Literature review: The Role of Carotenoids as Functional Foods in Disease prevention and Treatment.

Abstract

Considered the best biological marker of fruit and vegetable intake (Semba, Lauretani & Ferruci 2007:141), carotenoids are powerful antioxidants known to “protect against oxidative stress by quenching singlet oxygen, scavenging free radicals, inhibiting lipid peroxidation and modulating redox-sensitive transcription factors, such as NF-kB involved in upregulation of interleukin-6 and other proinflammatory cytokines (Semba et al 2007:142). This function has prompted researchers to investigate carotenoids in disease prevention and treatment. Three carotenoids have been extensively studied *in vitro*, *in vivo*, human epidemiological, case-controlled and intervention trials. Beta-carotene, lycopenes and lutein & zeaxanthin have demonstrated activity against a variety of cancers, cardiovascular disease, macular degeneration, cataracts and photosensitivity conditions. As a preventative they have been linked to ultraviolet light protection, gap-junction cellular communication, photoprotection, low-density lipoprotein cholesterol lowering, reducing oxidative stress and they act as immunomodulators. This report aims to review the current literature on these three carotenoids as functional food, including comparisons with supplementation, disease prevention and treatment, dietary sources, recommended daily intake, absorption requirements and discussion of current carotenoid issues.

Introduction

Carotenoids are tetraterpenoids of which there are over 600 carotenoids identified in plants, nonphotosynthetic bacteria, yeasts and moulds (Sies & Stahl 2005:101, Krinsky & Johnson 2005:461) and some animal foods such as salmon, lobster and egg yolk (Braun & Cohen 2007:162). They are responsible for the red, orange, pink and yellow pigment in natural foods (McGuire and Beerman 2007:437). Only twenty have been isolated in the human body, of these three are well research as functional foods (Roberts, Green & Lewis 2009:951). They

have been considered as one of the best biological markers of fruit and vegetable intake (Semba et al 2007:143).

Carotenoids are hydrophobic molecules commonly located within cell membranes (Semba, et al 2007:142). They are structurally similar to vitamin A and can be divided into two groups- those which can be converted to vitamin A, such as beta-carotene, alpha-carotene and beta-cryptoxanthin which are called provitamin A carotenoids and those which cannot. These are nonprovitamin A carotenoids and are mainly lycopene, lutein, and its isomer zeaxanthin (McGuire and Beerman 2007:437).

Beta-carotene

Beta-carotene is one of the most abundant carotenoids in the human body. Major food sources include green leafy vegetables, orange and yellow fruits and vegetables such as mangoes, carrots, sweet potato and pumpkin (Krinsky & Johnson 2005:465), rockmelon, broccoli, spinach (Braun & Cohen 2007:163), seaweed and algae (Jamison 2003:174). Bioavailability of β-carotene may be improved by chopping, light cooking and the presence of dietary fat (McGuire and Beerman 2007:438, Rock et al 1998, van het Hof et al 1998: cited in Krinsky & Johnson 2005:465). With consumption of the recommended two or more servings of fruit and five or more servings of vegetables daily the typical Western diet provides approximately 3-6mg/daily (Braun & Cohen 2007:173). In supplement form the recommended daily allowance is 15mg, with a safe dose range of 15-60mg/daily (Braun & Cohen 2007:163).

Lycopene

“Dietary lycopene is derived predominately from tomatoes and tomato products” (Krinsky & Johnson 2005:463). Other sources include pink grapefruit, apricots, watermelon (McGuire & Beerman 2007:443), guava (Jamison 2003:476), rosehip (Karppi 2009:512) and papaya (Krinsky & Johnson 2005:463). The bioavailability of lycopene depends on cooking and processing which increases lycopene availability, the presence of other carotenoids and dietary fat and the food source (Braun & Cohen 2007:471). It is estimated the dietary intake of lycopene is between 0.5-27mg/daily (Jonkers et al 2003: cited in Braun & Cohen

2007:472). Doses of up to 60mg/day may be required for specific condition, such as hypercholesterolaemia (Braun & Cohen 2007:474).

