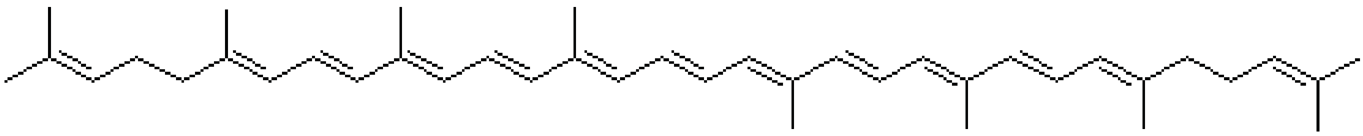
LYCOPENE:
ITS ROLE IN HUMAN HEALTH

Dr Lambit Kanwar
Parry Nutraceuticals, Division of EID Parry (India) Ltd, Chennai, India.
email: parrynutraceuticals@parry.murugappa.com www.parrynutraceuticals.com

Lycopene is a red plant pigment found in tomatoes, apricots, guavas, watermelons, papayas, pink grapefruits and rosehips, with tomatoes being the largest contributor to the dietary intake of humans (Chalabi et al., 2004). Chemically it is a 40-carbon acyclic carotenoid which contains 11 conjugated double bonds and belongs to a subgroup of carotenes consisting only of hydrogen and carbon atoms (Stahl and Sies, 1996).



Lycopene

Molecular Weight = 536.89
Exact Mass = 536
Molecular Formula = C40H56
Molecular Composition = C 89.49% H 10.51%

These eleven conjugated double bonds give it its deep red color and are responsible for its antioxidant activity. Lycopene exhibits higher singlet oxygen (O2) quenching ability. Due to its strong color and non-toxicity, lycopene is a useful food coloring (registered as E160d). Lycopene is not an essential nutrient for humans, but is commonly found in the diet, mainly from dishes prepared with tomato sauce. When absorbed from the stomach, lycopene is transported in the blood by various lipoproteins and accumulates in the liver, adrenal glands, and testes.

Dietary sources

Lycopene is present in variety of colored fruit and vegetable. At least 85% of our dietary lycopene comes from tomato fruit and tomato-based products, the remainder being obtained from watermelon, pink grapefruit, guava and papaya (Table 1).

Of the tomato products, juice, ketchup, soup and pizza and spaghetti sauces are the major contributors in the diet (Table 1). The range of values is related to varietal differences and the effects of growth conditions on carotenoid synthesis. The configuration of lycopene in these crops is predominantly all-trans, although processed tomato products contain between 1.7% and 10.1% cis isomers. Processing also affects the matrix of the tomato product (Shi and Le Mageur, 2000).

Lycopene content of fruit and tomato products

Fruit or tomato product	Lycopene content (ug/g wet weight)
Fresh tomato	8.8±42.0
Watermelon	23.0±72.0
Pink guava	54.0
Pink grapefruit	33.6
Papaya	20.0±53.0
Tomato sauce	62.0
Tomato paste	54.0±1500.0
Tomato juice	50.0±116.0
Tomato ketchup	99.0±134.4
Pizza sauce	127.1

Data taken from: Scott and Hart (1995), Tonucci et al. (1995),and Rao and Agarwal (1999).

Its Role in Human disease

Oxidative stress, induced by reactive oxygen species (ROS), is associated with the incidence of chronic diseases such as cancer, coronary heart disease (CHD) and osteoporosis (Rao and Agarwal, 1999). ROS are highly reactive oxidant molecules that are generated endogenously through normal metabolic processes, life style activity and the diet.

Antioxidants provide an effective means to combat the deleterious effects of ROS and are increasingly being considered as strategic chemo preventive agents in the management of human diseases. Lycopene - the carotenoid phytonutrient, is the most potent antioxidant naturally present in many fruits and vegetables. Lycopene in the presence of vitamin C, can repair both itself and other antioxidants to restore their antioxidant qualities. Tomatoes and processed tomato products constitute the major source of dietary lycopene accounting for upto 85% of the daily intake. (Rao and Agarwal, 2000)

Lycopene and prostate cancer

Lycopene has emerged from the scientific literature over the past few years to bear significant potential for consideration in both the treatment and prevention of prostate cancer.

