

## Dietary terpenoids and prostate cancer chemoprevention

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## 1. ABSTRACT

Cancer chemoprevention by phytochemicals may be one of the most feasible approaches for cancer control. Phytochemicals obtained from vegetables, fruits, spices, teas, herbs and medicinal plants, such as terpenoids and other phenolic compounds, have been proven to suppress experimental carcinogenesis in various organs in pre-clinical models. Recent studies have indicated that mechanisms underlying chemopreventive potential may be a combination of antioxidant, anti-inflammatory, immune-enhancing, and hormone modulation effects, with modification of drug metabolizing enzymes, influence on cell cycle and cell differentiation, induction of apoptosis, suppression of proliferation and angiogenesis playing roles in the initiation and secondary modification stages of neoplastic development. Specific features of prostate cancer, such as high prevalence and long latency period provides ample opportunities for chemopreventive agents to work at various stages of disease progression. Finally, suitable populations with appropriate risk factors, including the presence of pre-malignant lesions and genetic predispositions, need to be well characterized for future chemopreventive interventions. Here we review naturally occurring dietary terpenoids as useful agents for prostate cancer chemoprevention with reference to their classes and sources.

## 2. INTRODUCTION

It is estimated that 218,890 new cases of prostate cancer will be diagnosed in the United States in the year 2007. This makes prostate cancer the number one cancer diagnosis for men for the second year in a row, accounting for 29% of all new cancers. Besides, diagnosis of new cases, approximately, 27,050 men will die of prostate cancer this year which is down about one percent from 2006, but still contributes to 9% of total cancer-related deaths in American men (1). This continued decrease in deaths can hopefully be attributed in part to higher long term success in prostate cancer treatments and early screening for diagnosis. Prostate cancer is an important target for chemoprevention because of its long latency and high prevalence (2, 3). Surgery, radiotherapy, and brachytherapy are potentially curative treatments for localized prostate carcinoma, when watchful waiting is not an option. Hormonal therapies also known as 'androgen deprivation therapy' reduces the testosterone levels which drive prostate cancer cells to multiply are usually effective initially, but given enough time, hormone refractory disease eventually emerges (4, 5). This is a common and deadly form of the disease, lacks curative options and is the main cause of prostate cancer-related mortality. The only treatment with a demonstrated survival benefit is docetaxel, which lengthens the life of patients with a mean of less than

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3 months, despite often grueling side effects (6). Limited options for the management of prostate cancer and its increasing incidence necessitate search for novel preventive approaches for this disease. One such approach is through chemoprevention, a means of cancer management by which the occurrence of the disease can be entirely prevented, slowed, or reversed by the administration of one or more naturally occurring and/ or synthetic compounds, as an alternative to treatment of cancer cases after clinical symptoms have appeared (2, 3). Therefore, ultimate goal of cancer prevention is preferably to live without cancer or with cancer without suffering from symptoms until the natural termination of life (7, 8).

### 3. CANCER CHEMOPREVENTION

Cancer can be prevented by either avoiding life style-related risk factors such as the smoking habit, a high-fat western diet, physical inactivity and carcinogen containing foods, or alternatively by increasing exposure to beneficial influences, including intake of chemopreventive agents (2, 3, 9-13). The latter may be particularly practical because chemopreventive agents can be taken as supplements or by modulation of the current diet status (13). One can envisage subjects for cancer chemoprevention falling into two groups, one at high-risk of cancer because of the presence of precancerous lesions or predisposing conditions, and the other being the apparently healthy general population. Given difficulties in ensuring that the test compound will not have any toxicity besides proven efficacy and convenience for use in the long term, the practical aim of chemoprevention, for the present, should best be focused on 'high-risk' groups. Furthermore, there are advantages with application of natural compounds so that regulatory approval can be facilitated. Two basic concepts underlie in cancer chemoprevention: the multi-step nature of cancer development and field carcinogenesis. The development of cancer occurs over years and involves multiple genetic and phenotypic alterations that lead to invasive cancer. Chemoprevention is based on the premise that intervention is possible during the many steps of this process (2, 3, 13, 14).