Lutein and zeaxanthin

Lutein and zeaxanthin, an isomer of lutein, are the yellow pigment carotenoids (Braun and Cohen 2007:464). Lutein is found in green leafy vegetables, especially spinach and kale, sweet corn and egg yolks (Cardinault et al 2003:573). Zeaxanthin is in sweet corn, egg yolks, yellow capsicum, persimmons, tangerines, mandarins, oranges (Braun and Cohen 2003:465). Bioavailability is determined by amount to fat in the diet which is required for absorption and transportation (Braun and Cohen 2003:465). There is no recommended intake for lutein and zeaxanthin as they are not considered essential despite their role in macular pigment development. Supplementation of 6-20mg/daily of lutein and 2-5mg/daily of zeaxanthin is recommended in age-related macular degeneration, and 15mg/weekly of lutein to improve visual performance in those with cataracts (Braun and Cohen 2003:468).

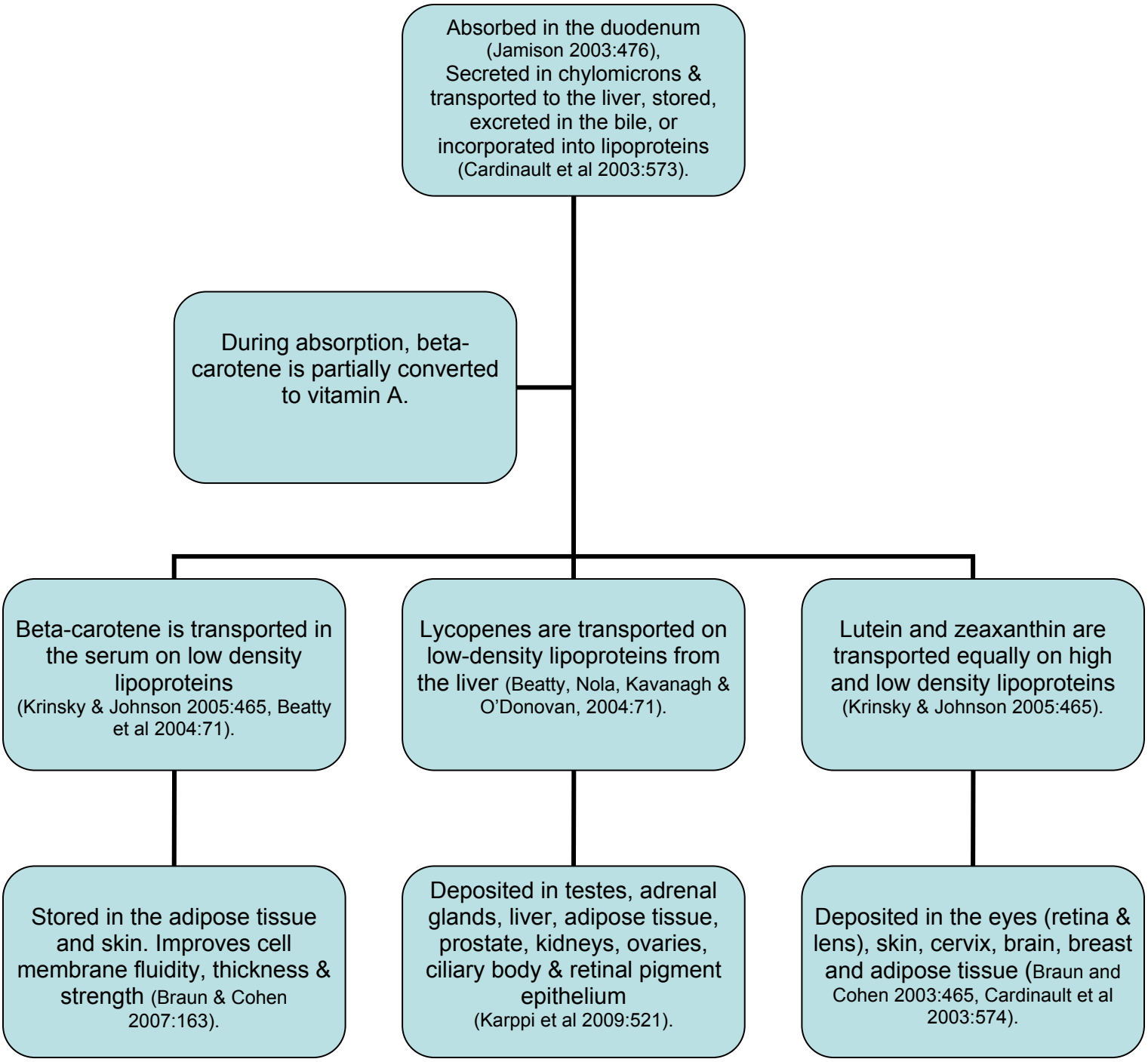
Good food sources of common carotenoids

Beta-carotene Food Content (mg/100 g wet wt)		Lycopene Food Content (mg/100 g wet wt)		Lutein and zeaxanthin Food Content (mg/100 g wet wt)	
Carrots, raw	18.3	Tomato paste	29.3	Kale, cooked	15.8
Mangos, canned	13.1	Ketchup	17.0	Spinach, raw	11.9
Sweet potato, cooked	9.5	Tomato puree	16.7	Spinach, cooked	7.0
Carrots, cooked	8.0	Pasta sauce	16.0	Lettuce, romaine, raw	2.6
Pumpkin, canned	6.9	Tomato sauce	15.9	Broccoli, raw	2.4
Kale, cooked	6.2	Tomato soup	10.9	Broccoli, cooked	2.2
Spinach, raw	5.6	Tomato, can, whole	9.7	Summer squash, zucchini	2.1
Spinach, cooked	5.2	Tomato juice	9.3	Corn, sweet, cooked	1.8
Winter butternut squash	4.6	Watermelon, raw	4.9	Peas, green, canned	1.4
Swiss chard, raw	3.9	Tomato, cooked	4.4	Brussels sprouts, cooked	1.3
Apricots, raw	2.6	Tomato, raw	3.0	Corn, sweet, canned	0.9
Pepper, red, raw	2.4	Others:		Beans, green, cooked/can	0.7
Pepper, red, cooked	2.2	pink grapefruit, apricots,		Beans, green, raw	0.6
Cantaloupe, raw	1.6	watermelon, guava,		Okra, cooked	0.4
Lettuce, romaine, raw	1.3	rosehip and papaya		Cabbage, white, raw	0.3
Tomato paste	1.2			Egg yolk, medium	0.3

Source: Krinsky & Johnson 2005

