"Carotenoids - From Occurrence to Bioavailability to Bioactivity“

What is New ?

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Overview of presentation

I - Background – why carotenoids?

II - Prominent food sources, “overlooked” carotenoids

III - Bioavailability – dietary & host factors

IV - Health aspects & metabolites

V - Summary
I. Background – Why Carotenoids?

• **Widely distributed** in nature:
  → fungi, algae, bacteria, animals

• **Wide range of colors**: colorless-yellow-red

• Consumed in many forms: plants, animals

• **Wide range of functions**:
  → antioxidants, light protection,
  pigmentation, vitamin A-precursors…

> 700 different compounds: diet – 1-2 dozen
I. Background – Why Carotenoids?

Diet & health – fruits & vegetables

Epidemiological viewpoint:

“5 a day”

Fruit/vegetable intake ↔ reduced risk of cardiometabolic diseases: T2D, metabolic syndrome, CVD, some cancers…

Prospective cohort study
N= >125,000 subjects; 8-14 y

- Fibre?
- Polyphenols?
- Vitamins?
- Minerals?
- Carotenoids?
I. Background – Why Carotenoids?

Diet & health – carotenoid intake & tissue levels

Meta-analysis:
Antioxidant intake & T2D, prospective cohort studies:

- 140,000 participants,
- mean follow-up: 13 y

Antioxidants ↔ 13% risk reduction: mainly vitamin E

→ Antioxidant protection of β-cells

Further meta-analyses:
dietary carotenoids:
Head-neck cancer (Leoncini et al., 2015)
Prostate cancer (Key et al. 2015)

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Hamer and Chida, J Hypert 2007
I. Background – Why Carotenoids?
Diet & health – carotenoid intake & tissue levels

Meta-analysis of plasma levels:
Plasma beta-carotene ↔ all-cause mortality in elderly, prospective cohort studies

- n=1168 elderly men and women. Follow-up: 10 y

Reduced overall mortality (30%) with highest β-carotene status. Similar: CVD, cancer.

Bjusse, AJCN, 2008
I. Background – Why Carotenoids?

Diet & health – carotenoid intake & tissue levels

Meta-analysis of intervention: Individual antioxidants & CVD

Carotenoids: Clinical intervention studies (pure comp): n=232,000.

<table>
<thead>
<tr>
<th>Experimental Antioxidant Supplements</th>
<th>References</th>
<th>No. of Trials</th>
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Bjelakovic, 2007, JAMA 297, 842-57

No effect of beta-carotene supplements

Rather, negative outcome!

(compare with ATBC, CARET studies !)

Why those differences??
I. Background - Why Those Differences?
Supplementation vs. dietary intake

1. Rather **U-shaped curve** of dose-effects?

2. Synergistic effects missing in supplements?
   - Synergism with other anti-oxidants (vitamin E, vitamin C)
   → If missing, pro-oxidant effects?

3. Dependency on individual (diseased) – especially critical?
   - Pro-oxidants following CYP activation in smokers: pro-carcinogen metabolites?

Most nutrients: Arbitrary effects if intake >>UL or > NOEL (esp. lipophilic vitamins !)
I. Background - Why Those Differences?
Supplementation vs. dietary intake – U – shape?

HepG2 cells: conc. >10 μM of RA: → Nrf2 translocation↑: toxicity
lower conc. ≤1.0 μM : → inhibit Nrf2 translocation (red. ox. stress, normal condition ? → biphasic, U-shaped activity behavior ?

Gap: Dose – response relation of carotenoids & degradation products!
II. Prominent (and not so prominent) Food Sources

Major carotenoids in our diet

**Carotenoids**

- Beta-carotene
- Lycopene
- Zeta-carotene

"Colorless" carotenones

- Phytoene
- Phytofluene

**Most common in plasma**:  
Lycopene: 696 nmol/L  
Beta-carotene: 455 nmol/L  
Alpha-carotene: 218 nmol/L  
Zeta-carotene: 200 nmol/L

**Sources**: carrots, tomatoes, leafy vegetables, sweet potatoes, squash, papaya

- Approx. 15% of carotenoid intake (Biehler et al. 2011).
- High bioaccessibility (Mapelli-Brahm et al. 2017) + bioavailability (Melendez-Martinez, 2015)
- Blood: 144 nmol/L* (phytfl>phyt)

**Sources**: tomato, watermelon, apricot, grapefruit


Compare to PP: 10x intake!
II. Prominent (and not so prominent) Food Sources

Major carotenoids in our diet

**Xanthophylls**

- Lutein
- Beta-cryptoxanthin
- Astaxanthin

**Epoxycarotenoids**

- Violaxanthin
- Neoxanthin

Gap: metabolized into ?

