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*Review*

# Anticancer properties of carotenoids in prostate cancer. A review

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**Summary.** Prostate cancer is the most common noncutaneous cancer of men in the world. Several epidemiological studies have linked increased carotenoids consumption with decreased prostate cancer risk. These findings are supported by *in vitro* and *in vivo* experiments showing that carotenoids not only enhance the antioxidant response of prostate cells, but that they are able to inhibit proliferation, induce apoptosis and decrease the metastatic capacity of prostate cancer cells. However, clear clinical evidence supporting the use of carotenoids in prevention or treatment of prostate cancer is not available, due to the limited number of published randomized clinical trials, and the varying protocols used in the existing studies. The scope of the present review is to discuss the potential impact of carotenoids on prostate cancer by giving an overview of the molecular mechanisms and *in vitro* / *in vivo* effects.

**Key words:** Carotenoids, Chemoprevention, Antioxidant activity, Prostate cancer

## Introduction

Carotenoids are a group of natural pigments widespread in nature, found in plants, algae, bacteria and fungi. The term carotenoid encompasses two classes of related compounds: carotenes, unsaturated hydrocarbons, and their oxygenated derivatives, the xanthophylls. Carotenoids are derived chemically from a basic structure formed by the linear sequence of eight isoprene units, associated head-to-tail in two groups of four units (geranylgeranyl) (Britton, 1995; Olson and Krinsky, 1995). This linear basic structure ($C_{40}H_{56}O_n$) with many conjugated double bonds is lycopene, and all other carotenoids are derived by cyclization, dehydrogenation and oxidation. The biosynthetic sequence of the carotenoids in plants is as follows: phytoene → phytofluene → ζ-carotene → neurosporene → lycopene → γ-carotene or β-carotene. Each enzymatic step from phytoene to lycopene adds one double bond to the molecule, resulting in lycopene, which is a symmetrical molecule containing 13 double bonds. The biosynthetic step after lycopene involves enzymatic cyclization of the end groups, which results in γ-carotene (one beta ring) or β-carotene (two beta rings) (Beecher, 1998) (Fig. 1).

In principle, each double bond in the carbon chain may result in an isomer: trans (or E) when the substituents are on opposite sides of the double bond, in which case the molecule is generally linear, or cis (or Z) when they are on the same side. This configuration leads to strong steric constraints and therefore instability (Khoo et al., 2011). Carotenoids are essentially in trans form, and for β-carotene, for example, only the cis forms of carbons 9, 13 and 15 are stable enough to be detected routinely. Steric isomers of carotenoids are absorbed and metabolized differently by the human body, and this is species-dependent among mammals (Boileau et al., 1999).

Carotenoids are localized in subcellular organelles (plastids), i.e. chloroplasts and chromoplasts. They contribute to the yellow color found in many fruits and

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vegetables (Lancaster et al., 1997). The colors of fruits and vegetables depend upon conjugated double bonds and presence of various functional groups that the carotenoid molecule may contain (Rodriguez-Amaya and Kimura, 2004). The higher number of conjugated double bonds leads to higher absorption maxima (λmax) (Rodriguez-Amaya, 2001). As a result, the color ranges from yellow, red to orange in many fruits and vegetables (Hornero-Méndez and Mínguez-Mosquera, 2000). Esterification of carotenoids with fatty acids can also occur during fruit ripening, which may affect the color intensity (Mínguez-Mosquera and Hornero-Méndez, 1994).

The natural functions and actions of carotenoids are determined by physical and chemical properties of the molecules, and these properties are defined by molecular structure (Dutta et al., 2005). First, the overall molecular geometry is vital to allow the carotenoid to fit into cellular and subcellular structures in the correct location and orientation to allow it to function efficiently. Second, the conjugated double bond system determines the photochemical properties and chemical reactivity that form the basis of these functions (Britton, 1995). In addition, specific interactions with other molecules in the immediate vicinity are crucial for correct functioning.

At present, more than 600 carotenoids have been isolated from natural products, but only twenty can be detected in animal tissues or serum. The most prevalent carotenoids in human serum are β-carotene, lycopene, lutein, α-carotene, zeaxanthin, and β-cryptoxanthin (Gerster, 1997) (Fig. 2). These molecules attracted interest due to their provitamin A and antioxidant properties. Subsequently, epidemiological studies suggested a protective effect against cancer and cardiovascular pathologies. The antioxidant effect of carotenoids that protects LDL from peroxidation has been the subject of a lot of research, but other activities have recently been shown, such as photoprotection, regulation of intercellular communications and immunomodulation (Krinsky, 1993; Paiva and Russell, 1999).

## Metabolism, absorption and bioavailability of carotenoids

The carotenoids of fruits, vegetables and those obtained from animal products are usually fat-soluble

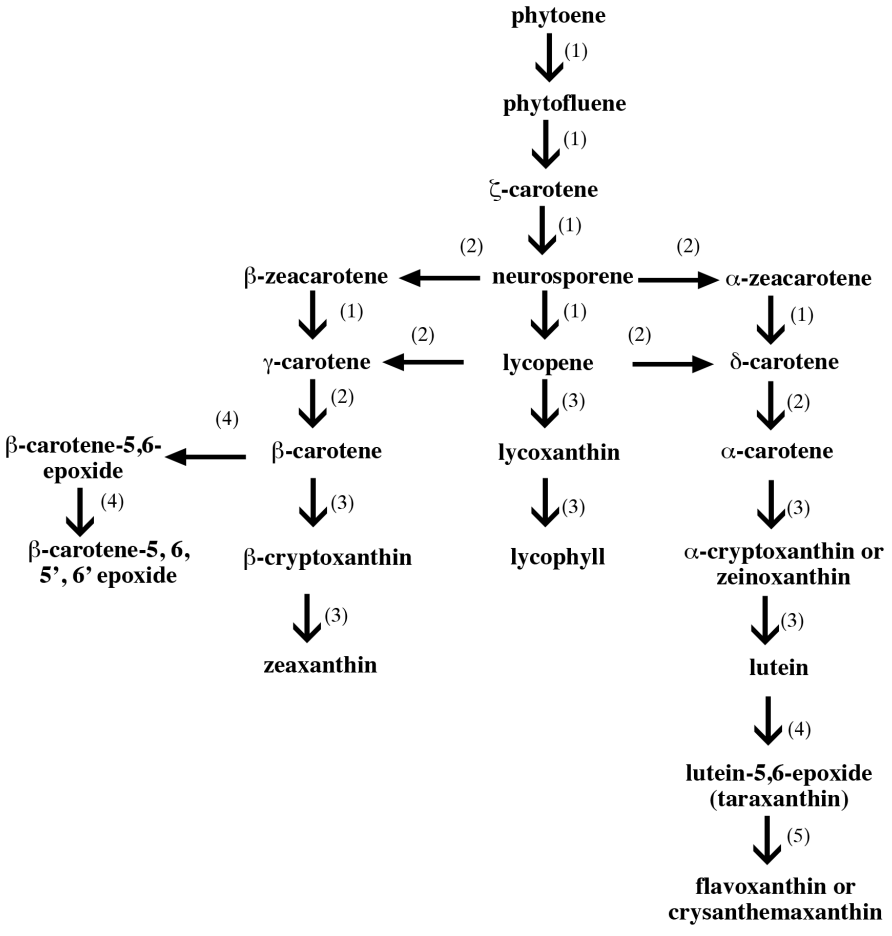


**Fig. 1.** Stages, biosynthesis and possible transformations of carotenoids. Reactions: 1) desaturation, 2) cyclization, 3) hydroxylation, 4) epoxidation, and 5) epoxidefuranoxide rearrangement. (Modified from Rodriguez-Amaya, 2001).

and are associated with lipid fractions. Early in the digestive process, carotenoids are partially released from the food matrix by mastication, gastric action, and digestive enzymes (Dutta et al., 2005; Tanaka et al., 2012). Due to the hydrophobic character, carotenoids are associated with lipid compounds present in human tissues and cells. During proteolytic digestion, carotenoids are released from associated proteins and they aggregate with other lipids. The bioavailability of carotenoids in foods and in commercial preparations varies widely. Only about 5% of the carotenoids in whole, raw vegetables are absorbed by the intestine, whereas 50% or more of the carotenoid is absorbed from micellar solutions. Thus, the physical form in which the carotenoid is presented to intestinal mucosal cells is of crucial importance (O'Connell et al., 2007).