Absorption

Carotenoids are not produced by the body being required in the diet (Roberts et al 2009:195, Richer et al 2004:225). They have similar absorption pathways, however, differ in transportation on lipoproteins from the liver to target organs.



Results

Cancer

Beta-carotene

There is strong evidence from observational epidemiological studies that people consuming a higher level of fruit and vegetables have a reduced risk of developing certain types of cancer (Krinsky & Johnson 2005:488). Further investigation suggested carotenoids may be the chemoprotective agent due mainly to their high antioxidant activity (Krinsky & Johnson 2005:488), but also through intracellular gap junction communication, interference with cell proliferation, hormonal and immune system modulation and up regulation of phase II in the detoxification system (Karppi et al 2009:512, Rao & Agarwal 1999:305).

In cell cultures beta-carotene is among the most effective stimulators of gap-junction communications which can inhibit progression of carcinogenic pathways (Sies & Stahl 2004:102). *In vivo* mammary tumours (Fujii et al 1993: cited in Braun & Cohen 2007:166), skin carcinomas (Ponnamperuma et al 2000: cited in Braun & Cohen 2007:166) and oral cancer (Garewal 1995: cited in Braun & Cohen 2007:166) have reduced with beta-carotene exposure.

Observational epidemiological studies have found a positive correlation between beta-carotene and a reduced risk of cancer, in particular, lung cancer (Braun & Cohen 2007: 168). However, three large interventional studies, The Alpha-Tocopherol Beat-Carotene Cancer Prevention Study, The Carotene and Retinol Efficacy Trial and a prospective cohort study on French women (Touvier, Clavel-Chapelon & Boutron-Ruault 2005:1319), found smokers and asbestos workers had a higher risk of lung cancer with supplementation of beta-carotene, with one trial abandoned when participants developed cancer (Heinonen et al1994 and Omenn et al 1996 cited in Braun & Cohen 2007: 168). This correlation did not occur in non smokers or former smokers (Braun & Cohen 2007: 168).