Most common in plasma*:

- Lutein: 315 nmol/L
- Beta-cryptoxanthin: 272 nmol/L
- (Zeaxanthin: 44 nmol/L)

Sources: leafy vegetables, salmon (<2 mg/100g), shrimps, eggs, algae (10-200mg/100 g DM) !

*High bioavailability from animals !?

- Approx. 10% of carotenoid intake (Biehler et al. 2011).
- Stability during gut passage ?
- Breast milk, plasma (low conc. – Asai et al. 2008).

**Sources:** bell-peppers, green leafy vegetables

**Original Article**

Contribution of violaxanthin, neoxanthin, phytoene and phytofluece to total carotenoid intake: Assessment in Luxembourg

Eric Biehler+4, Ala’a Alkerwi+5, Lucien Hoffmann+6, Elmar Krause+7, Michèle Guillaume+2, Marie-Lise Lair+8, Torsten Bohn+2

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II. Prominent (and not so prominent) Food Sources

Not so recognized carotenoids - apocarotenoids

**Apo-carotenoids**: carotenoid metabolites, oxidative cleavage by carotenoid oxygenases (9 identified)

Norbixin, Bixin – E160b (annato seeds)

Crocetin (safflour)

Abscisic acid (apples, leafy vegetables, artichoke, ca. 1-5µg/100g): plant hormone

**C30 & C50 carotenoids !**

The pharmacokinetic profile of crocin in healthy adult human volunteers after a single oral administration

N. Umigai*1, K. Murakami*1, M.V. Ullt*1, L.S. Antonio*1, M. Shiratori*2, H. Morikawa*1, T. Nakano*1

Abscisic acid ameliorates experimental IBD by downregulating cellular adhesion molecule expression and suppressing immune cell infiltration

Abscisic acid is an endogenous cytokine in human granulocytes with cyclic ADP-ribose as second messenger

The FASEB Journal • Research Communication

Microgram amounts of abscisic acid in fruit extracts improve glucose tolerance and reduce insulinemia in rats and in humans

Mirko Magnone,1,2 Pietro Amenta,1 Annika Salis,1 Gabriella Andreaghi,1 Laura Emanuele,1 Giovanni Maruoli,1 Antonio De Vito,1 and Enzo Zucchi1,2

Insulin improvement in humans?

Anti-inflammatory properties?
III. Bioavailability – Dietary Factors and Host Factors

Overview

Food pieces

Mouth + stomach: → mastication, processing

Stomach: → homogenization, proteases, gastric lipase

Protease, lipase, etc.

Lipid droplets

Pancreatic lipase?

Pancreatin, bile salts

Mono-, diglycerides, FFA

Mixed micelles

Passive enterocytes

SR-BI

NPC1L1

CD36

ABC5/8?

Chylomicrons, HDL?

Liver

VLDL → LDL, HDL

Tissues

Colon?

Microflora?

Excretion?

Excretion?

No measurable $^{13}$C apo-carotenol abs. (Kopec, EB 2017 abstract): plasma or TRL!

- Too low absorption?
- Excretion (ABCA1…)?
- Re-esterification?

Further metabolism?
- Hydroxylation?
- Glucuronidation, sulfation?
III. Bioavailability – Dietary Factors

Bioavailability of phptoene, phytofluene

Total in vitro bioaccessible content of carotenoids from juices for a portion (250 mL):

- Some juices: phyt + phytf contribute to most available carotenoids!