Absorption efficiency of carotenoids is known to be affected by the presence or absence of other carotenoids in the diet, as well as of the dietary fats and proteins (Shiau et al., 1990) and by bile salts. The formation of micelles is a necessary precondition for absorption of carotenoids, underlying the importance of the concomitant dietary fat intake (Kayden and Traber, 1993). An increased total amount of carotenoids in the diet decreases the absorption efficiency, raising the question of the benefit of carotenoid supplementation (Tang et al., 1999). The formation of micelles is a necessary precondition indicating the importance of dietary fat intake for the absorption of carotenoids. As the amount of carotenoids in the diet increases, the absorption efficacy decreases (El-Qudah, 2008). Mechanical homogenization, heat treatment, and addition of fat during the processing of vegetables are feasible techniques to enhance the bioavailability of carotenoids. While mild heating (e.g. steaming) increases carotenoid bioavailability, excessive heating (e.g. boiling) causes isomerization and oxidation of carotenoids (van het Hof et al., 1998).

Carotenoids are absorbed in the intestinal mucosa with the participation of dietary fat. The uptake seems to be mediated by passive diffusion along a concentration gradient between the mixed micelle and the mucosal cell membranes (Fernández-García et al., 2012). After their absorption, dietary carotenoids are in large part incorporated by intestinal mucosal cells into chylomicrons, which are released into the lymph (Harrison, 2012) (Fig. 3).

Chylomicrons are digested very rapidly by lipoprotein lipase within the systemic circulation, and the chylomicron remnants are quickly removed by the liver and other tissues. Very low density lipoproteins (VLDL) next appear as major carriers for carotenoids, followed by low density lipoproteins (LDL). Carotenoids also appear in high density lipoproteins (HDL). Thus, the distribution of carotenoids among plasma lipoproteins is roughly similar to that of cholesterol (Park, 1996; Iqbal and Hussain, 2009).

The different structural features of carotenoids account for their selective distribution in organs and tissues, as well as for their biological activity and their provitamin A capacity. Adipose tissue is the largest body pool of carotenoids, where about 80-85% of carotenoids are found, whereas the serum concentrations are fairly constant and slow to change during periods of low intake (Dutta et al., 2005). In general, the pattern of various carotenoids in tissues reflects that in the serum. This relationship of carotenoid patterns in the serum and tissues does not hold in all cases, however, and, clearly, the ability of some tissues to concentrate carotenoids from the serum indicates that some specialized uptake processes for carotenoids exist (El-Sohemy et al., 2002; Thyagarajan et al., 2011). The estimated half-life was found to be 11-14 days for lycopene, alpha-carotene, beta-carotene, lutein and zeaxanthin (Micozzi et al., 1992). Dietary carotenoids that are not absorbed are excreted in feces.

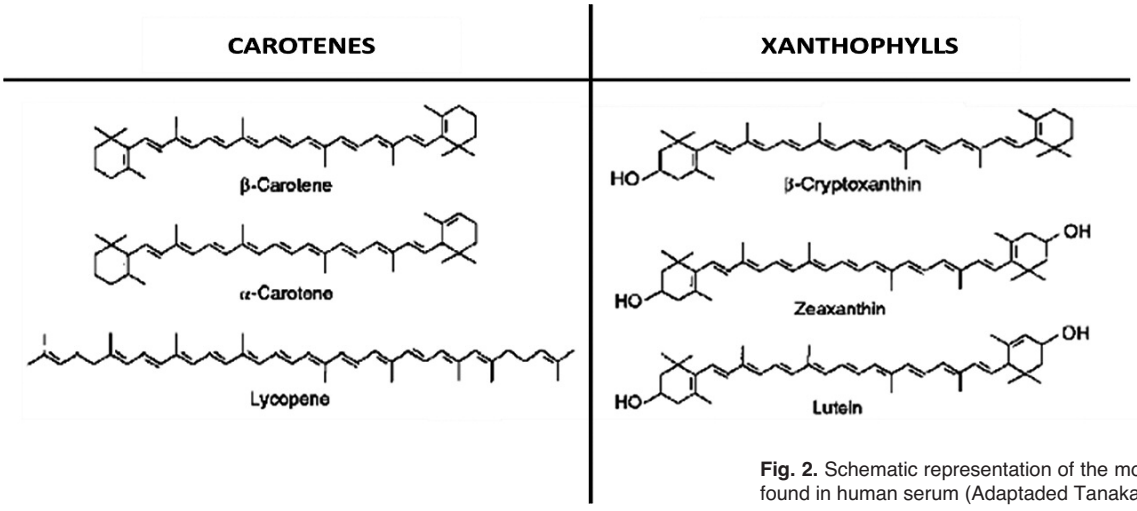


**Fig. 2.** Schematic representation of the most common carotenoids found in human serum (Adaptaded Tanaka et al., 2012).

Numerous epidemiological studies have suggested an association between the high intake of carotenoid rich fruits and vegetables and a reduced risk of cancer (Riboli and Norat, 2003; Liu, 2003; Boggs et al., 2010). Fruits and vegetables contain more than 40 carotenoids that are routinely absorbed and metabolized by humans (Arab et al., 2001; Khachik et al., 2002). The presence of carotenoids in various human organs and tissues were reported as early as 1990 (Tanumihardjo et al., 1990; Stahl et al., 1992). There has been particular interest in the potential anticarcinogenic properties of the major carotenoids, including β-carotene and lycopene (Norrish et al., 2000). The detection of a more comprehensive list of dietary carotenoids in human is shown in the Table 1.

The pathways in which different mammals and humans metabolize carotenoids, however, are still far from clear. A major focus has been the conversion of beta-carotene and other provitamin A carotenoids into

**Table 1.** Dietary Carotenoids in Human Tissues.

| Dietary carotenoids | Average concentration (ng/g) of carotenoids in human tissues | | | | | | |
|---|---|---|---|---|---|---|---|
| | Liver (n=3) | Lung (n=3) | Breast (n=3) | Cervix (n=3) | Prostate (n=5) | Colon (n=3) | Skin (n=3) |
| α-carotene | 67 | 47 | 128 | 23.6 | 50 | 128 | 8 |
| β-carotene + Z-isomers | 470 | 226 | 356 | 125.3 | 163 | 256 | 26 |
| γ-carotene | ND | ND | ND | ND | 48 | ND | 20 |
| Lycopene | 352 | 300 | 234 | 95.0 | 374 | 534 | 69 |
| ζ-carotene | 150 | 25 | 734 | 57.2 | 187 | 134 | 13 |
| Phytofluene | 261 | 195 | 416 | 106.3 | 201 | 116 | 15 |
| Phytoene | 168 | 1275 | 69 | ND | 45 | 70 | 65 |
| α-cryptoxanthin | 127 | 31 | 23 | 4.0 | 32 | 21 | ND |
| β-cryptoxanthin | 363 | 121 | 37 | 24.3 | 146 | 35 | ND |
| Lutein + Z-isomers | 1701 | 212 | 90 | 23.8 | 128 | 452 | 26 |
| Zeaxanthin + Z-isomers | 591 | 90 | 14 | ND | 35 | 32 | 6 |

ND, not detected. Modified Khachik et al., 2002.