Beta-carotene may prevent other cancers from developing. Studies indicated beta-carotene may protect against precancerous oral leucoplakia (Nagao et al 2000, Garaweel et al 1999:1305) and urothelial carcinoma (Roswell et al 2009: cited in Braun & Cohen: 168). The

Physician Health Study II found a possible benefit on total cancers and prostate cancer (Christen, Gaziano, & Hennekens 2000:132). A number of smaller interventional studies report a relationship between beta-carotene intake, blood serum levels and total cancer prevention (Krinsky & Johnson 2005:491). The Linixan Cancer Prevention Study of nutrient deficient population found a reduction in cancer, especially stomach, with supplementation of beta-carotene, vitamin E and selenium (Blot et al 1993 cited in Krinsky & Johnson 2005:591).

Lycopene

Lycopene is the most efficient quencher of singlet oxygen, and protects cell lipids, lipoproteins, proteins and DNA from oxidative damage (Karppi et al 2009:512). The evidence supporting lycopene in the prevention of cancer has come from epidemiological studies, tissue cultures on human cancer cell lines, animal studies and human clinical trials (Karppi et al 2009:512). The strongest evidence is for prostate cancer (Krinsky & Johnson 2005:491). A review of epidemiological studies suggested a diet high in lycopene reduce the risk of prostate cancer with the most beneficial relationship coming from processed tomatoes (Karppi et al 2009:512, Braun & Cohen 2007:472, Sies & Stahl 2005:103, Jamison 2003:405). Clinical trials consistently report low lycopene serum levels and high prostate specific antigen (PSA) in prostate cancer patients (Rao & Rao 2007:211, Braun & Cohen 2007:472). In one study lycopene decreased the prostate specific antigen (PSA) level significantly when tomato sauce was administered to those with a diagnosis of prostate cancer (Rao & Rao 2007:211, Braun & Cohen 2007:472). A Harvard university study (1995) found “eating 10 or more servings a week of tomato products was associated with a reduced risk of prostate cancer by as much as 34 percent” (American Diabetic Association, 2002).

There is growing evidence supporting lycopene as preventative against other cancers. *In vitro* and *in vivo* studies show lycopene may inhibit growth of breast, lung, cervical, ovarian and pancreatic tumours (Rao & Rao 2007:211). Lycopene has been associated with a decrease in cancer risk, in particular stomach, colon and rectum (Rao & Agarwal 1999:314). Serum lycopene levels have also been inversely related to bladder cancer (Rao & Agarwal 1999:314). Lycopene also suppressed insulin-like growth factor-I-stimulated growth. This

growth factor is a major hormonal regulator of mammary and endometrial cancer cell growth (Omoni & Aluko 2005).

Lutein

A high dietary intake of lutein has been associated with a reduced risk of some cancer, in particular, endometrial (McCann et al 2000: cited in Braun & Cohen 2007:468) and ovarian (Bertone et al 2001: cited in Braun & Cohen 2007:468) in epidemiological evidence. Cervical (Garcia-Closas et al 2005: cited in Braun & Cohen 2007:468), breast (Tamimi et al 2005, Toniolo et al 2001, Dorgan et al 1998: all cited in Braun & Cohen 2007:468) and laryngeal cancer (Bidoli et al 2003: cited in Braun & Cohen 2007:468) may also be prevented with a high dietary lutein intake according to several studies. Currently lutein is used in general antioxidant supplements to be used in case of known oxidative stress (Braun & Cohen 2007:468).

Cardioprotective

Oxidative stress pathways, predominantly lipid oxidation, are strongly associated with the development of atherosclerosis. Early observational epidemiological studies suggested a high carotenoid diet reduced the risk cardiovascular disease through antioxidant activity in particular (Kritchesky 1999 cited in Braun & Cohen 2007:169, Mayne 1996: cited in Krinsky & Johnson 2005:493).