### 4. CANCER: A THREE STEP MODEL

Based on animal model studies, carcinogenesis has been broadly divided into three phases: initiation, promotion, and progression. In initiation, a carcinogen interacts with DNA, producing a fixed mutation. The specific molecular change depends on the carcinogen and can be influenced by a number of factors, including the rate and type of carcinogenic metabolism and the response of the DNA repair function. During promotion, the initiated cells proliferate. This stage occurs over a long period and can be altered by chemopreventive agents and affect growth rates (15). Progression is the phase between a pre-malignant lesion and the development of invasive cancer. During this stage, genetic and phenotypic changes occur, with the rate of progression based on the rate of genetic mutation and cell proliferation (16-19). Carcinogenesis is the concept that, in patients at risk, extensive, multi-focal, genetically distinct pre-malignant and malignant lesions

can occur within the whole carcinogen-exposed region. The classical example is exposure of the upper aero-digestive tract and lungs to the carcinogenic effects of tobacco (20). The finding of one neoplasm in the exposed area provides evidence for the presence of multiple pre-malignant lesions of independent origin (21). In this setting, lesion-specific therapy is insufficient; interventions that prevent the promotion and progression of unrecognized lesions are needed. Thus chemopreventive agents aim to directly modulate specific steps in the carcinogenic process, block mutagenic carcinogens, prevent DNA damage by free radicals, suppress epithelial cell hyper-proliferation, and/or modulate epithelial cell differentiation and apoptosis. The molecular targets of these agents include cell signaling, cell-cycle regulators, and survival/apoptotic molecules, which are implicated in uncontrolled cancer growth and progression. Furthermore, angiogenic and metastatic targets, including vascular endothelial growth factor (VEGF), hypoxia-inducing factor (HIF)-1 $\alpha$ , matrix metalloproteinases (MMPs), and urokinase-type plasminogen activator (uPa) are also modulated by many chemopreventive agents to suppress the growth and invasive potential of cancer (17, 18). In contrast, chemotherapy is the use of specific drugs that can destroy cancer cells. Chemoprevention differs from cancer treatment in that the individuals most appropriate for chemopreventive intervention are generally healthy people at 'high-risk' for developing the specific cancer who have not contracted the disease. However, most healthy individuals never contract the clinically evident disease; thus, for practical reasons (i.e. achievable sample sizes, duration of follow-up) chemoprevention trials have often focused on individuals with precancerous lesions or with history of previously treated cancers (secondary prevention). Such individuals may already have cancer that has not been diagnosed and are actually receiving cancer treatment rather than cancer prevention. Drugs developed to treat cancer are fundamentally different from those developed to prevent it. Because some subjects receiving chemoprevention are both symptom- and disease- free, toxic drugs are not nearly as acceptable in this group compared with cancer patients who are receiving treatment to save or extend their lives. Also, preventive agents are often taken for long periods of time to produce desired effects. An ideal chemopreventive agent should be inexpensive, safe, and well tolerated with long-term administration, and effective in preventing cancer without compromising with the quality of life (3). The main goal of administering a chemopreventive agent is to prevent the development of cancers.

### 5. CANCER CHEMOPREVENTION WITH DIETARY AGENTS

The importance of developing totally new classes of chemopreventive agents is stressed, with particular emphasis on the bioactive agents derived from vegetables, fruits, spices, teas, herbs and medicinal plants. The need for new agents with novel mechanisms of action to prevent cancer is perhaps the most urgent need in the entire field of chemoprevention. Although 'proof of principle' of chemoprevention has been clearly demonstrated, in both