Several epidemiology studies strongly suggest the hypothesis that the consumption of foods containing high concentrations of lycopene reduces the risk for certain types of cancer (Gann et al., 1999; Giovannucci et al., 2002; Jian et al., 2005).

Numerous epidemiological studies and reviews have been carried out describing the role of lycopene in association with the prevention of prostate cancer (Rao and Agarwal, 1988). One of the earliest epidemiological studies showing an inverse relationship between the consumption of tomatoes and tomato products and the risk of prostate cancer was published in 1995 (Giovannnucci et al 2002). In this study, the beneficial properties of tomato products were attributed to lycopene. Since then, several other epidemiological, experimental and tissue culture studies have been reported providing further evidence for the role of lycopene in prostate cancer. One case control study in particular, conducted in 1982, examined the relationship between serum lycopene and other antioxidant levels on prostate cancer risk as well as aggressive prostate cancer incidence (Parker 1997). Odds ratios were calculated for prostate cancer incidence using logistic regression models after a thirteen-year follow-up. Lycopene was the only antioxidant for which plasma lycopene was very strongly related to lower prostate cancer risk (upper quintile odds ratio = 0.40; P, trend = 0.006 for aggressive cancer). In tissue distribution studies carried out in rats, lycopene was found in liver, testes, stomach, intestine and prostates of rats fed a tomato oleoresin. In another experiment by Rao et al (1999) to know the status of oxidative stress and antioxidant in prostrate cancer patient, it was found that there was difference in levels of serum carotenoids and biomarker of oxidation and prostate specific levels in these subjects. Although there were no difference in the level of beta carotene, lutein, cryptoxanthin, vitamin E and vitamin A between cancer patient and their control, level of lycopene were significantly lower in cancer patients. As expected the PSA levels were significantly elevated in the cancer patients who also had higher levels of lipid and protein oxidation indicating higher level of oxidative stress in cancer patients. In the same study, serum PSA levels were shown to be inversely related to the serum lycopene (Rao et al., 1999). Over all, epidemiological studies, in vitro tissue culture studies, animal studies, now some human intervention studies are showing that increase intake of lycopene will result in increase circulatory and tissue levels of lycopene. In vivo lycopene can act as a potent antioxidant and protect cells against oxidative damage and thereby prevent or reduce the risk of several cancers. Further studies are needed and ongoing to get further proof and to gain better understanding of the mechanisms involved.

LYCOPENE AND CORONARY HEART DISEASE (CHD)

In vitro studies have shown that lycopene can protect native LDL from oxidation and also inhibit cholesterol synthesis (Dugas et al., 1999; Fuhrmann & Aviram 1997). Animal intervention studies have also shown lycopene to increase the resistance of the extracted LDL in vitro to oxidation. However, epidemiological studies provide the main evidence in support of the role of lycopene in the prevention of CHD (Rao 2002; Rao and Balachandran 2003; Rao and Heber 2001). In a cross sectional study (Kritenson, 1997) Lithuanian population, who are at a high risk of mortality from CHD was compared to a lower risk Swedish population and were shown to have lower blood lycopene levels. These observations suggested low blood lycopene levels to be associated with increased risk and mortality from CHD. In another case control population study (Iribarren,1997), cases that exceeded 90th percentile of intima-media thickness for all arterial segments, had lower levels of lycopene.