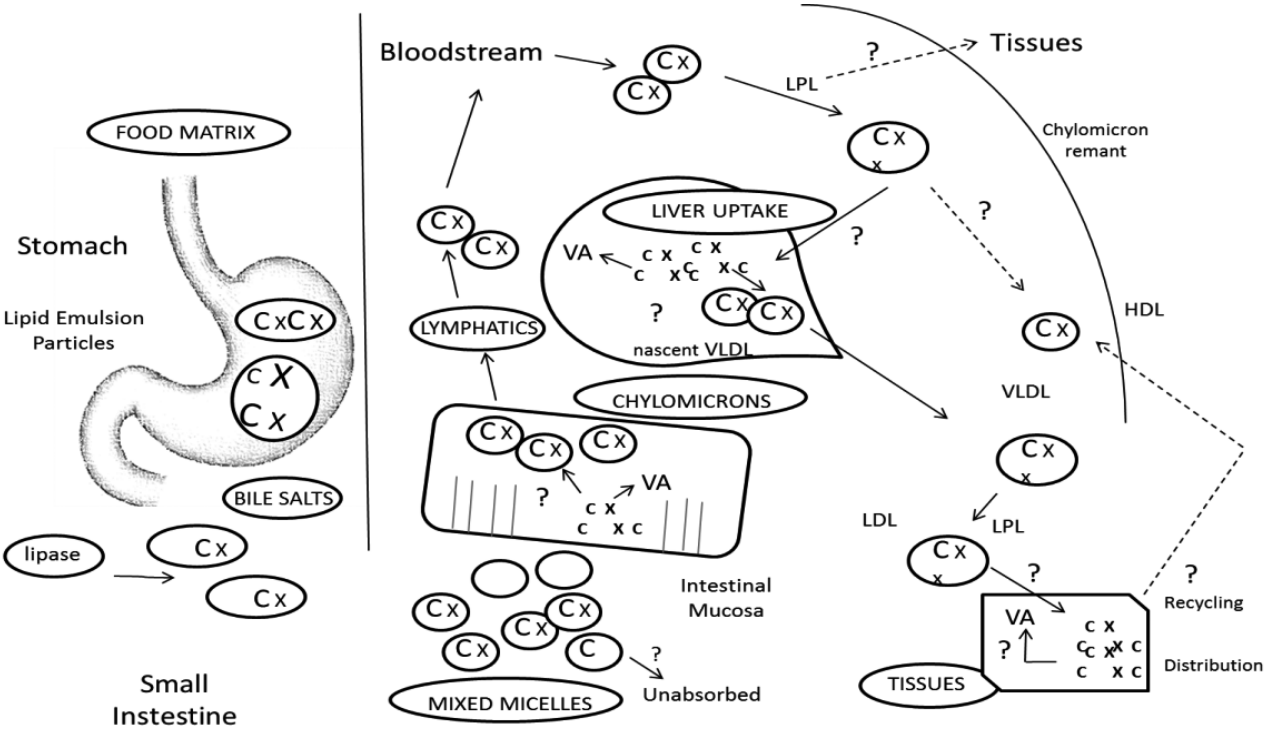


**Fig. 3.** Pathway of carotenoid absorption and metabolism: C, carotene; X, xanthophyll; LPL, lipoprotein lipase; HDL, high density lipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein. (Adapted Deming and Erdman Jr, 1999).

vitamin A (Olson, 1994).

Humans metabolize carotenoids in quite different ways from most other species. Therefore, the development of new procedures, such as the use of carotenoids labeled with heavy isotopes for studies of their absorption and metabolism in humans, is well worth pursuing. With current interest in relation to their possible protective effects against chronic diseases, the need exists to understand better their absorption, transport, tissue distribution, and metabolism (Waart et al., 2001; Voutilainen et al., 2006).

## Mechanisms of prostate cancer chemoprevention by carotenoids

Prostate cancer is the second most frequently diagnosed cancer of men, and the fifth most common cancer overall (GLOBOCAN, 2008). This is a hormone-dependent illness, in which the hormonal status and the patient's tissue responsiveness to hormones interact with environmental elements, known to be important in its etiology, incidence and mortality (Alkaff, 2007; Hsing et al., 2007). In particular, androgen is an important promoter of prostate cancer, and removal of androgenic stimulation has been used to treat metastatic disease (Jamaspishvili, 2011; Sahu, 2012). The vast majority of prostate cancers are thus clearly an androgen-driven illness.

Nutritional factors have been correlated with a greater risk of disease (Álvarez-León et al., 2006). Populations with higher circulating levels of androgen and insulin-like growth factor tend to have a higher risk of prostate cancer (Chokkalingam et al., 2001; Hsing et al., 2007). Accordingly, levels of circulating androgens and insulin-like growth factor are affected by diet (Allen et al., 2000; Smith et al., 2000). The intake of vitamin A from plant sources was reported to be associated with decreased prostate cancer risk, whereas the intake of vitamin A from animal sources may be associated with increased prostate cancer risk (Kolonel et al., 1999; Wilkinson and Chodak, 2003). These findings may also be due to a lower fat content in the diets of men with high plant vitamin A intake and a higher fat content in the diets of men with high animal vitamin A intake. Prospective epidemiologic studies also suggest that lycopene, which belongs to the vitamin A group, is associated with a decreased risk of prostate cancer (Heber and Lu, 2002; Vaishampayan et al., 2007). Lycopene is commonly found in tomato products. Its interaction with fats, such as occurs during its cooking with oils in the preparation of tomato sauces and tomato paste increases the bioavailability of lycopene (Fielding et al., 2004; Alda et al., 2009).

The mechanisms underlying the anticancer and/or cancer chemopreventive activities of carotenoids may involve changes in cell interactions with the

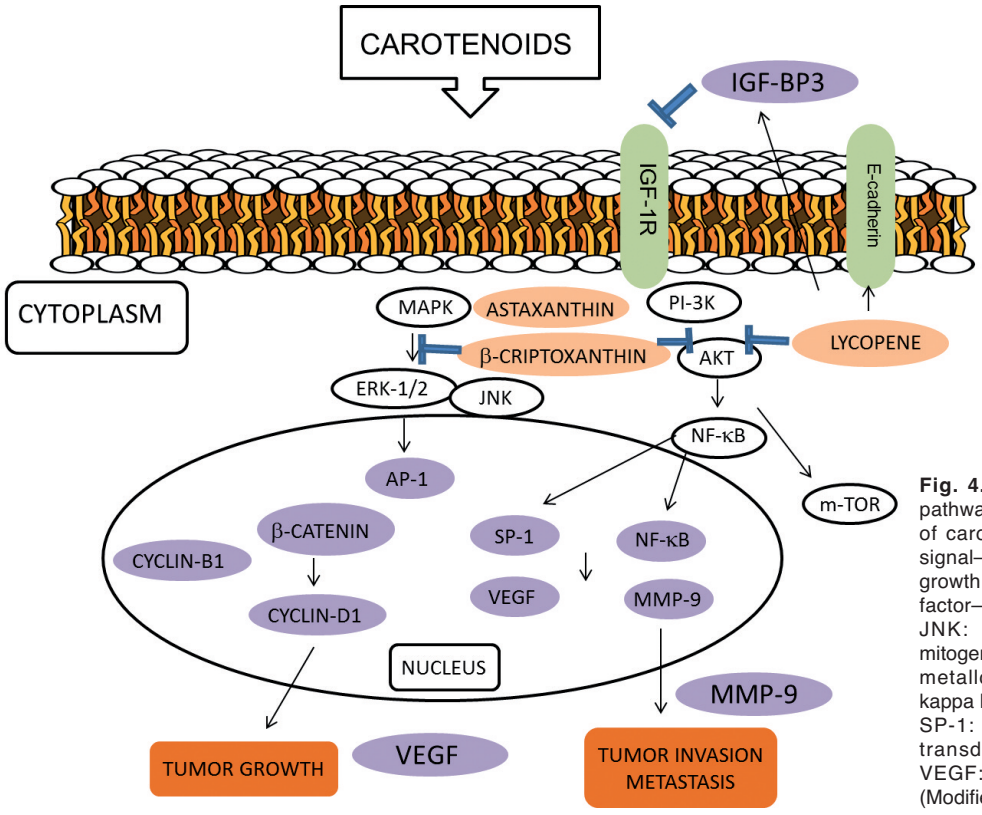


**Fig. 4.** Possible mechanisms of signaling pathways associated with anticancer activity of carotenoids. Legend: ERK: extracellular signal–regulated kinase; IGF-1R: insulin-like growth factor 1; IGF-BP3: insulin-like growth factor–binding protein-3; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; NF-κB: nuclear factor-kappa B; PI-3 K: phosphatidylinositol-3 kinase; SP-1: stimulating protein-1; STAT: signal transducer and activator of transcription; VEGF: vascular endothelial growth factor. (Modified Tang, 2012).

environment, in pathways leading to cell growth or to cell death. These include hormone and growth factor signaling, regulatory mechanisms of cell cycle progression, cell differentiation, and apoptosis. The possible mechanisms involved in anticancer effects of carotenoids are illustrated in the Fig. 4.

