **significantly decreased HbA1c** in healthy and prediabetic adults (n=53). Shown here glucose levels from 75 g OGTT, which shows **significantly reduced glucose at 120 mins**. Study also showed insulin sensitivity is improved with astaxanthin supplementation



- **Astaxanthin at 12 mg/d** for 24 weeks significantly lowered serum Triglycerides and LDL in adults with dyslipidemia and prediabetes (n=34)



Ciaraldi TP et al. Diabetes Obes Metab 2023

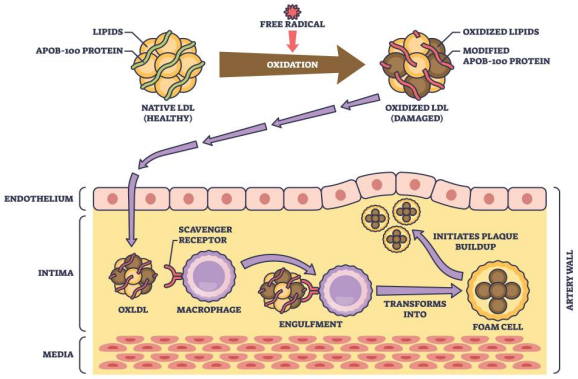
LNxxxx 00/25

Glucose and lipid metabolism are involved in maintaining metabolic homeostasis, and their dysregulation contributes directly to the development of metabolic disorders. – which are all risk factors for CVD.

Urakaze 2021, HbA1c is a reflection of your blood sugar over the past 2-3 months. ASTX significantly reduced the glucose level at 120 min as determined by 75 g OGTT, which was concomitant with a decrease in serum immunoreactive insulin concentration relative to baseline.

Astaxanthin has beneficial effects on heart health

- Lipid peroxidation has an important role in the etiology of atherosclerosis
- **Astaxanthin can protect HDL and LDL from oxidation, important for healthy arteries and heart.** Oxidized LDL is more readily taken up macrophages which can trigger a cascade of inflammatory reaction leading to plaque formation.



Oxidation of LDL and atherosclerosis pathway

Data from RCTs that show astaxanthin can modulate different biomarkers of lipid peroxidation	
4 mg/d for 12 weeks	Improves PON1 activity (antioxidant enzyme protects LDL and HDL from oxidation)
At 1.8 mg/d, 3.6 mg/d, 14.4 mg/d or 21.6 mg/d for 2 weeks	Significantly decreased LDL oxidation
At 5 mg/d or 20 mg/d	Significantly lowered MDA and Isoprostanes Significantly increased SOD and total antioxidant capacity

Martin HD et al. Pure and Applied Chemistry 1999;71(12):2253-62, Karppi et al. Int J of Vitamins and Nutr Res 2007;77(1):3-11 Choi et al 2011, Baralic 2013, Iwamoto 2000.

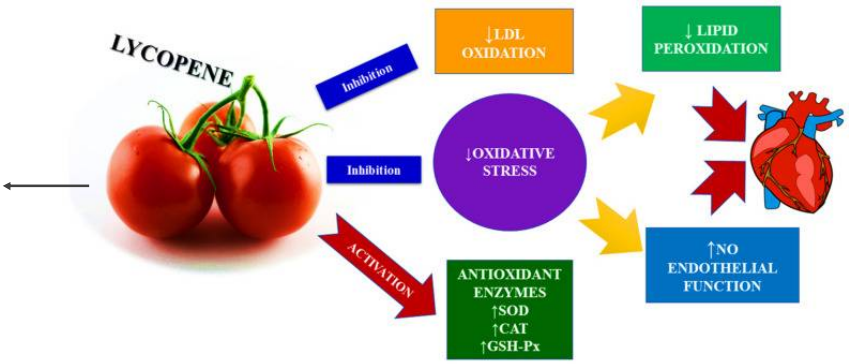
Lipid peroxidation has an important role in the etiology of many pathological conditions including atherosclerosis, which is the narrowing of blood vessels caused by deposition of inflammatory plaques. One of the important risk factors for atherosclerosis is elevated plasma LDL-C, and LDL-C is highly susceptible to oxidation. Oxidized LDL is more readily taken up by macrophages via scavenger receptors, which trigger a cascade of inflammatory reactions leading to formation of atherosclerotic lesions. Lipid oxidation is thus an important step in rendering LDL atherogenic. Thus, preventing lipid/LDL or HDL from oxidation is crucial for maintaining healthy arteries and ultimately heart health.