Similarly, Rissanen et al (2000) using a randomized, double blind, placebo-controlled population study showed a direct association between low plasma lycopene concentrations and the onset of early arteriosclerosis, manifested as increased intima-media thickness of the common carotid artery, in middle-aged men living in Eastern Finland. The same authors, in a follow-up study, showed low level of serum lycopene to be associated with

an increased risk of arteriosclerosis vascular events in middle-aged men who were previously free of CHD and stroke (Rao and Heber, 2001). Based on the observed inverse relationship between plasma lycopene and intima-media thickness, Gianetti et al., suggested a protective role for lycopene

against arteriosclerosis (Gianetti et al., 2002). The EUEAMIC study (Kohlmeier et al., 1997) which is a multicenter case-control study evaluating the relationship between adipose tissue antioxidant status and acute myocardial infarction is perhaps the strongest population based evidence in support of the role of lycopene in the prevention of CHD. In this study, subjects recruited from 10 different European countries with acute myocardial infarctions were compared with controls. Adipose tissue samples were taken by needle aspiration biopsy procedures shortly after the infarction and used to measure α and β-carotenes, lycopene, and α -tocopherol levels.

Only lycopene, and not the other antioxidants, was found to have a significant inverse relationship with the risk of myocardial infarction (Kohlmeier et al 1999, Gomez-Aracena J et al 1997). In addition to the epidemiological studies, a few dietary intervention studies have also been reported in the literature.

In one study, upon consuming a lycopene-free diet by healthy human subjects for a period of two weeks, serum lycopene levels were reduced by 50% (Rao and Agarwal, 1998). An increase of 25% in serum lipid oxidation was also observed in this study. In another one small study, six healthy human subjects consumed 60 mg/day of lycopene for a period of 3 months. A significant 14% drop in their plasma LDL cholesterol level was observed (Fuhrmann and Elis, 1997) at the end of the treatment period suggesting a hypocholesterolemic property of lycopene. However, other studies, using different levels of lycopene intake for shorter periods of time did not report

reductions in serum total or LDL cholesterol levels upon ingesting lycopene. A significant reduction in LDL oxidation was observed in another randomized, cross-over dietary intervention study (Agarwal and Rao, 1988) when 19 healthy human subjects consumed 20-150 mg lycopene daily from tomato juice, tomato sauce and a nutritional supplement for a period of one week. In summary, although there is convincing epidemiological and in vitro evidence in support of the role of lycopene in the prevention of CHD, only a few clinical trials have so far been undertaken. More dietary intervention studies are needed to fully understand the mechanisms of action of lycopene in CHD as stated diet rich in lycopene may be heart protective.

Lycopene and bone health

Research also suggests that lycopene has lot of benefit in bone health. Oxidative stress and antioxidants may contribute to the pathogenesis of the skeletal system including osteoporosis, the most prevalent metabolic bone disease (Rao, 2006). Oxidative stress controls the functions of both osteoclasts (Silvertron and Suda et al., 1993) and osteoblasts (Liu et al., 1999). Endogenous (Key et al., 1990) and synthetic antioxidants counteract the effects of oxidative stress in these cells.

Recent studies reported that antioxidants from natural sources, such as the lycopene from tomatoes, can also counteract the damaging effects of oxidative stress. The findings that lycopene has a stimulatory effect on the cell proliferation (Kim et al., 2003) and the differentiation marker alkaline phosphatase of osteoblasts (Kim et al 2003, Park et al 1997) as well as its inhibitory effects on osteoclasts formation and resorption (Rao et al., 2003, Ishimi et al., 2003) are evidence of the involvement of lycopene in bone health and warranted further investigation in clinical studies. Epidemiological studies have shown that oxidative stress is associated with osteoporosis and that antioxidants may counteract this effect. Certain antioxidants including vitamin C, E and beta-carotene may reduce the risk of osteoporosis [Melhus et al., 1999; Morton et al., 1999; Singh, 1992; Leveille et al., 1997] and counteract the adverse effects of oxidative stress on bone that are produced during strenuous exercise [Singh, 1992] and among smokers [Melhus, 1999]. Osteoporotic women have been shown to have reduced levels of antioxidant vitamins and enzymes indicating a decrease in their antioxidant defences [Maggio et al., 2003].