### *Gap junctional communication*

Multiple lines of evidence support the notion that gap junctional communication is an important homeostatic control mechanism for regulating cell growth and differentiation. One of the earliest discoveries related to carotenoid-mediated modulation of protein levels refers to carotenoid-dependent increase of connexin 43 synthesis, a component of the gap junction structure and function (Heber and Lu, 2002; Palozza et al., 2006). This effect was independent of provitamin-A or the antioxidant properties of the carotenoids (Livny et al., 2002; Vine and Bertram, 2005). Loss of gap junctional communication has been involved in the pathogenesis of several types of cancers, and mutations in several Cx genes have been detected in genetic disorders characterized by aberrant cellular proliferation and differentiation (Wei et al., 2004; Naus and Laird, 2010). In PC-3 prostate cancer cells, the inhibition of growth by lycopene was mirrored by increased connexin 43 levels (Forbes et al., 2003; Livny et al., 2003).

### *Growth factor signaling*

Growth factors are important for cancer cell growth. Recently, insulin-like growth factor type 1(IGF-1) has been involved as a major cancer risk factor (LeRoith and Roberts Jr., 2003; Voskuil et al., 2005). High blood levels of IGF-1 may exist years before the detection of malignancy, and they could predict an increase in risk for prostate cancer (Mantzoros et al., 1997). Lycopene,

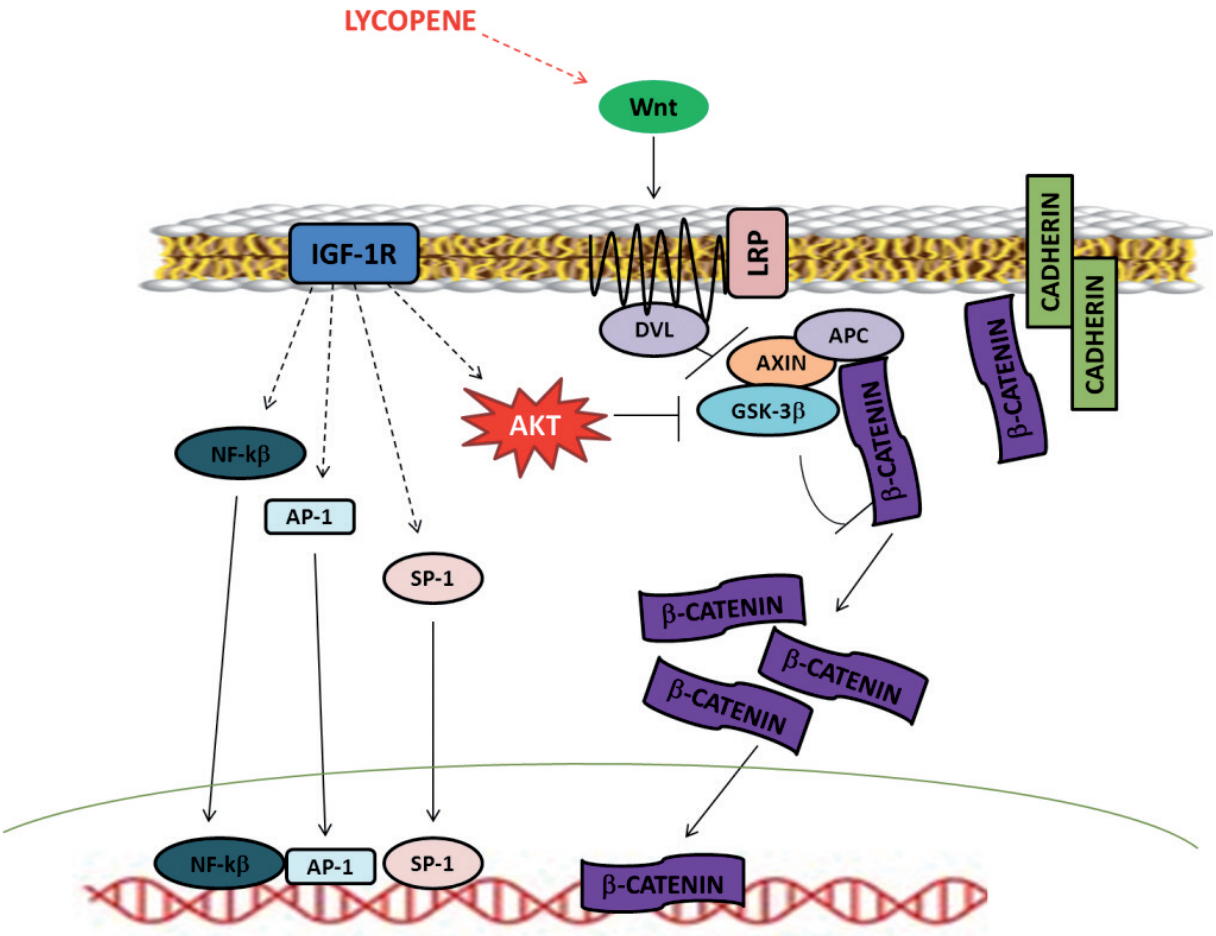


**Fig. 5.** Lycopene inhibits the Wnt/β-catenin pathway. In the absence of Wnt, a multiprotein complex that includes axin, APC, and GSK3β destabilises β-catenin. β-catenin is phosphorylated by GSK3β and is subsequently degraded by the proteasome. Binding of Wnt to its cell surface receptor Lrp 5/6 inhibits the phosphorylation of β-catenin by GSK3β, allowing β-catenin to accumulate within the cytosol. β-catenin then translocates into the nucleus, where it induces gene expression. Lycopene also induces its antimetastatic effects through the inactivation of transcription factors (NF-κB, AP-1, SP-1) (Modified Trejo-Solís et al., 2013).

in dietary or supra-dietary concentrations, inhibits prostate cancer cell IGF-I receptor (IGF-R) expression induced by high concentrations of IGF-I, and inhibits Akt phosphorylation in prostate cancer cells incubated in serum-rich medium (Ivanov et al., 2007; Kanagaraj et al., 2007). In another study, lycopene treatment markedly reduced IGF-1 stimulation of both tyrosine phosphorylation of insulin receptor substrate-1 and the DNA binding capacity of the activator 1 (AP-1) transcription factor (Karas et al., 2000). These effects were not associated with changes in the number or affinity of IGF-1 receptors, but rather with an increase in membrane-associated IGF-binding proteins (IGFBPs). This finding can explain the suppression of IGF-1-signaling by lycopene based on the finding that membrane-associated IGFBP-3 inhibits IGF-1 receptor signaling in an IGF-dependent manner (Karas et al., 1997). A significant trend towards lower serum IGF-1 and higher insulin growth factor binding protein-3 (IGFBP-3) was found with higher weekly consumption of ketchup and tomato juice in 344 disease free men (Gunnell et al., 2003), and a similar decrease in the ratio of IGF-1 to IGFBP-3 was found in ferrets fed lycopene (Liu et al., 2003). A lower ratio of IGF-1 to IGFBP-3 is considered beneficial, because IGFBP-3 binds IGF-1, thereby preventing IGF-1 from stimulating cell proliferation. Both lycopene and tomato polyphenols, including quercetin, kaempferol, and rutin, were shown to interfere with IGF-1 signaling *in vitro*, thus preventing the growth factor from stimulating cell proliferation (Karas et al., 2000).

### *Cell cycle progression*

Growth factors have a major effect in promoting cell cycle progression, primarily during G1 phase (Nahum et al., 2001). Lycopene-induced delay in progression through the G1 and S phases has also been observed in human cancer cell lines derived from prostate (Mantzoros et al., 1997; Venier et al., 2012). In addition, metabolites of lycopene, apo-10'-lycopenoic acid (Lian et al., 2007) and apo-12'-lycopenal (Ford et al., 2011) can induce cell cycle arrest in cancer cells. Cancer cells arrested by serum deprivation in the presence of lycopene cannot return to the cell cycle after serum re-addition (Nahum et al., 2001). This inhibition is correlated with a reduction in cyclin D1 protein levels that results in inhibition of both Cdk4 and Cdk2 kinase activity and hypophosphorylation of retinoblastoma protein (pRb). pRb is a tumor suppressor that prevents premature G1/S transition via physical interaction with transcription factors of the E2F family (Li et al., 2010; Henley and Dick, 2012). Phosphorylation of pRb by Cdks results in the release of E2F, which leads to the synthesis of various cell growth-related proteins (Dyson, 1998; Harbour and Dean, 2000). Cdk activity is modulated in both a positive and negative manner by cyclins and Cdk inhibitors, respectively. It is known that growth factors affect the cell cycle apparatus primarily during G1 phase, and that the D-type cyclins are the main elements acting as growth factor sensors (Pestell et al., 1999; Sherr and Roberts, 1999; Levy and Sharoni, 2004).