Lycopene

Several reports support lycopene in cardiovascular disease prevention as an antioxidant and by lowering low density lipoprotein cholesterol (Rao & Rao 2007:212). A multicentre case-controlled study showed a dose-relationship between tissue lycopene and myocardial infarction risk (Rao & Rao 2007:212). The Kuopio Ischaemic Heart Disease Study (Finland) confirmed that lower serum lycopene levels were associated with enhanced risk of arthrosclerosis formation in the carotid artery (Ferrari 2007:329). Lycopene has been shown to significantly reduce the levels of oxidized low density lipoproteins in subject who consumed tomato sauce (Rao & Rao 2007:212).

Lutein and zeaxanthin

Low serum lutein has been associated with a greater progression of intima-media thickness the humans carotid arteries (Dwyer et al 2001 cited in Alves-Rodrigues & Shao 2004:67). Consistent with these findings an epidemiological study reported that individuals with the highest serum levels of lutein and zeaxanthin had a significantly reduced risk of coronary heart disease (Iribarren et al 1997: cited in Alves-Rodrigues & Shao 2004:67). A large cohort study found a significantly inverse association between the intake of lutein and the risk for ischemic stroke (Ascherio et al 1999: cited in Alves-Rodrigues & Shao 2004:67).

Beta-carotene

In observational studies where beta-carotene rich foods have been consumed, with other important nutrients, a cardioprotective effect has been demonstrated. However, interventional studies where synthetic supplementation with beta-carotene, in isolation from other nutrients, has found no benefit. Therefore, in a diet high in beta-carotene containing foods, cardioprotection most likely occurs (Braun & Cohen 2007:170, Tavani & La Vecchia 1999).

Cataracts and age-related macular degeneration, retinitis pigmentosa

Lutein and zeaxanthin

Lutein and zeaxanthin have been strongly associated with a reduced risk of cataract formation, age-related macular degeneration and the hereditary diseases of the retinal photoreceptors, known as, retinitis pigmentosa. With normal aging, high ongoing oxidative stress and ultraviolet light exposure, damage can occur to parts of the eye including the lens and retina (Braun & Cohen 2007).

Cataracts form when proteins in the lens become oxidized, reducing transparency (Krisnky & Johnson 2005:461). Lutein and zeaxanthin are believed to be responsible for absorbing the majority of the damage causing, high energy, blue light in the lens (Roberts, Green & Lewis 2009:196). Numerous observational studies have found that an increased consumption of foods high in lutein and zeaxanthin is associated with a decreased risk of cataracts (Brown et al 1999 & Tavani 1996: both cited in Braun & Cohen 2007:467). The Nurse's Health Study

with 77,466 female participants, found those with the highest consumption of lutein and zeaxanthin containing foods had 22% reduced risk of cataract formation (Ferrari 2007:328).

The central portion of the retina, the yellow macula lutea, contains a high concentration of lutein and zeaxanthin (Ferrari 2007:328) collectively known as macular pigment (Wenzel, Sheehan, Burke, Lefsrud & Curran-Celentano 2007:462). Damage to the macular pigment is characterized by the condition age-related macular degeneration (Porth 2005:1316). In the retina cells, high energy blue wavelengths are very effective inducers of free radical formation (Ferrari 2007:328). Lutein and zeaxanthin are believed to filter these high energy blue wavelengths and protect the retina (Roberts et al 2009:196, Ferrari 2007:328).

Epidemiological studies recognized the link between low risk of developing age-related macular degeneration and intake of high lutein and zeaxanthin containing fruit and vegetable. Placebo-controlled studies supported this role whether in the diet or as a supplement (Roberts et al 2009:197). A 2004 double-blind, randomized, placebo controlled study found a 50% improvement in macular pigment optical density (MPOD) and a significant improvement in visual function including glare recovery, visual acuity and contrast sensitivity (Richer, Stiles & Starkute 2004 cited in Roberts et al 2009:197) with high lutein and zeaxanthin intake. Macular pigment optical density has been shown to be higher in those with a high lutein and zeaxanthin food dietary intake (Wenzel et al 2007:463).