A recently published clinical study showed a direct correlation between serum lycopene and decrease in the risk of osteoporosis among postmenopausal women [Rao et al., 2007]. The relationship between serum lycopene, oxidative stress parameters and bone turnover markers in postmenopausal women were investigated. Study participants were asked to complete a seven-day food intake record prior to giving fasting blood samples. Oxidative stress parameters, total antioxidant capacity, serum lycopene and the bone turnover markers including bone alkaline phosphatase (bone formation) and cross-linked N-telopeptides of type I collagen (NTx) (bone resorption) were measured in the serum samples. Results showed a direct correlation between lycopene intake and serum lycopene levels. Increase in serum lycopene levels resulted in significant decreases in protein oxidation and NTx values [Rao et al., 2007]. Based on these results an important role for lycopene mediated via its antioxidant property in reducing the risk of osteoporosis is suggested. Dietary intervention studies with varying levels of lycopene are currently being conducted with the objective of demonstrating the beneficial effects of lycopene in the prevention and management of osteoporosis.

Other human diseases

Hypertension is commonly referred to as the 'silent killer' since symptoms of this disorder are not observed until a more advanced and fatal stage of the diseases is reached. A causal relationship between oxidative stress and the incidence of hypertension is now recognized. The antioxidant property of lycopene has attracted scientific research into its protective role in hypertension.

A recent study showed lycopene supplementation at the rate of 15 mg per day for 8 weeks to significantly decrease systolic blood pressures from the baseline value of 144mmHg to 134mmHg in mildly hypertensive subjects (Paran and Engelhard 2001, Paran, 2006). In another study a significant reduction in plasma lycopene was observed in the hypertensive patients compared to normal subjects (Moriel et al., 2002).

When patients with liver cirrhosis, a condition closely associated with hypertension and disorders of the lymphatic circulation, were compared with matched controls a significant reduction in serum lycopene was observed along with other carotenoid antioxidants, retinol and vitamin E in the cirrhotic group (Rao et al., 2006, Paran and Engelhard, 2001).

Recognizing the importance of antioxidants in the management of hypertension a 'dietary approach to control hypertension (DASH)' diet is recommended that contains substantially higher levels of lycopene along with other carotenoids, polyphenols, flavanols, flavanones and flavan-3-ols (Most, 2004). Male infertility, a common reproductive disorder, is now being associated with oxidative damage of the sperm leading to loss of its quality and functionality. Significant levels of ROS are detectable in the semen of up to 25% of infertile men, whereas fertile men do not produce detectable levels of ROS in their semen (Iwasaki and Gagnon 1999, Zini et al., 1993). A number of studies have reported the beneficial effects of vitamins C and E. and other antioxidants, including taurine (Alverej and Storey, 1983), l-carnitine (Monkada et al., 2002), coenzyme Q10 (Alleva et al., 1997, Lewin and lavon, 1997), and glutathione (Lenzi et al., 1998) on sperm quality. Researchers are beginning to investigate the role of lycopene in protecting sperm from oxidative damage leading to infertility. Men with antibody-mediated infertility were found to have lower semen lycopene levels than fertile controls (Palan and Naz, 1996). In another study infertile men consumed a daily dose of 8mg lycopene in capsule form. After consuming lycopene for 12 months, a significant increase in serum lycopene concentration and improvements in sperm motility, sperm motility index, sperm morphology and functional sperm concentration were observed. Lycopene treatment resulted in 36% successful pregnancies. Other studies are now in progress and their results will further advance our knowledge of the beneficial role of lycopene in male infertility. A recent review article elaborated on the possible role of lycopene in neurodegenerative diseases including Alzheimer's disease (Rao and Balachandra, 2003).