### *Differentiation-related proteins*

Induction of malignant clonogenic cells to decrease proliferation and to differentiate into mature cells with functions similar to those of nonmalignant cells has been proposed as an alternative to cytotoxic chemotherapy, and it may be useful for chronic chemoprevention (Trosko et al., 2004; Hazra et al., 2011). Differentiation therapy is currently being investigated for the treatment of solid tumors (Kawamata et al., 2006; Cruz and Matushansky, 2012). Differentiation inducers that are presently under laboratory and clinical investigation include vitamin D and its analogs, retinoids, polyamine inhibitors and others. Lycopene alone induces differentiation of HL-60 promyelocytic leukemia cells (Amir et al., 1999). A similar effect has been described for other carotenoids such as β-carotene, lutein and the saffron carotenoids (Tarantilis et al., 1994; Gross et al., 1997). The differentiation effect of lycopene was associated with high expression of several differentiation-related proteins such as cell surface antigen (CD14) and oxygen burst oxidase (Sharoni et al., 2004; Tang, 2012). The mechanism of the differentiating activity of lycopene and its ability to synergize with $1,25(OH)_2D_3$ in this effect is largely unclear. However, the differentiation-enhancing effect of another phytonutrient, carnosic acid, is associated with the induction of multiple differentiation-related proteins such as Cdk inhibitor, growth response gene-1 (EGR-1) and Cdk5 (Danilenko et al., 2001; Sharoni et al., 2009). Most importantly, carnosic acid and its combinations with $1,25(OH)_2D_3$ and retinoic acid transcriptionally activated the expression of nuclear hormone receptors such as vitamin D3 receptor (VDR), retinoic acid receptor (RARα), and retinoid X receptor (RXRα) (Danilenko et al., 2001; Sharoni et al., 2009). The possibility that carotenoids and/or their derivatives may affect nuclear signaling pathways is an attractive suggestion, but requires experimental proof.

### *Inflammatory cytokines*

Cancer frequently develops in inflamed tissues, suggesting that the inflammatory condition is closely related to carcinogenesis. The chronic inflammation leads to an increased incidence of cancer (Tanaka and Suzuki, 2007). The role of inflammation in prostate diseases is suggested by the presence of inflammatory cells within the benign prostatic hyperplasia and prostate cancer. Inflammation may influence the balance between prostate cell growth and apoptosis by increasing the presence of cytokines, COX-2 and by oxidative stress. These factors stimulate proliferation and minimize cell apoptosis (Hamid et al., 2011). Consequently, a decrease

in inflammatory cytokine expression may lead to inhibition of carcinogenesis.

The major inflammatory cytokines include IL-1β, IL-6 and tumor necrosis factor-α (TNF-α). Cytokine expression is mainly regulated by NF-ϰB. A recent study demonstrated that astaxanthin suppressed the expression of the inflammatory cytokines and NF-ϰB (Yasui et al., 2011). Another one showed that lycopene reduces the Ras-dependent activation of nuclear factor-kappaB (NF-ϰB). Such a reduction was parallel to an inhibition of reactive oxygen species production (Palozza et al., 2010). This observation provides additional evidence that inflammation and oxidative stress play a role in the etiology of this malignancy. These interactions are biologically plausible because chronic inflammation leads to oxidative stress, a condition that promotes carcinogenesis and is counteracted by antioxidants.

### *Wnt/β-Catenin Pathway*

The Wnt/β-catenin pathway modulates cell proliferation, migration, apoptosis, differentiation and stem cell self-renewal (Polakis, 2000). The link between Wnt/β-catenin and PI3K/Akt pathway has been established by several studies. Furthermore, the PI3K/Akt pathway is important in regulating the mammary stem/progenitor cells by promoting β-catenin downstream events through the phosphorylation of glycogen synthase kinase 3β (GSK3β) (Korkaya et al., 2009). In cancer cells, lycopene suppresses Akt activation and nonphosphorylated β-catenin protein levels, and increases the phosphorylated form of β-catenin, which was associated with reduced protein expression of cyclin D1 (Tang et al., 2008). Hence, lycopene may inhibit Wnt/β-catenin signaling via the connection along the Akt/GSK3β/β-catenin (Lin et al., 2011) (Fig. 5). Palozza et al. (2008) showed that β-carotene in different cancer cell lines acts as a growth-inhibitory agent in cav-1-positive cells. The carotenoid down-regulated, in a dose- and time-dependent manner, the expression of cav-1 protein and messenger RNA levels, and inhibited AKT phosphorylation which, in turn, stimulated apoptosis by increasing the expression of β-catenin and c-myc and the activity of caspases-3, -7, -8 and -9. When the carotenoid was removed from culture medium, a progressive increase in cell growth was observed as compared to β-carotene-treated cells. This effect was accompanied by a reduction of both cav-1 and AKT phosphorylation and by an increase of c-myc and β-catenin expression.

### *Apoptosis*

For the maintenance of the normal prostate growth and cell renewal, the complex equilibrium between cell proliferation or differentiation-factors and apoptosis-inducing factors is essential. Similar to other tissues, prostate is normally composed of cells that divide and replicate in an orderly and controlled manner, but it can also contain cells with altered division patterns that give rise to benign or malignant tumors (Dini and Koff, 2006). In prostate, the benign excessive cell growth known as benign prostate hyperplasia can coexist with malignant prostate cancer, as well as with cells that show a normal growth pattern (Srougi and Simon, 1996). The deregulation of growth in prostatic cells includes loss of differentiation and uncontrolled proliferation leading to hyperplasia. In advanced metastatic cancer and in the appearance of therapeutic resistance of prostate tumors, the major event is the loss of sensitivity and the resistance to induction of apoptosis (Reynolds and Kyprianou, 2006).

Many investigators have reported growth inhibition with lycopene in numerous prostate cancer cell lines. The effect appears to involve cell cycle arrest and apoptosis, and it occurs at physiological concentrations. The treatment of LNCaP cells with physiologically attainable concentrations of lycopene (0.3-3.0 μM) significantly reduced mitochondrial transmembrane potential, induced the release of mitochondrial cytochrome c, and increased annexin V binding, compatible with induction of apoptosis (Hantz et al., 2005). In PC-3 cell line, the increase of lycopene concentration inhibited cell growth and DNA synthesis, and lycopene could change the cell cycle distribution, increasing the proportion of cells in the G0/G1 phase and decreasing the proportion of S and G2/M phases. Lycopene also induced apoptosis in PC-3 cells, down-regulating the expression of cyclin D1 and Bcl-2 and up-regulating the expression of Bax, restraining consequently the cell proliferation (Wang and Zhang, 2007).

Soares et al. (2013) demonstrated that lycopene promoted apoptosis in prostate cancer (PCa) cells with an average 1.35-fold increase after 48 h treatment, reaching the maximum 2.25-fold increase after 96 h, at the highest lycopene concentration (10 μM). It also modified the equilibrium of Bcl-2/Bax expression in PCa cells exposed to lycopene. Induction of apoptosis is a central event in the tumor suppressive function of p53 (Schmitt et al., 2002). Through transcription-dependent pathways, p53 can function as a transactivator to up-regulate downstream proapoptotic genes, such as Bax, and/or functions as a repressor to down-regulate antiapoptotic genes, such as Bcl-2, promoting apoptosis (Kolluri et al., 2008; Green and Kroemer, 2009). This cue may be relevant for the understanding of lycopene effects on PCa cells.