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animal and clinical studies, none of the existing chemopreventive agents is ideal, either because of lack of efficacy and potency or because of toxic side effects that preclude widespread, long term use. During the last decade several bioactive agents are identified from the diets which are being developed as chemopreventive agents (9-11). For example, glucobrassicin and glucoraphanin from broccoli, Chinese cabbage, radish and watercress; sinigrin from brussels sprouts, cabbage and cauliflower are being developed as chemopreventive agents. The isothiocyanates formed from indole glucosinolates, indole-3-carbinol, indole-acetonitrile, thiocyanate and 3, 3'-diindolylmethane and sulforaphane act as chemopreventive agents (22). These agents favorably modifying carcinogen metabolism *via* selective alteration of cytochrome P450 enzyme involved in carcinogen metabolic activation and induction of phase II enzymes. Flavanoids including flavones (apigenin, luteolin), flavanols (quercetin, kaempferol), flavanones (hesperetin, naringenin), flavanols (epigallocatechin, epigallocatechin-3-gallate), anthocyanins (cyanidin, delphinidin) and isoflavones (genistein, daidzein) (23) has been shown to possess free radical scavenging properties and modulate COX-2, inhibit EGFR, IGF-RI and NF- $\kappa$ B signaling (24). Phytoestrogens compete with endogenous estrogens for binding to estrogen receptor. Therefore, they may have beneficial effects in prevention of steroid hormone-dependent cancers such as breast and prostate cancer. There are evidences that different berries such as black raspberries, blackberries and strawberries inhibit carcinogen-induced malignancy in animal models. Some of the known chemopreventive agents in berries include vitamin C, E and folic acid; small amount of calcium and selenium,  $\beta$ - and  $\alpha$ -carotene, polyphenols such as ellagic acid, ferulic acid, p-coumaric acid, quercetin, several anthocyanins. It has been observed that they could inhibit the growth of pre-malignant cells through down-regulation of COX-2 and also expression of other genes associated with tumor development such as iNOS and VEGF (25). Reverastrol, a phytoalexin present in grapes, berries and peanuts suppress the activity of COX-2, causes cell cycle arrest and pro-apoptotic cell death in many types of cancer cells (26). Tea contains large quantities of polyphenolic compounds known as catechins. The leading catechins in green tea are epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) whereas black tea contains thearubigin and theaflavins. Several studies based on cell culture and animal models have demonstrated the cancer preventive role of tea associated with the inhibition of c-fos and cyclin D1 promoter activity, decrease Bcl-XL, inhibition of VEGF, p53 stabilization and downregulation of NF- $\kappa$ B activation (27, 28). The bioactive ingredients of different spices such as curcumin, gingerol, paradol, and capsaicin are the members of vanilloid compounds possessing chemopreventive activities (29). Similarly, terpenoids are an extensive group of natural compounds and from the nutritional standpoint, monoterpenes, limonene, menthol, perillyl alcohol, diterpenes, retinoids and tetraterpenes include carotenoids provide health benefits in decreasing the risk of certain diseases including cancer (30). The triterpenoids, oleanolic acid and ursolic acid are commonly present in many plant species and

exhibit anti-inflammatory and anti-carcinogenic activities (31). Structure-activity studies among several oleanolic and ursolic acid derivatives have identified 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid and related compounds as potent anti-inflammatory compounds that inhibit growth and induce apoptosis in several cancer cells and tumor types (32).

## 6. PROSTATE CANCER CHEMOPREVENTION

The criteria for selecting chemopreventive agents that are ultimately evaluated in clinical trials can rely on leads from several distinct areas of investigation. Epidemiologic, experimental and basic mechanistic carcinogenesis data in all can provide rationale for pursuing the development of a particular pharmaceutical agent, micronutrient, or dietary substance (33, 34). There is strong evidence that high intakes of vegetables, fruits, and whole grains are associated with reduced cancer risk. Comprehensive reviews of case control and prospective cohort studies found that the relationship between high vegetable, fruit, spices, teas, grains intake and reduced cancer risk (35, 36). The epidemiologic data from dietary questionnaires in the Health Professional's Follow-up Study suggested that consumption of tomato products was one of the few discernable food use patterns to be strongly associated with a decreased risk of prostate cancer development. Other case control studies provide support that use of soy products and green and black teas often decrease the risk of prostate cancer (37). The beneficial effect of vegetables, fruits and whole grains may be due to their individual and combined effects of their constituents, including fiber, micronutrients, and phytochemicals.