Due to high levels of oxygen uptake and utilization, high lipid content and low antioxidant capacity, human brain represents a vulnerable organ for oxidative damage. Although the role of antioxidant vitamins in neurodegenerative diseases have been reported in the literature, only a small number of studies have been reported for lycopene. Lycopene was shown to cross the blood brain barrier and be present in the central nervous system in low concentrations. Significant reduction in the levels of lycopene was reported in Parkinson's disease and vascular dementia patients (For et al., 1999). In the Austrian Stroke Prevention study, lower serum lycopene and α -tocopherol levels were associated with increased risk of microangiopathy (Schmidt et al., 1997).

Lycopene was also suggested as providing protection against amyotrophic lateral sclerosis (ALS) disorder in humans [Longnecker et al., 2000]. When a population of elderly subjects were tested for functional capacity including the ability to perform self-care tasks, a significant positive correlation was observed between blood lycopene levels and functional capacity [Snowdon et al., 1966]. On the basis of the relationship between oxidative stress and neurodegenerative diseases and the potent antioxidant properties of lycopene it is logical to expect further intervention studies to be carried out in the future to address this important area of human health. Incidence of emphysema, a disorder of the lungs is reported to be high is certain countries of the world. A recent study showed protective role of lycopene in the prevention of emphysema in a mouse model. At a recent conference on the role of processed tomatoes in human health, data was provided for the protective role of lycopene in the prevention of emphysema in a Japanese population. Undoubtedly, future research will also explore the role of lycopene in other human diseases including diabetes, ocular and skin disorders, rheumatoid arthritis, periodontal diseases and inflammatory disorders [Rao et al., 2006]. The antioxidant property of lycopene is also opening up new applications in pharmaceutical, nutraceutical and cosmoceutical products [Stahl, 2006].

The scientific interest to explore innovative strategies for the prevention of human diseases underlines the common etiological and mechanistic nature of these diseases.

Epidemiological studies involving lycopene, lycopene-containing foods and chronic diseases

Disease	Major conclusion	Reference
Prostate cancer	Intake of tomato products inversely associated with prostate cancer	Giovannucci et al. (1995); Clinton et al. (1996)
Digestive tract cancer	Reduced risk with high tomato intake	Franceschi et al. (1994)
Bladder cancer	Serum lycopene associated with decreased risk	Helzlsour et al. (1989)
Skin cancer	Decrease in skin lycopene on exposure to light	Ribago-Mercado et al. (1995)
Breast cancer	Serum lycopene associated with decreased risk	Dorgan et al. (1998)
Cervical cancer	Lycopene level showed inverse risk	Sengupta and Das (1999)
Cardiovascular disease	Adipose tissue lycopene associated with lower risk,	Kohlmeier et al. (1997);
	low serum lycopene with increased mortality	Kristenson et al. (1997)

The hypothesis that oxidation of cellular components as an initial event eventually leading to the incidence of several diseases brings the focus to the use of antioxidants. Examples of this hypothesis include oxidation of LDL leading to increases risk of CVD; oxidation of DNA as an early step in the progression of cancers; and protein oxidation resulting in possible alterations in the activity of several metabolic enzymes and influencing many disease conditions. Lycopene by acting as an antioxidant can prevent the progression of many human diseases at an early stage and improve the quality of life.

Daily intake level estimations and suggested levels of intake

In general optimal level ranges from 3.7 to 16.2 mg. It is evident that the average intake levels of lycopene are lower than required to provide its beneficial effects. Although the beneficial effects of lycopene in the prevention of human diseases have been well documented, it is not yet recognized as an essential nutrient. As a result there is no official recommended nutrient intake (RNI) level set by health professionals and government regulatory agencies. However, based on reported studies a daily intake level of 5–7 mg in normal healthy human beings may be sufficient to maintain circulating levels of lycopene at levels sufficient to combat oxidative stress and prevent chronic diseases [Rao and Shen 2002]. Under the condition of disease such as cancer and cardiovascular diseases, higher levels of lycopene ranging from 35 to 75 mg per day may be required [Heath 2006].