## Conclusion

The gradual increase in understanding of cancer biology during recent years has resulted in the elucidation of several approaches for intervention in carcinogenesis. The antioxidant, anti-inflammatory, and proapoptotic activities of carotenoids and their metabolites might contribute to the prevention of and therapy for prostate cancer by modulating diverse

biochemical processes involved in carcinogenesis. The potentially beneficial effects of carotenoids include the inhibition of carcinogenic activation, proliferation, angiogenesis, invasion and metastasis, the blocking of tumor cell-cycle progression, and the induction of apoptosis through alterations in various signaling pathways. More large-scale clinical trials are required to evaluate the potential value of carotenoids and their metabolites in the prevention and treatment of prostate cancer, to determine the optimal dosing and route of administration and to identify cancer targets and potential interactions with other drugs.

## References

Alda L.M., Gogoaşă I., Bordean D-P., Gergen I., Alda S., Moldovan C. and Niţă L. (2009). Lycopene content of tomatoes and tomato products. J. Agroalim. Process. Technol. 15, 540-542.

Allen N.E., Appleby P.N., Davey G.K. and Key T.J. (2000). Hormones and diet: low insulin-like growth factor-I but normal bioavailable androgens in vegan men. Br. J. Cancer 83, 95-97.

Alkaff H.M. (2007). Rarity of carcinoma of the prostate in Yemini patients. J. Trop. Nephrourol. 5, 18-23.

Álvarez-León E-E., Román-Viñas B. and Serra-Majem L. (2006). Dairy products and health: a review of the epidemiological evidence. Br. J. Nutr. 96, S94-S99.

Amir H., Karas M., Giat J., Danilenko M., Levy R., Yermiahu T., Levy J. and Sharoni Y. (1999). Lycopene and 1,25-dihydroxyvitamin D3 cooperate in the inhibition of cell cycle progression and induction of differentiation in HL-60 leukemic cells. Nutr. Cancer 33, 105-112.

Arab L., Steck-Scott S. and Bowen P. (2001). Participation of lycopene and beta-carotene in carcinogenesis: defenders, aggressors, or passive bystanders? Epidemiol. Rev. 23, 211-230.

Beecher G.R. (1998). Nutrient content of tomatoes and tomato products. Proc. Soc. Exp. Biol. Med. 218, 98-100.

Boggs D.A., Palmer J.R., Wise L.A., Spiegelman D., Stampfer M.J., Adams-Campbell L.L. and Rosenberg L. (2010). Fruit and vegetable intake in relation to risk of breast cancer in the black Women's Health Study. Am. J. Epidemiol. 172, 1268-1279.

Boileau A.C., Merchen N.R., Wasson K., Atkinson C.A. and Erdman J.W. Jr (1999). Cis-lycopene is more bioavailable than trans-lycopene *in vitro* and *in vivo* in lymph-cannulated ferrets. J. Nutr. 129, 1176-1181.

Britton G. (1995). Structure and properties of carotenoids in relation to function. FASEB J. 9, 1551-1558.

Chokkalingam A.P., Pollak M., Fillmore C-P., Gao Y-T., Stanczyk F.Z., Deng J., Sesterhenn I.A., Mostofi F.K., Fears T.R., Madigan M.P., Ziegler R.G., Fraumeni J.F. Jr and Hsing A.W. (2001). Insulin-like Growth Factors and Prostate Cancer: A Population-based Case-Control Study in China. Cancer Epidemiol. Biomarkers Prev. 10, 421-427.

Cruz F.D. and Matushansky I. (2012). Solid tumor differentiation therapy - is it possible? Oncotarget 3, 559-567.

Danilenko M., Wang X. and Studzinski G.P. (2001). Carnosic acid and promotion of monocytic differentiation of HL60-G cells initiated by other agents. JNCI 93, 1224-1233.

Deming D.M. and Erdman J.W. Jr (1999). Mammalian carotenoid absorption and metabolism. Pure Appl. Chem. 71, 2213-2223.

Dini L.I. and Koff W.J. (2006). Perfil do câncer de próstata no hospital de clínicas de Porto Alegre. Rev. Assoc. Med. Bras. 52, 28-31.

Dutta D., Chaudhuri U.R. and Chakraborty R. (2005). Structure, health benefits, antioxidant property and processing and storage of carotenoids. Afr. J. Biotechnol. 4, 1510-1520.

Dyson N. (1998). The regulation of E2F by pRB-family proteins. Genes Dev. 12, 2245-2262.

El-Qudah J.M. (2008). Dietary intake of selected common vegetable foods and their total carotenoids determination. AJABS 3, 729-733.

El-Sohemy A., Baylin A., Kabagambe E., Ascherio A., Spiegelman D. and Campos H. (2002). Individual carotenoid concentrations in adipose tissue and plasma as biomarkers of dietary intake. Am. J. Clin. Nutr. 76, 172-179.

Fernández-García E., Carvajal-Lérida I., Jarén-Galán M., Garrido-Fernández J., Pérez-Gálvez A. and Hornero-Méndez D. (2012). Carotenoids bioavailability from foods: From plant pigments to efficient biological activities. Food Res. Int. 46, 438-450.

Fielding J.M., Li D., Stockmann R. and Sinclair A.J. (2004). The effect of different plant oils used in preparing tomato sauces on plasma concentrations of lycopene and oxidative status: a dietary intervention study. Asia Pac. J. Clin. Nutr. 13, pS49.

Forbes K., Gillette K. and Sehgal I. (2003). Lycopene increases urokinase receptor and fails to inhibit growth or connexin expression in a metastatically passaged prostate cancer cell line: a brief communication. Exp. Biol. Med. 228, 967-971.

Ford N.A., Elsen A.C., Zuniga K., Lindshield B.L. and Erdman J.W. Jr (2011). Lycopene and apo-12′-lycopenal reduce cell proliferation and alter cell cycle progression in human prostate cancer cells. Nutr. Cancer 63, 256-263.

Gerster H. (1997). The potential role of lycopene for human health. J. Am. Coll. Nutr. 16, 109-126.

GLOBOCAN. Prostate Cancer Incidence and Mortality Worldwide in 2008. Avaiable: http://globocan.iarc.fr/factsheets/cancers/prostate.asp

Green D.R. and Kroemer G. (2009). Cytoplasmic functions of the tumour suppressor p53. Nature 458, 1127-1130.

Gross M.D., Bishop T.D., Belcher J.D., Jacobs D.R. Jr (1997). Induction of HL-60 cell differentiation by carotenoids. Nutr. Cancer 27, 169-173.

Gunnell D., Oliver S.E., Peters T.J., Donovan J.L., Persad R., Maynard M., Gillatt D., Pearce A., Hamdy F.C., Neal D.E. and Holly J.M.P. (2003). Are diet-prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of diet, IGF-I and IGFBP-3 in healthy middle-aged men. Br. J. Cancer 88, 1682-1686.

Hamid A.R., Umbas R. and Mochtar C.A. (2011). Recent role of inflammation in prostate diseases: chemoprevention development opportunity. Acta Med. Indones. 43, 59-65.

Hantz H.L., Young L.F. and Martin K.R. (2005). Physiologically attainable concentrations of lycopene induce mitochondrial apoptosis in LNCaP human prostate cancer cells. Exp. Biol. Med. 230, 171-179.

Harbour J. and Dean D. (2000). Chromatin remodeling and Rb activity. Curr. Opin. Cell Biol. 12, 685-689.

Harrison E.H. (2012). Mechanisms involved in the intestinal absorption of dietary vitamin A and provitamin A carotenoids. Biochim. Biophys. Acta 1821, 70-77.

Hazra B., Ghosh S., Kumar A. and Pandey B.N. (2011). The prospective role of plant products in radiotherapy of cancer: a current overview. Front. Pharmacol. 2, 94.

Heber D. and Lu Q-Y. (2002). Overview of mechanism of action of

lycopene. Exp. Biol. Med. 227, 920-923.

Henley S.A. and Dick F.A. (2012). The retinoblastoma family of proteins and their regulatory functions in the mammalian cell division cycle. Cell Division 7, 10.

Hornero-Méndez D. and Mínguez-Mosquera I. (2000). Xanthophyll esterification accompanying carotenoid overaccumulation in chromoplast of *Capsicum annuum* pipening fruits is a constitutive process and useful for ripeness index. J. Agric. Food Chem. 48, 1617-1622.