The hereditary diseases of the retinal photoreceptors, known as, retinitis pigmentosa, can cause complete blindness at varying rates in effected individuals (Porth 2005:1310). In two 2006 studies there where demonstrated improvements in macular pigment optical density (MPOD), contrast sensitivity in (Kyansakul, Rodriguez-Carmona & Edgar 2006 cited in Roberts et al 2009:197), and visual acuity in patients with retinitis pigmentosa (Bahrami, Melia & Dagnelic 2006: cited in Roberts et al 2009:197).

Lycopene

In combination with other carotenoids, lycopene has been known to be used in supplementation for general eye care, reducing the risk of development of age-related macular degeneration (Cardinault et al 2005). Deposited in the retinal epithelium, high levels of lycopene has been linked to lower risk of cataract formation and in vitro lycopene reduced oxidative changes to human lens epithelium (Braun & Cohen 2007:474)

Beta-carotene

A high dietary intake of beta-carotene has been associated with age-related macular degeneration and cataract prevention. The role of supplementation is not so clear. In an antioxidant combination, beta-carotene could be effective (Braun & Cohen 2007:172-3).

Photoprotection and ultraviolet light protection

The skin is potentially exposed to ongoing light-induced free radical damage, in particular blue light filter which is the most damaging ultraviolet light (Pathak 1982: cited in Braun & Cohen 2007). Carotenoids have been shown to provide photoprotection from ultraviolet-induced free radical damage which can eventually suppress immune function (Roberts et al 2009:198, Alves-Rodrigues & Shao 2004:68, Hughes 2001:824). Carotenoids may work better together in skin protection as they act by quenching oxygen species repairing ultraviolet light damage, modulating enzyme activity and gene expression, enhancing cell-cell communications and suppressing cellular responses and inflammation (Sies & Stahl 2004: cited in Braun & Cohen 2007:165).

Lutein and zeaxanthin

Lutein, especially, may have the potential to absorb damaging blue-light wavelengths (Roberts et al 2009:198). Lutein and zeaxanthin has shown protection against skin damage, such as oedema and hyperplasia, caused by ultraviolet light (Hata et al 2000, Wingerath, Seis & Stahl 1999: cited in Roberts et al 2009:198) and ultraviolet light induced immunosupression *in vivo* (Lee, Faulhaber & Hanson 2004: cited in Roberts et al 2009:198). Human studies, however, are in the early stages. (Roberts et al 2009:199). A 2006 report using topical and oral administration suggested lutein and zeaxanthin may potentially

increase skin elasticity and superficial lipids, stimulate skin hydration and reduce lipid peroxidation (Roberts et al 2009:199). An Australian study found a high dietary intake of lutein and zeaxanthin is associated with a reduced incidence of squamous cell carcinoma in persons at high risk of skin cancer (Heinen et al 2007:2716).

Beta-carotene

Beta-carotene may provide some protection for ultraviolet-induced erythema especially when used with other antioxidants (Sies & Stahl 2004). A 2002 randomized, double, blind, placebo-controlled study found an antioxidant combination significantly decreased ultraviolet light induced erythema (Gruel et al 2002: cited in Braun & Cohen 2007:170). supplementation may is known to be effective in providing protection for photosensitive individuals. In high doses, 30-300mg/daily for at least two months, it has been “shown to reduce photosensitivity in people with the genetic condition erythropoietic protoporphyria” and other photosensitivity conditions as a preventative or in treatment regimes (Sies & Stahl 2004, Matthew-Roth et al 1993, Thomsen et al 1979: cited in Braun & Cohen 2007:170, 173).

To date, carotenoids have been associated with a vast range of diseases, especially degenerative diseases. Studies into carotenoids continue demonstrate the importance of these phytochemicals. These include: oxidative stress, vitamin A deficiency, asthma and chronic obstructive pulmonary disease, Alzheimer’s disease (Rindali et al 2003), cystic fibrosis, human immunodeficiency virus and many more (Braun & Cohen 2007).

Vitamin A deficiency

Beta-carotene other provitamin A carotenoids are required for conversion to vitamin A. Beta-carotene is converted to retinoic acid which is regulated by vitamin A status. Conversion may be enhanced by alpha-tocopherol & zinc (Braun & Cohen 2007163).