- Bioaccessibility >50% → shorter apparent molecule structure?
- 15-cis phytoene: dominant
- 15-cis phytofluene isomers
- High bioaccessibility due to processing, matrix macerization (also in vivo)
III. Bioavailability – Dietary Factors

Lipids – an old hat? Yes, and no…

More lipids:
• emulsifying compounds↑
• GI passage time↑
• Chylomicron sequestration↑

- More lipids: higher absorption (TRL)
- Stronger effect of LCFA vs. SCFA (portal vein, less TGs for sequestration!)
- Also: lower bioaccessibility of carotenes with SCFA (Failla et al. MNFR, 2014)
III. Bioavailability – Dietary Factors

Lipids

Effect of heat treatment & lipids on bioaccessibility:

- \( \omega-3 \) FA: beta-carotene abs.↓
  - Reduce PPAR(\( \alpha \)) receptors (EPA)
  - Decreased expression of SR-BI & NPC1L1: beta-carotene abs.↓

Oral administration (rats) with spinach & butter (3d): higher fasting plasma lutein concentration than with olive/fish oil. Smaller+more stable micelles (zeta-p.)

More studies warranted!
Conversion to retinyl esters

Also on studies with other vitamins!

Interactions:
→time of digestion ?
→pre-treatment ?
→matrix - phospholipids ? (lipolysis↓ ?)
→oxidation of carotenoids by MUFA ?
III. Bioavailability – Dietary Factors

Proteins

Protein – xanthophyll interactions:
Salmon: actomyosin binding of Ast: bioaccessibility↓
β-ionone rings of Ast & Cxn: bind to hydrophobic surface of actomyosin (hydroxyl & carbonyl groups)

Proteins as emulsifiers during digestion?

→ Higher bioaccessibility from cream vs. canola oil, at comparable amounts of lipids

Gap: interaction of proteins and carotenoid bioaccessibility?
III. Bioavailability – Dietary Factors

Fiber

Inverse correlation pectin ↔ carotenoids from leafy vegetables:

→ Formation of gel-like structure with pectins inhibiting carotenoid bioaccessibility
III. Bioavailability – Dietary Factors

Encapsulation

Pectins & alginates: carotenoid encapsulation?
- Oxidation during food storage ↓
- Protection in upper GI tract?
- Targeted delivery?

Chemical stability

multi-layer capsule with emulsified carotenoids. Yellow = core (lipid phase), red = carotenoids, green = cationic biopolymers, blue = anionic biopolymers.

bioaccessibility

β-carotene encapsulated in conventional (blue) & structured emulsions (green & red) containing Na-alginate (fluid gels: agitated). Gels contained Ca.

High stability + high bioaccessibility - protection during food storage + GI digestion?
III. Bioavailability – Dietary Factors

Dietary divalent minerals

Calcium, magnesium:
→ complexation + precipitation with bile acids
→ fatty acids → soaps

“Confirmed” by several in vitro studies:
• Pure carotenoids
• Carotenoid-rich test meals (tomato-, carrot- juice, spinach, apricot…)
• At various ratios bile/pancreatin: minerals
• Both bioaccessibility & cellular uptake

IC 50 concentrations:

Estimated intake:
210 mg, Fe
250 mg, Zn
300 mg, Ca
300 mg, Mg

→ Reachable with supplements for Ca, Mg (50-100% RDA)
III. Bioavailability – Dietary Factors

Dietary divalent minerals

Human trial (Corte-Real et al. 2017, unpublished):
- 500 or 1000 mg Ca (carbonate) vs. placebo: spinach carotenoids:

No significant effect on TRL-AUC for β-carotene, β-cryptoxanthin, lutein, TGs
III. Bioavailability – Dietary Factors

Dietary divalent minerals

Human trial (Borel et al. BJN, 2017):
500 mg Ca (carbonate) vs. placebo: lycopene (tomato paste):
83% reduced absorption

- Observation time 7 h: rather short?
- Gel with pectins?
- Effect of plasma vs. TRL different?
- Stronger effects on apolar carotenoids?
- Stronger effects with higher response from liquid meals?

More human trials needed!
Interest for vegans/vegetarians taking supplements
Subjects with pancreatitis…
III. Bioavailability – Host Factors

Life style & SNPs

Inter-individual variation:
• Variation: Bioaccessibility<TRL<plasma<tissues
• Inter>intra-individual variability (half)
• >40 genes with SNPs reported to be involved in carotenoid ADME

• Also explaining biological/health responses?
III. Bioavailability – Host Factors

Life-style & SNPs

Individual variation due to:

- Age ↓
- BMI ↓
- Alcohol consumption ↓
- Asthma ↓
- Gender (w: ↑)
- Helicobacter pylori ↓
- HIV ↓
- Hyperthyroidism ↓
- Low zinc status ↓
- Low blood lipids ↓
- Drug intake ↓
- Malaria ↓
- Menstrual cycle ↓
- Microbiota ↓
- Physical activity ↓
- Ethnicity ↓↑
- Smoking ↓

Gene/SNP association studies:

Absorption of beta-carotene, TRL response from 100 g tomato puree:

→ 25 SNPs in 12 genes: explained 69% variance

→ More studies needed
III. Bioavailability – Host Factors

Mucus layer?