Hsing A.W., Sakoda L.C. and Chua S.C. Jr (2007). Obesity, metabolic syndrome, and prostate cancer. Am. J. Clin. Nutr. 86, 843S-857S.

Iqbal J. and Hussain M.M. (2009). Intestinal lipid absorption. Am. J. Physiol. Endocrinol. Metab. 296, E1183-E1194.

Ivanov N.I., Cowell S.P., Brown P., Rennie P.S., Guns E.S. and Cox M.E. (2007). Lycopene differentially induces quiescence and apoptosis in androgen-responsive and -independent prostate cancer cell lines. Clin. Nutr. 26, 252-263.

Jamaspishvili T. (2011). Biomarkers and models for differentiating prostate cancer from non-cancerous diseases. Thesis PhD. Palacky University Olomuc, Olomuc-Czech Republic. 109p.

Kanagaraj P., Vijayababu M.R., Ravisankar B., Anbalagan J., Aruldhas M.M. and Arunakaran J. (2007). Effect of lycopene on insulin-like growth factor-I, IGF binding protein-3 and IGF type-I receptor in prostate cancer cells. J. Cancer Res. Clin. Oncol. 133, 351-359.

Karas M., Amir H., Fishman D., Danilenko M., Segal S., Nahum A., Koifmann A., Giat Y., Levy J. and Sharoni Y. (2000). Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. Nutr. Cancer 36, 101-111.

Karas M., Danilenko M., Fishman D., LeRoith D., Levy J. and Sharoni Y. (1997). Membrane-associated insulin-like growth factor-binding protein-3 inhibits insulin-like growth factor-I-induced insulin-like growth factor-I receptor signaling in Ishikawa endometrial cancer cells. J. Biol. Chem. 272, 16514-16520.

Kawamata H., Tachibana M., Fujimori T. and Imai Y. (2006). Differentiation-inducing therapy for solid tumors. Curr. Pharm. Des. 12, 379-385.

Kayden H.J. and Traber M.G. (1993). Absorption, lipoprotein, transport and regulation of plasma concentrations of Vit E in Humans. J. Lipid Res. 34, 343-358.

Khachik F., Carvalho L., Bernstein P.S., Muir G.J., Zhao D-Y. and Katz N.B. (2002). Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health. Exp. Biol. Med. 227, 845-851.

Khoo H.E., Prasad K.N., Kong K.W., Jiang Y. and Ismail A. (2011). Carotenoids and their isomers: color pigments in fruits and vegetables. Molecules 16, 1710-1738.

Kolluri S.K., Zhu X., Zhou X., Lin B., Chen Y., Sun K., Tian X., Town J., Cao X., Lin F., Zhai D., Kitada S., Luciano F., O'Donnell E., Cao Y., He F., Lin J., Reed J.C., Satterthwait A.C. and Zhang X.K. (2008). A short Nur77-derived peptide converts Bcl-2 from a protector to a killer. Cancer Cell 14, 285-298.

Kolonel L.N., Nomura A.M. and Cooney RV. (1999). Dietary fat and prostate cancer: current status. J. Natl. Cancer Inst. 91, 414-428.

Korkaya H., Paulson A., Charafe-Jauffret E., Ginestier C., Brown M., Dutcher J., Clouthier S.G. and Wicha MS. (2009). Regulation of mammary stem/progenitor cells by PTEN/Akt/β-catenin signaling. PLoS Biol. 7, e1000121.

Krinsky N.I. (1993). Actions of carotenoids in biological systems. Ann. Rev. Nutr. 13, 561-587.

Lancaster J.E., Lister C.E., Reay P.F. and Triggs C.M. (1997). Influence of pigment composition on skin color in a wide range of fruit and vegetables. J. Am. Soc. Hortic. Sci. 122. 594-598.

LeRoith D. and Roberts C.T. Jr (2003). The insulin-like growth factor system and cancer. Cancer Lett. 195, 127-137.

Levy J. and Sharoni Y. (2004). The functions of tomato lycopene and its role in human health. J. American Botanical Council. 62, 49-56.

Li Z., Jiao X., Wang C., Shirley L.A., Elsaleh H., Dahl O., Wang M., Soutoglou E., Knudsen E.S. and Pestell RG. (2010). Alternative cyclin D1 splice forms differentially regulate the DNA damage response. Cancer Res. 70, 8802-8811.

Lian F., Smith D.E., Ernst H., Russell R.M. and Wang X.D. (2007). Apo-10'-lycopenoic acid inhibits lung cancer cell growth *in vitro*, and suppresses lung tumorigenesis in the A/J mouse model *in vivo*. Carcinogenesis 28, 1567-1574.

Lin M.C., Wang F.Y., Kuo Y.H. and Tang F.Y. (2011). Cancer chemopreventive effects of lycopene: suppression of MMP-7 expression and cell invasion in human colon cancer cells. J. Agric. Food Chem. 59, 11304-11318.

Liu C., Lian F., Smith D.E., Russell R.M. and Wang X.D. (2003). Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis via up-regulating insulin-like growth factor binding protein 3 in cigarette smoke-exposed ferrets. Cancer Res. 63, 3138-3144.

Livny O., Kaplan I., Reifen R., Polak-Charcon S., Madar Z. and Schwartz B. (2002). Lycopene inhibits proliferation and enhances gap-junction communication of KB-1 human oral tumor cells. J. Nutr. 132, 3754-3759.

Livny O., Kaplan I., Reifen R., Polak-Charcon S., Madar Z. and Schwartz B. (2003). Oral cancer cells differ from normal oral epithelial cells in tissue like organization and in response to lycopene treatment: an organotypic cell culture study. Nutr. Cancer 47, 195-209.

Mantzoros C.S., Tzonou A., Signorello L.B., Stampfer A., Trichopoulos D. and Adami H.O. (1997). Insulin-like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia. Br. J. Cancer 76, 1115-1118.

Micozzi M.S., Brown E.D., Edwards B.K., Bieri J.G., Taylor P.R., Khachik F., Beecher G.R. and Smith J.C. Jr (1992). Plasma carotenoid response to chronic intake of selected foods and β-carotene supplements in men. Am. J. Clin. Nutr. 55, 120-125.

Mínguez-Mosquera M.I. and Hornero-Méndez D. (1994). Changes in carotenoid esterification during the fruit ripening of Capsicum annuum cv Bola. J. Agric. Food Chem. 42, 640-644.

Nahum A., Hirsch K., Danilenko M., Watts C.K., Prall O.W., Levy J. and Sharoni Y. (2001). Lycopene inhibition of cell cycle progression in breast and endometrial cancer cells is associated with reduction in cyclin D levels and retention of p27(Kip1) in the cyclin E-cdk2 complexes. Oncogene 20, 3428-3436.

Naus C.C. and Laird D.W. (2010). Implications and challenges of connexin connections to cancer. Nat. Rev. Cancer 10, 435-441.

Norrish A.E., Jackson R.T., Sharps S.J. and Skeaff CM. (2000). Prostate cancer and dietary carotenoids. Am. J. Epidemiol. 151, 119-123.

O'Connell O.F., Ryan L. and O'Brien N.M. (2007). Xanthophyll carotenoids are more bioaccessible from fruits than dark green vegetables. Nutr. Res. 27, 258-264.

Olson J.A. (1994). Absorption, transport, and metabolism of carotenoids in humans. Pure Appl. Chem. 66, 1011-1016.

Olson J.A. and Krinsky N.I. (1995). The colorful, fascinating world of the carotenoids: important physiologic modulators. FASEB J. 9, 1547-1550.

Paiva S.A.R. and Russell R.M. (1999). Beta-carotene and other carotenoids as antioxidants. J. Am. Coll. Nutr. 18, 426-433.

Palozza P., Serini S. and Calviello G. (2006). Carotenoids as modulators of intracellular signaling pathways. Curr. Signal. Transd. T. 1, 325-335.

Palozza P., Sestito R., Picci N., Lanza P., Monego G. and Ranelletti F.O. (2008). The sensitivity to β-carotene growth-inhibitory and proapoptotic effects is regulated by caveolin-1 expression in human colon and prostate cancer cells. Carcinogenesis 29, 2153-2161.

Palozza P., Colangelo M., Simone R., Catalano A., Boninsegna A., Lanza P., Monego G. and Ranelletti F.O. (2010). Lycopene induces cell growth inhibition by altering mevalonate pathway and Ras signaling in cancer cell lines. Carcinogenesis 31, 1813-1821.