Lycopene has beneficial effects on heart health

- **Lycopene** is a highly researched and well-established carotenoid with heart health benefits. The mechanisms by which lycopene acts on the cardiovascular system includes its antioxidant activity (shown in the figure here) and anti-inflammatory activity.

Anti-inflammatory activity
Inhibit the synthesis and release of pro-inflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α

Inhibit MAPK, COX-2 and LOX



Przybylska S et al. Int J Mol Sci 2022

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Lycopene is considered an effective singlet oxygen quencher in the carotenoids group. It is a much more potent antioxidant than alpha-tocopherol (10× more potent) or beta-carotene (twice as potent)

Lycopene has beneficial effects on heart health – Clinical evidence of lycopene supplementation and heart health related outcomes

Reduced systolic blood pressure 	**15 mg lycopene** for 8 weeks in untreated hypertensive individuals, n=46 *(Wolack 2019)* **15 mg lycopene** for 6 weeks in treated uncontrolled hypertensive patients *(Paran 2009)* **7 mg lycopene** for 2 months in patients with statin-treated CVD and healthy volunteers, n=72 *(Gajendragadkar 2014)* **Meta-analysis of 10 RCTs**, greater effects on systolic BP at **≥15 mg lycopene**, duration ≥8 weeks, in hypertensive subjects. Changes in diastolic BP significant in studies on hypertensive subjects (those with high diastolic BP) *(Asbaghi 2022)*
Reduction of inflammatory biomarkers	**Tomato juice (200/400 ml)** for 4 weeks in population at risk of CVD, n=28 *(Colman 2017)* 15 mg Lycopene in healthy men aged 22-57 y *(Kim 2011)*
Reduction of oxidized LDL	**30 mg lycopene** single dose in healthy weight individuals who consumed high fat meals that are known to induce postprandial oxidative stress *(Burton-Freeman 2012)* **7 mg lycopene** for 30 days in patients with coronary heart disease, n=142 *(Petyaev 2018)* **12 mg/27 mg lycopene as tomato paste** for 4 weeks in cross over study, n=30 *(Abete 2013)*

Studies list here are double blind, randomized placebo-controlled trials unless otherwise stated. Colman 2017 – open, prospective, cross-over controlled trial.


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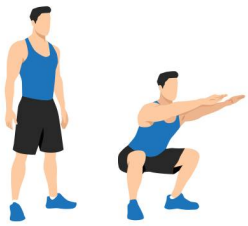
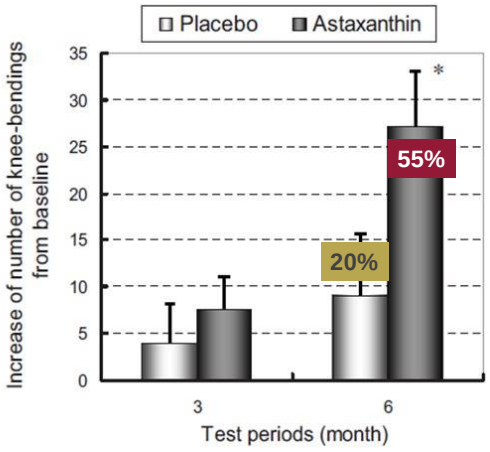
Exercise Performance and Muscle Recovery

Astaxanthin supports exercise performance - Squats

- In a double blind, placebo-controlled trial in healthy male students aged 17 to 19 y, supplementation with **4 mg/d of astaxanthin for 6 months** significantly increased number of knee bendings – **35% improved gains** compared to placebo





Malmsten CL et al. Carotenoid Science 2008

Strength endurance was tested in this R, Double, P, cont trial – by measuring number of knee bendings/squats after warm up exercise

Astaxanthin supports exercise performance – timed cycling

- In randomized placebo-controlled trial 21 competitive cyclists (ages 18-39) had their performance tested in a 20km timed trial after supplementing with placebo or **4 mg/d astaxanthin for 28 days**

Astaxanthin Group:

121 sec improvement (5%) in average time.
20W increase (15%) in average power output.