Discussion

Research into carotenoids has highlighted some important areas for discussion. These include prooxidation, dietary intake versus supplementation and the importance of using whole foods for synergistic effect.

Prooxidation-

Research into beta-carotene and lung caner had surprising results. The increased risk of lung cancer with beta-carotene supplementation led researchers to consider beta-carotene to be a prooxidant in certain circumstances. The increased risk occurred in heavy smokers and asbestos workers in at least three large interventional studies (Braun and Cohen 2007:168) and increased mortality from cardiovascular disease.

Some hypothesis for the increased risk includes:

- The dose exceeding normal dietary intake (Sies & Stahl 2005:103, Hughes 2001:826), duration of the studies, and the type of beta carotene used may be to blame. It is reported that beta-carotene in its *trans* form may be a prooxidant (Jamison 2003:475).
- The use of supplementation with synthetic beta-carotene alone may inhibit the absorption of other carotenoids, which may otherwise have work in synergy with beta-carotene (Omenn et al 1996: cited in Braun and Cohen 2007:166). In observational studies, where beta-carotene demonstrated an antioxidant effect in cancer and cardiovascular disease, dietary beta-carotene was used (Tavani & Vecchia 1999:414).
- The beta-carotene may have been unstable due to reduced levels of other antioxidants in smokers, such as ascorbic acid, and high oxidative stress occurring (Braun & Cohen 2007:167). Russell 2002 (cited in Braun & Cohen 2007:166) found other antioxidants stabilized beta-carotene giving a protective effect. It is therefore recommended that beta-carotene is taken in dietary form or as a mixed supplement with other carotenoids (Jamison 2003:478).
- The heavy smokers and asbestos workers could be considered a high risk group and may have already had undetected carcinogenesis in progression (Braun and Cohen 2007:166, Hughes 2001:826). Increased risk was also found in those who consumed greater than 11g/day alcohol in one study (Albanes et al 1996: cited in Braun and Cohen 2007:168).

- Improved lung function, from the beta-carotene supplementation, may have exacerbated any existing tumour growth. Lung capacity may have been increased, facilitating the spread of carcinogens to deeper lung tissue (Braun & Cohen 2007:169).
- Beta -carotene may be a pro-oxidant when there is high oxygen tension, such as in the lungs (Sies & Stahl 2005:103, Hughes 2001:826).
- The interaction between cigarette components and high concentrations of beta-carotene might lead to oxidative damage by causing the formation of oxidized metabolites which appear to facilitate carcinogenesis (Krinsky & Johnson 2005:476).

Dietary intake versus synthetic supplementation

The efficacy and safety of synthetic supplementation is not completely understood (Krinsky and Johnson 2007:499) and the prooxidant effect of beta-carotene demonstrated high synthetic supplementation doses can, in certain circumstances, be harmful. Supplementation does not provide accurate information about absorption, metabolism and synergetic effects. Recommended daily allowance of dietary intake of carotenoid rich foods is considered safe and effective (Rao & Rao 2007:210). The overall protective nature of foods containing carotenoids is most likely due to a multifactoral effect from using 'real' foods (Hughes 2001:826) and synthetic supplementation is not optimal.

Synergy

There is no argument that carotenoids as a part of whole foods can benefit human health (Krinsky & Johnson 2005:491). "Carotenoids may interact with each other at any point during the absorption, metabolism, and transport processes" (Alves-Rodrigues & Shao 2004:74). This synergetic effect was demonstrated with the use of synthetic beta-carotene supplementation in cancer and cardiovascular disease (Jamison 2003:478). The absent of other carotenoids may have contributed to it being harmful. For example, the activity of lycopene in tomatoes may be increased by the presence of other phytochemicals which are known to be beneficial (Karppi 2009:516, Stacewicz-Sapuntzakis & Bowen 2005: 204). It is possible that individual carotenoids serve as markers for the need to increase overall fruit and vegetable intake, rather than increase the individual carotenoid and recognize that other nutrients are important, such as the role of oil on absorption (Krinsky & Johnson 2005:491).

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