Research shows that lycopene can be absorbed more efficiently by the body after it has been processed into juice, sauce, paste, or ketchup. In fresh fruit, lycopene is enclosed in the fruit tissue. Therefore, only a portion of the lycopene that is present in fresh fruit is absorbed. Processing fruit makes the lycopene more bioavailable by increasing the surface area available for digestion. More significantly, the chemical form of lycopene is altered by the temperature changes involved in processing to make it more easily absorbed by the body. Also, because lycopene is fat-soluble (as are vitamins, A, D, E, and beta-carotene), absorption into tissues is improved when oil is added to the diet. Although lycopene is available in supplement form, it is likely there is a synergistic effect when it is obtained from the whole fruit instead, where other components of the fruit enhance lycopene's effectiveness.

REFERENCE

Agarwal S and Rao AV, Lipids 33 981 (1988)

Alleva R, Sacararmucci A, Mantero F, Bompadre S, Leoni L, Littarru GP.(1997).,The protective role of ubiquinol-10 against formation of lipid hydroperoxides in human seminal fluid. Mol Aspects Med ;18:S221–8.

Alvarez J.G, Storey B.T.(1983) Taurine, hypotaurine, epinephrine and albunib Inhibit lipid peroxide in rabbit spermatozoa and protect against loss of motility. Biol Reprod ; 29 548-55

Chalabi, N., Le Corre, L., Mauizis, J.-C., Bignon, Y.-J., Bernard-Gallon, D., (2004). The effects of lycopene on the proliferation of human breast cells and BRCA1 and BRCA2 gene expression. European Journal of Cancer 40, 1768–1775.

Dorgan, J.F., Sowell, A., Swanson, C.A., Potischman, N., Miller, R.,
Schussler, N., Stephenson Jr., H.E., (1998). Relationship of serum carotenoids, retinol, a-tocopherol and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri. Cancer Causes Control 9, 89±97.

Dugas TR, Morel DW, and Harrison EH, (1999) Free Radic Biol Med 26 1238 .

Foy C.J, Passmore A.P, Vahidassr M.D, Young I.S, Lawson J.T. (1999) Plasma chain -breaking antioxidants in Alzheimer's disease, vascular dementia and Parkinson's disease. QJM ;92:39–45.

Franceschi, S., Bidoli, E., La Veccia, C., Talamini, R., D'Avanzo B., Negri, E., (1994) Tomatoes and risks of digestive tract cancers. Int J. cancer 59 181-184.

Fuhrman B, Elis A, and Aviram M,(1997) Biochem Biophys Res Commun 233 658.

Gann P, Ma J, Giovannucci E, Willett W, Sacks FM, and Hennekens CH (1999) Cancer Res 59 1225.

Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, and Willett WC, (1995)J Natl Cancer Inst 87 1767

Giovannucci E, Liu Y, Stampfer M.J, Willett W.C (2002) Journal of the National Cancer Institute 94 391.
Heath E, Seren S, Sahin K, Kucuk O. (2006) The role of tomato lycopene in the treatment of prostate cancer. In: Rao AV, editor, Tomatoes, lycopene and human health. Scotland: Caledonian Science Press; p. 127–40.

Helzlsouer, K.J., Comstock, G.W., Morris, J.S., (1989). Selenium, lycopene, a-tocopherol, b-carotene, retinol and subsequent blad- der cancer. Cancer Res. 49, 6144±6148.