**Carotenoid cellular uptake:**

Influence of mucus layer (glycosylated polymer network)?
Mostly neglected in cellular models.

1\textsuperscript{st} cell model:
Caco-2 (TC-7) cells

2\textsuperscript{nd} cell model:
Caco-2 cells
HT-29 cells
Mucin-glycoproteins: hydrophobic
media
mucus
III. Bioavailability – Host Factors

Mucus layer?

- TEER was comparable
- Increased unstirred water layer?
- Mucus pores bigger than mixed micelles
- Increased surface?

Higher uptake of carotenoids from co-culture (Caco-2/HT-29-MTX) vs. Caco-2 cells. Approx. 2 times.

No neg. effect of mucus layer on curcumin uptake
III. Bioavailability – Host Factors

My goodness – my gut?

- Carotenoids bioaccessible in colon
- Carotenoids present in colon cells
- Polar products ?!

Recovery (fermentation):
- 10-50%, depending on study (matrix).
  → Majority of carotenoids not recovered.
- Degradation products ??

A world (of potential metabolites) missing !?
Explanation for inter-individual differences ?

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<th>Colon</th>
<th>Microbiota</th>
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<td>Lower circulating carotenoids in subjects with higher <em>Collinsella</em> and atherosclerosis</td>
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<td>Higher liver storage of α- and β-carotene in germ-free rats</td>
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<td>β-carotene</td>
<td>Unclear</td>
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<td>α-, β-carotene</td>
<td>Prevention of breakdown products? Transit time? Bile-salts?</td>
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[133] [45]
IV. Health Aspects & Metabolites

Breakdown products & metabolites

BCO1 & BCO2 → more polar products:

- Binding to cysteine residues of NF-κB (subunits) & Nrf-2 (or keap):
- Affecting inflammatory and antioxidant responses

→ α,β-unsaturated carbonyls: Michael adduct with nucleophilic protein thiols of TF
Carotenoid derivatives: interact with IKKβ & p65 subunit.

Higher activity of hydrophilic extracts or lycopene degradation products. Same: Nrf2 Confirmed recently in a rat trial with lutein degradation products! (Nidhi et al., FdFct, 2014)

Compounds with
a) Higher cytosolic solubility,
b) Higher electrophilic potential,
appear better repressors/activators of NF-κB/Nrf2.
V. Health Aspects & Metabolites

RAR/RXR binding

Vitamin A deficiency marker genes

Lycopene: restores RAR (retinoic acid receptor) target genes & vitamin A deficiency marker gene expression

Vitamin A like activity of lycopene metabolites?
V. Health Aspects & Metabolites

Relation of carotenoids and obesity?

apocarotenoids + RALD: interact with TF/NR

Scavenging of ROS & repressing adipocyte hypertrophy (suppressing PPARγ; enhancing energy utilization).

If obesogenic conditions persist + diet low in carotenoids:
→ development of pathological obesity.
V. Summary

**Epidemiological studies**: Carotenoid dietary intake & tissue levels ↔ chronic diseases↓. Supplements: contradictory

**Under-recognized carotenoids**: >25% to carotenoid intake & plasma concentrations: phytoene, phytofluene, epoxycarotenoids, zeta-carotene.

**Apocarotenoids** (bixin…) ? C30 and C50 carotenoids ? Bioactive ?

**Bioavailability**: phyt/phytf cis-isomers well bioaccessible (bioavailable?). Lipids: interacting factors ? Minerals ?? Fibre: ↑↓ Proteins ??

Host-factors: **SNPs**: digestive enzymes, transporters, further metabolism

**Mucus** layer – no negative effect. **Role of colon ???**

**Metabolites**: preferred binding to TF → NR → gene expression ? inflammation, ox. stress, adipocytes etc., RAR/RXR (vit. A) ?
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