Placebo Group:
19 sec improvement (0.8%) in average time
1.6W increase (0.5%) in average power output

Hecht KA et al. Chapter 22 – Astaxanthin for improved muscle function and enhanced physical performance. Global Perspectives on Astaxanthin 2021 (picture)
Earnest et al. Int J of Sports Med 2011;32:882-888

Endurance was measured in this RCT – as timed 20 km cycling trial

Astaxanthin supports exercise performance – muscle recovery

- In a double blind, RCT supp with **4 mg/d astaxanthin for 90 days** reduced serum markers of muscle damage in healthy male soccer players.

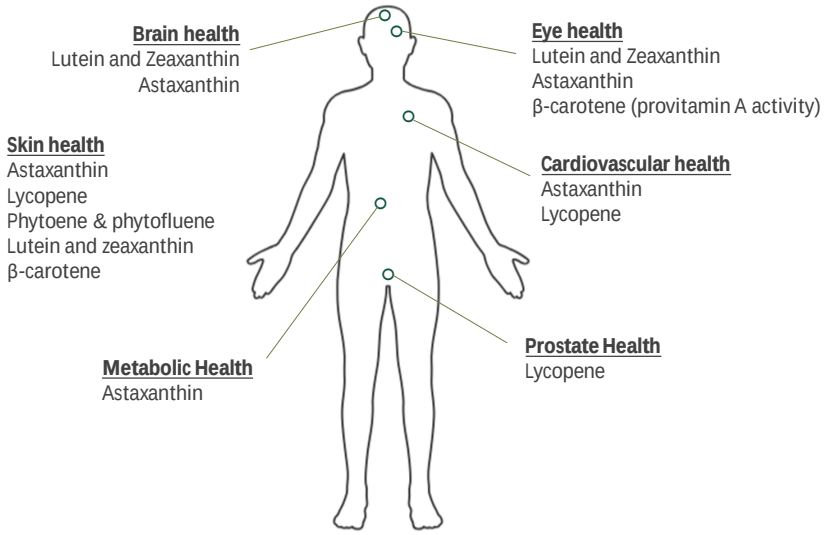
  Lactate dehydrogenase (LDH) decreased by 27%.
  Creatine kinase decreased by 45%

Other RCT data on supplementation with astaxanthin show,

- **6 mg/d** for 4 weeks significantly decreased serum lactate (muscle damage marker) post 1200-meter run
- **12 mg/d** for 4 weeks significantly decreased subjective markers of DOMS (delayed onset muscle soreness) following resistance training
- **12 mg/d** supplementation increased preference

Baralic et al. Phytotherapy Research 2012
Sawaki 2002

Carotenoids and Whole-body Health



Adapted from Honda, M. (2020). Nutraceutical and Pharmaceutical Applications of Carotenoids. In: Jacob-Lopes, E., Queiroz, M., Zepka, L. (eds) Pigments from Microalgae Handbook. Springer, Cham.

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Summarize – Health benefits – We started with our eyes – both front of the eye where AX plays a role in supporting accommodative function thus reducing digital eye strain, improved dry eye symptoms and depth perception which is an imp visual function in sports performance. Car L&Z are imp for both front and the back of the eye – back they function as MP and protect the retina from blue light damage – both as ablue light filter and an antioxidant. B-car of course has pro…

Retina is neural tissue and MPOD can be used as a biomarker to assess brain car status and cogn functioning. New research studies are also looking at AX for brain health…

We looked at skin – protecting shield of our body. Car deposit in the skin and protect the skin from UV induced photodamage, through their light absorbing and antioxidant activity

Metabolic Health/CVD health – we have astaxanthin shown to improve blood flow and maintain healthy BP. Help maintain healthy arteries protecting HDL and LDL from

oxidation. Lycopene also shown in clinical studies to protect LDL from oxidation, reduce sys BP and inflammatory markers

We were not able to get into the details but evidence is still mixed on lycopene intake and risk of prostate cancer. One sys review that looked at 66 population-based studies found that men who consumed the highest amt of lycopene has 11% lower risk of prostate cancer than those who consumed the least.


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Thank you!
Questions...