Ishimi Y, Ohmura M, Wang X, Yamaguchi M, Ikegami S. (1999) Inhibition by Carotenoid and retinoic acid of osteoclast – like cell formation induced by bone resorbing agent in vitro. J Clin Biochem Nutr 27: 113-22

Iwasaki A, Gagnon C.(1992) Formation of reactive oxygen species in spermatozoa of infertile patients. Fertil Steril ;57:409–16.
Key L . L, Ries W.L, Taylor R. G, Hays B. D, Pitzer B. L.(1990) Oxygen derived free radical in osteoclast : the specificity and location of the nitroblue tetrazoliun reaction. Bone 1990; 11: 115-119

Kim L, Rao AV, Rao LG. (2003)Lycopene II—Effect on osteoblasts: the carotenoid lycopene stimulate cell proliferation and alkaline phosphatase activity of SaOS 2 cells. J Med Food ; 6(2): 79-86

Kohlmeier L, Kark J.D, Gomez-Garcia E, Martin BC, Steck SE, Kardinaal AFM, Ringstad J, Thamm M, Masaev V, Riemersma R, Martin-Moreno JM, Huttunen JK, and Kok F, Am J Epidemiol 146 618 (1997)

Kritenson M, Zieden B, Kucinskiene Z, Elinder LS, Bergdahl B, Elwing B, Abaravicius A, Razinkoviene L, Calkauskas H, and Olson A,(1997) Br Med J 314 629 .

Lenzi A, Gandini L, Picardo M.(1998) A rationale for glutathione therapy.Debate on: is antioxidant therapy a promising strategy to improve human reproduction. Hum Reprod ;13:1419–24.

Leveille S.G, LaCroix A.Z,Koepsell T.D, Beresford S.A,VanBelle G, Buchner D.M. (1997) Dietary vitamin C and bone mineral density in postmenopausal women in Washington State, USA. J Epidemiol Community Health 1997 ;51:479–85.

Lewin A, Lavon H.(1997) The effect of coenzyme Q10 on sperm motility and function. Mol Aspects Med ;18:S213–9.

Liu H-C, Cheng R-M, Lin F-H, Fang H-W. (1999) Sintered beta-dicalcium phosphate particles induce intracellular reactive oxygen species in rat osteoblasts. Biomed Eng Appl Basis Commun;11:259–64.

Longnecker MP, Kamel F, Umbach DM, et al (2000). Dietary intake of calcium, magnesium and antioxidants in relation to risk of amyotrophic lateral sclerosis. Neuroepidemiology ;19:210–6.

Maggio D, Barabani M, Pierandrei M, (2003). Marked decrease in plasma antioxidants in aged osteoporotic women: results of a cross-sectional study J Clin Endocrinol Metab ; 88 (4):1523–7.

Melhus H, Michaelsson K, Holmberg L, Wolk A, Ljunghall S. (1999) Smoking, Antioxidant vitamin, and risk of hip fracture. J Bone Miner RES ;14;129-35

Moncada ML, Vicari E, Cimino C, Calogero AE, Mongioi A, D'Agata R.(2002) Effect of acetyl carnitine in oligoasthenospermic patients. Acta Eur Fertil 23 : 221-4.

Morton DJ, Barrett-Connor EL, Schneider DL.(2001) Vitamin C supplement and bone mineral density in postmenopausal women . J Bone Miner Res ; 16 : 135-40

Most M.M. (2000) Estimated phyto chemical content of the dietary approaches to stop hypertension (DASH) diet is higher than in the control study diet. A Am Diet Assoc ;104:1725–7.

Palan P, Naz R. (1996) Changes in various antioxidant levels in human seminal plasma related to immunofertility. Arch Androl ;36:139-43.

Park CK, Ishimi Y, Ohmura M, Yamaguchi M, Ikegami S.(1990) Vitamin A and radicals in osteoclasts: the specificity and location of the nitroblue tetrazolium reaction. Bone ;11:115–9.

Rao A.V and Balachandran B (2003) , in "Antioxidants and cardiovascular dusease", K. M. Nath R, Singal PK, Eds.), in press, Narosha Publishing House,

Rao A.V, Balachandran B.(2003) Role of oxidative stress abd anti- oxidants in neuro degenerative diseases. Nutr Neurosci 2003;5(5):291–309.

