β-Cryptoxanthin prevents lifestyle-related diseases?

- Findings from the recent nutritional epidemiologic survey -

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Fruit production in Japan

Japanese mandarin orange (C. unshiu) is the most popular fruit in Japan.

Data & picture source: Ministry of Agriculture, Forestry and Fisheries (2013)
In Japan…

• **Japanese fruit is very sweet**
  ‘Fruit is high-calorie food!’

• **Fruit contains much fructose**
  ‘High intake of fruit causes hyperlipidemia or diabetes!’

Does high intake of fruit cause obesity, hyperlipidemia, or diabetes?
‘Does high intake of fruit cause obesity, hyperlipidemia, or diabetes?’

To test this hypothesis, we undertook the simple questionnaire survey. A total of 6,049 responses were obtained. (2,118 male and 3,931 females)

**Subjects:**
General consumer who lives in the area with one of the highest Japanese mandarin consumption levels in Japan.

**Questions:**
Age, sex, height, weight, frequency of mandarin eating (in season), and the history of disorders.
Japanese mandarin eater

Frequency of mandarin intake (in season, Oct - Feb)

Ⅰ: Rarely eat
   (2.7%)

Ⅱ: Less than 3 fruits / one week
   (29.7%)

Ⅲ: 1-3 fruits daily
   (53.3%)

Ⅳ: More than 4 fruits daily
   (14.3%)
Results from the self-administered questionnaire survey

There were no relationship between mandarin intake and hyperlipidemia or obesity

Results from the self-administered questionnaire survey

Low prevalence of lifestyle-related disease of big mandarin eater

What ingredients are contained in Japanese Mandarin orange?

**Ingredients**

- Carbohydrate (Glucose, Sucrose, Fructose)
- Vitamins (Vitamin C, B₁, B₂, Folic acid)
- Citric acid
- Carotenoids (β-Cryptoxanthin, β-Carotene)
- Minerals (Potassium, calcium, iron)
- Fiber (soluble, insoluble)
- Flavonoids (Hesperidin, Naringin)
- Limonoids (Limonin, Nomilin)
- Odorous constituents (D-Limonene, Linalool)

New functional food factor?
Serum β-cryptoxanthin level greatly increased according to an increase of Japanese Mandarin intake

β-cryptoxanthin with the risk of lifestyle-related diseases

Recent nutritional epidemiologic findings
Nutritional Epidemiologic Survey: Mikkabi Study

Population
The study utilized data derived from health examination of inhabitants aged from 30 to 70 years performed in the town of Mikkabi in Shizuoka Prefecture, Japan.

Research Schedule

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Baseline survey (Cohort 1)</td>
<td>886</td>
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<tr>
<td>2004</td>
<td>Follow-up survey</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Baseline survey (Cohort 2)</td>
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</tr>
<tr>
<td>2008</td>
<td>Cohort 2 survey</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Cohort 1 survey</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Cohort 2 survey</td>
<td></td>
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</tbody>
</table>

- **Cohort 1**: Diabetes, Atherosclerosis, Liver dysfunction survey
- **Cohort 2**: Osteoporosis, Metabolic syndrome survey
From the Mikkabi Study...
Serum β-cryptoxanthin with lower risk for.....

- **Liver dysfunction**
  - Alcohol-related increased serum gamma-GTP
  - Hyperglycemia-related increased serum ALT

- **Insulin resistance**
  - HOMA-IR estimated Insulin resistance

- **Arteriosclerosis**
  - Brachial-ankle pulse wave velocity

- **Metabolic syndrome**
  - Interaction of smoking

- **Osteoporosis**
  - Bone mineral density at radius

- **Oxidative stress**
  - Induced by smoking and drinking

Publications

- *J Epidemiol*
  - 16: 71-78 (2006)

- *Diabetes Res Clin Pract*
  - 71: 82-91 (2006)

- *Atherosclerosis*

- *Br J Nutr*
  - 100: 1297-1306 (2008)
  - 102: 1211-1219 (2009)

- *Osteoporosis Int*
  - 22: 143-152 (2011)

- *PLoS ONE*
  - 7: e52643 (2012)
β-cryptoxanthin with the risk for liver dysfunction
High $\beta$-cryptoxanthin is inversely associated with serum $\gamma$-GTP in alcohol drinkers

Serum gamma-GTP: gamma-glutamyltransferase
Specific indicator for alcohol liver disease

Excessive Alcohol Intake
→ Generation of Free radical Species
→ Liver Cell Damage

Alcohol-related Liver dysfunction

Serum $\gamma$-GTP (IU/L)

Non drinkers

Light-drinkers

Moderate-drinkers

Heavy-drinkers

Daily ethanol intake

Alcohol 25 g = Whisky 80 mL
Confounding factors adjusted mean of serum γ-GTP

Confounding factors:
Age, BMI, total energy intake, smoking habits, etc.

These factors associate with serum γ-GTP level.

β-cryptoxanthin may act as a suppressor against liver cell damage and may inhibit progression of liver dysfunction induced by alcohol.

High β-cryptoxanthin is inversely associated with serum aminotransferases in hyperglycemic subject

Diabetes (hyperglycemia) → Glucose auto-oxidation → Generation of Free radical Species → Liver Cell Damage

Alanine aminotransferase (ALT): Marker of liver dysfunction

IFG: Impaired fasting glucose
Confounding factors adjusted mean of serum ALT

β-cryptoxanthin may act as a suppressor against liver cell damage in the earlier pathogenesis of liver dysfunction induced by hyperglycemia.
β-cryptoxanthin with the risk for Osteoporosis
Serum β-cryptoxanthin (mandarin intake) with the risk for osteoporosis

- Low intake (66g/day)
- High intake (271g/day)


β-cryptoxanthin might affect on bone health
Defending against oxidative stress induced by smoking and drinking

Even if the same amount of β-cryptoxanthin is consumed, the serum concentration of β-cryptoxanthin would be extremely lower in alcohol drinkers among current smokers compared with non-drinkers among non-smokers.

Conclusion

High Serum β-cryptoxanthin associated with the lower risk for...

- Alcohol- and Diabetes-related Liver dysfunction
- Osteoporosis in post-menopausal female
- Insulin Resistance
- Arteriosclerosis
- Metabolic syndrome in current smokers
- Oxidative stress in smokers among regular alcohol drinkers

Further cohort and intervention studies, and mechanism studies will be required.
Thank you