Park R.S. (1996). Absorption, metabolism and transport of carotenoids. FASEB J. 10, 542-551.

Pestell R.G, Albanese C., Reutens A.T., Segall J.E., Lee R.J. and Arnold A. (1999). The cyclins and cyclin-dependent kinase inhibitors in hormonal regulation of proliferation and differentiation. Endocr. Rev. 20, 501-534.

Polakis P. (2000). Wnt signaling and cancer. Genes Dev. 14, 1837-1851.

Reynolds A.R. and Kyprianou N. (2006). Growth factor signalling in prostatic growth: significance in tumor development and therapeutic targeting. Br. J. Pharmacol. 147, S144-S152.

Riboli E. and Norat T. (2003). Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am. J. Clin. Nutr. 78, 559S-569S.

Rodriguez-Amaya D.B. (2001). A guide to carotenoid analysis in foods. ILSI Press. Washington DC.

Rodriguez-Amaya D.B. and Kimura M. (2004). HarvestPlus handbook for carotenoid analysis. HarvestPlus Technical Monograph 2. International Food Policy Research Institute and International Center for Tropical Agriculture. Washington DC and Cali.

Sahu B. (2012). Genome-wide analysis of androgen receptor function in prostate cancer. Academic Dissertation. University of Helsinki, Helsinki-Finland. 89p.

Schmitt C.A., Fridman J.S., Yang M., Baranov E., Hoffman R.M. and Lowe S.W. (2002). Dissecting p53 tumor suppressor functions *in vivo*. Cancer Cell 1, 289-298.

Sharoni Y., Danilenko M., Dubi N., Ben-Dor A. and Levy J. (2004). Carotenoids and transcription. Arch. Biochem. Biophys. 430, 89-96.

Sharoni Y., Danilenko M., Walfisch S., Amir H., Nahum A., Ben-Dor A., Hirsch K., Khanin M., Steiner M., Agemy L., Zango G. and Levy J. (2009). Role of gene regulation in the anticancer activity of carotenoids. Pure Appl. Chem. 2009. 74, 1469-1477.

Sherr C. and Roberts J. (1999). CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev. 13, 1501-1512.

Shiau A., Mobarhan S.A. and Stacewicz-Sapuntzakis M. (1990). Assessment of the intestinal retention of beta-carotene in humans. J. Am. Coll. Nutr. 9, 533.

Smith G.D., Gunnell D. and Holly J. (2000). Cancer and insulin-like growth factor-I: a potential mechanism linking the environment with cancer risk. BMJ 321, 847-848.

Soares N.C.P, Teodoro A.J., Oliveira F.L., Santos C.A.N., Takiya C.M., Saback O. Jr, Bianco M., Palumbo A. Jr, Nasciutti L.E., Ferreira L.B., Gimba E.R.P. and Borojevic R. (2013). Influence of lycopene on cell viability, cell cycle, and apoptosis of human prostate cancer and benign hyperplastic cells. Nutr. Cancer. 65, 1076-1085.

Srougi M. and Simon S.D. (1996). Câncer urológico, 2nd ed. Ed. Platina. São Paulo. Brazil.

Stahl W., Schwarz W., Sundquist A.R. and Sies H. (1992). Cis-trans isomers of lycopene and β-carotene in human serum tissues. Arch. Biochem. Biophys. 294, 173-177.

Tanaka T. and Suzuki R. (2007). Inflammation and cancer. In: Cancer: disease progression and chemoprevention. Tanaka T. (ed). Research Signpost: Kerala-India.

Tanaka T., Shnimizu M. and Moriwaki H. (2012). Cancer chemoprevention by carotenoids. Molecules 17, 3202-3242.

Tang F-Y. (2012). The silver bullet for cancer prevention: Chemopreventive effects of carotenoids. BioMedicine 2, 117-121.

Tang G., Gu X., Hu S.S., Xu Q., Qin J., Dolnikowski G.G., Fjeld C.R., Gao X., Russell R.M. and Yin S. (1999). Green and yellow vegetables can maintain body stores of vitamin A in Chinese children. Am. J. Clin. Nutr. 70, 1069-1076.

Tang W., Zeve D., Suh J.M., Bosnakovski D., Kyba M., Hammer R.E., Tallquist M.D. and Graff JM. (2008). White fat progenitor cells reside in the adipose vasculature. Science 322, 583-586.

Tanumihardjo S.A., Furr H.C., Amedee-Manesme O. and Olson J.A. (1990). Retinyl ester (Vimamin A ester) and carotenoid composition in human liver. Int. J. Vitam. Nutr. Res. 60, 307-313.

Tarantilis P.A., Morjani H., Polissiou M. and Manfait M. (1994). Inhibition of growth and induction of differentiation of promyelocytic leukemia (HL-60) by carotenoids from Crocus sativus L. Anticancer Res. 14, 1913-1918.

Thyagarajan B., Meyer K., Smith L.J., Beckett W.S., Williams O.D., Gross M.D. and Jacobs D.R. Jr (2011). Serum carotenoid concentrations predict lung function evolution in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am. J. Clin. Nutr. 94, 1211-1218.

Trejo-Solís C., Pedraza-Chaverrí J., Torres-Ramos M., Jiménez-Farfán D., Salgado A.C., Serrano-García N., Osorio-Rico L. and Sotelo J. (2013). Multiple molecular and cellular mechanisms of action of lycopene in cancer inhibition. Evidence-based complementary and alternative medicine. 2013, 705121.

Trosko J.E., Chang C.C., Upham B.L. and Tai M.H. (2004). Ignored hallmarks of carcinogenesis: stem cells and cell-cell communication. Ann. N.Y. Acad. Sci. 1028, 192-201.

Vaishampayan U., Hussain M., Banerjee M., Seren S., Sarkar F.H., Fontana J., Forman J.D., Cher M.L., Powell I., Pontes J.E. and Kucuk O. (2007). Lycopene and Soy Isoflavones in the Treatment of Prostate Cancer. Nutr Cancer 59, 1-7.

van het Hof K., Gartner C., West C.E. and Tijberg L.B.M. (1998). Potential of vegetable processing to increase the delivery of carotenoids to man. Int. J. Vit. Nutr. Res. 68, 366-370.

Venier N.A., Colquhoun A.J., Fleshner N.E., Klotz L.H. and Venkateswaran V. (2012). Lycopene enhances the anti-proliferative and pro-apoptotic effects of capsaicin in prostate cancer *in vitro*. J. Cancer Ther. Res.

Vine A.L. and Bertram J.S. (2005). Upregulation of connexin 43 by retinoids but not by non-provitamin A carotenoids requires RARs. Nutr. Cancer 52, 105-113.

Voskuil D.W., Vrieling A., van't Veer L.J., Kampman E. and Rookus M.A. (2005). The insulin-like growth factor system in cancer prevention: potential of dietary intervention strategies. Cancer

Epidemiol. Biomarkers 14, 195-203.
Voutilainen S., Nurmi T., Mursu J. and Rissanen T.H. (2006). Carotenoids and cardiovascular health. Am. J. Clin. Nutr. 83, 1265-1271.
Waart F.G., Schouten E.G., Stalenhoef A.F.H. and Kok F.J. (2001). Serum carotenoids, a-tocopherol and mortality risk in a prospective study among Dutch elderly. Inter. J. Epidemiol. 30, 136-143.
Wang A. and Zhang L. (2007). Effect of lycopene on proliferation and cell cycle of hormone refractory prostate cancer PC-3 cell line. J. Hyg. Res. 36, 575-578.
Wei C.J., Xu X. and Lo C.W. (2004). Connexins and cell signaling in development and disease. Annu. Rev. Cell. Dev. Biol. 2, 811-838.
Wilkinson S. and Chodak G.W. (2003). Critical review of complementary therapies for prostate cancer. J. Clin. Oncol. 21, 2199-2210.
Yasui Y., Hosokawac M., Mikamic N., Miyashitac K. and Tanaka T. (2011). Dietary astaxanthin inhibits colitis and colitis-associated colon carcinogenesis in mice via modulation of the inflammatory cytokines. Chem-Biol. Interact. 193, 79-87.

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