Rao A.V,(2002) Exp Bio Med 227 908 (2002)

Rao A.V, Shen HL.(2002) Effect of low dose lycopene intake on lycopene bio- availability and oxidative stress. Nutr Res ;22:1125–31.

Rao L.G, Mackinnon ES, Josse RG, Murray TM, Strauss A, Rao AV.(2007) Lycopene consumption decreases oxidative stress and bone resorption markers in postmenopausalwomen. Osteoporosis Int ;18(1):109–15.

Rao L.G, KrishnadevN, Banasikowska K, RaoAV. Lycopene I—Effect on Osteoclasts: lycopene inhibits basal and parathyroid hormone – stimulated osteoclast formation and mineral resorption mediated by ROS species in rat bone marrow cultures. J Med Food 2003;6(2):69–78.

Rao L G. Tomato lycopene and bone health: Preventing osteoporosis. In: Rao A V, editor, Tomatoes, lycopene and human health. Scotland: Caledonian Science Press; 2006. p. 153–68.

Rao .V and Heber .D, Future directions and intake recommendations; Caledonian Science Press, Scotland U.K., 2001, p.43

Rao, A.V., Agarwal, S., (1999) Role of lycopene as antioxidant caro- tenoid in the prevention of chronic diseases: a review. Nutr. Res. 19, 305±323.

Ribago-Mercado, J.D., Garmyn, M., Gilchrest, B.A., Russell, R.M., (1995) Skin lycopene is destroyed preferentially over b-carotene during UV irradiation in humans. J. Nutr. 125, 1854±1859.

Schmidt R, Fazekas F, Hayn M, et al.(1997) Risk factors for microangiopathy related cerebral damage in Aistrian stroke prevention study. J Neurol Sci 152:15–21.

Scott, K.J., Hart, D.J., (1995). Development and evaluation of an HPLC method for the analysis of carotenoids in foods and the measurement of carotenoid content of vegetables and fruits commonly consumed in the UK. Food Chem. 54, 101±111.

Sengupta, A., Das, S., (1999). The anti-carcinogenic role of lycopene,abundantly present in tomato. Eur. J. Cancer Prevention 8, 325± 330.

Shi, J., Le Mageur, M., (2000). Lycopene in tomatoes: chemical and physical properties affected by food processing. Crit. Rev. Food Sci. Nutr. 40, 1±42.

Silverton. S., (1994). Osteoclast radicals. J Cell Biochem 1994 ; 56 :367–73.

Singh V. N.(1992) A current perspective on nutrition and exercise. J Nutr ;122:760–5.

Snowdon D.A, Gross M.D, Butler S.M.(1966) Antioxidants and reduced functional capacity in the elderly: finding from the Nun study. J Gerontol Series A Biol Sci Med Sci ;51:M10–6.

Stahl W. Tomato lycopene in photoprotection and skin care. In: Rao AV editor, Tomatoes, lycopene and human health. Scotland: Caledonian Science Press, 2006 p 199-211.

Stahl, W., Sies, H., 1996. Lycopene: a biologically important carotenoid for humans. Archives of Biochemistry and Biophysics 336, 1–9.

Suda N, Morita I, Kuroda T, Murota S. (1993) Participation of oxidative stress in the process of osteoclast differentiation. Biochim Biophys Acta 1157:318–23.

Tonucci, L.H., Holden, J.M., Beecher, G.R., Khachik, F., Davis, C.S., Mulokozzi, G., (1995). Carotenoid contents of thermally pro- cessed tomato-based food products. J. Agric. Food Chem. 43, 579±586.

Zini A, de Lamirande E, Gagnon C.(1993) Reactive oxygen species in semen of infertile patients: levels of superoxide dismutase and catalase-like activities in seminal plasma and spermatozoa. Int J Androl ;16:183–8.

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