## 6. TERPENOIDS: A CLASS OF CANCER CHEMOPREVENTIVE AGENT

Terpenoids are natural constituents of plants and of invertebrate and vertebrate animals. The terpenoids are the most diverse group of plant substituents that play a variety of roles in many different plant species. All terpenes are constructed from isoprenoid units by biochemically unusual pathways involving highly reactive intermediates. They mostly occur as monoterpenoids (essential oils), diterpenoids, triterpenoids, sesquiterpenoids (phytosterols, saponins), and tetraterpenoid carotenoids (38). All are related by being derived from a common isopentenyl precursor. The distributional patterns and functions of terpenoids are as diverse as the chemical structures. The importance of terpenes to plants relates to their necessity to fix carbon through photosynthetic reactions using photosensitizing pigments. A monoterpene contains ten carbons (two isoprene units); a sesquiterpene, fifteen carbons (three isoprene units); a diterpene, twenty carbons (four isoprene units), triterpenes (thirty carbons) are important structural components of plant cell membranes. Many plant pigments, including the yellow and red carotenoids, are tetraterpenes (forty carbons). Natural rubber is a polyterpene containing many isoprene units. The monoterpenes and sesquiterpenes are common components of the essential oils of herbs and spices (peppermint, lavender), of flower scents (rose), and of

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turpentine, derived from the resin of evergreen trees (38, 39). Animals have evolved to utilize these compounds for hormonal growth regulatory functions (vitamin A) and, as it is now being understood, the presence of these molecules in normal tissues also provides a measure of protection from certain diseases, especially those related to chronic damage and growth deregulation. Several hundred terpenoids have been reported to have chemopreventive activity, and promising agents and agent combinations are currently being evaluated clinically for cancer chemoprevention (40, 41). A list of dietary terpenoids which are being evaluated for their anti-cancer activity is listed in Table 1.

### 6.1. Monoterpenes

Monoterpenes are the focus of much investigation in the areas of both cancer prevention and therapy. Cancer prevention, inhibition, and regression are the most noteworthy attributes of the monoterpenes. D-Limonene, the most abundant monocyclic monoterpene present in orange peel oil has shown to inhibit neoplasia in animal models (42, 43) and cell growth *in vitro* (44). D-limonene and perillyl alcohol (POH) have been shown to be chemopreventive against various types of human cancers (45-48). D-limonene is a monocyclic monoterpene with POH a metabolite of D-limonene, being its hydroxylated form. There are a number of synonyms for limonene, include the following: 1, 8(9)p-Menthadiene; 1-methyl-4-(1-methylethenyl) cyclohexene; 1-methyl-4-isopropenyl-1-cyclohexene; alpha-limonene; dipentene; limonene; pmentha-1,8-diene. They are found in essential oils of many plants including lemons, oranges, grapefruit, caraway, dill, bergamot, peppermint, spearmint, grasses and tomatoes. They are also associated with vegetables and some evergreen trees. POH is often distilled from lavender, found in cherries, mint, celery seeds and can be produced synthetically. It is typically used as flavoring agents, food additive, and fragrance and has been found to be a major volatile component of mother's milk (49). D-limonene has different metabolites for different animals. In humans, the three major metabolites after an oral dosage are perillic acid, dihydroperillic acid, and limonene-1, 2-diol. It is thought that the metabolic precursors of the first two are perillyl alcohol and perillyl aldehyde (50). D-limonene is found in orange juice at concentrations ranging from 10-100 ppm and chewing gum, which contains up to 2,300 ppm (51). D-Limonene has been shown to be effective anti-cancer agent (52-54). Studies from our laboratory have shown that treatment of human prostate cancer cells with D-limonene cause inhibition of cell growth, decrease in mitochondrial activity leading to cell death which is independent of androgen association and p53 status (55). More recent studies have demonstrated that some derivatives of D-limonene increased the anti-proliferative effects in human prostate cancer cells *via* activation of ERK pathway and induction WAF1/p21 leading to cell cycle arrest (56). Similar to D-Limonene, perillyl alcohol is effective in prostate cancer. Studies have shown that perillyl alcohol caused sensitization of hormone insensitive prostate cancer cells and kill them. Exposure of these cells to perillyl alcohol induced a transient G2/M arrest and enhanced the expression of the membrane bound form of

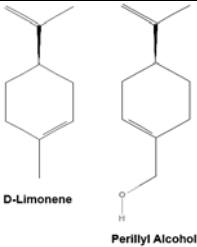
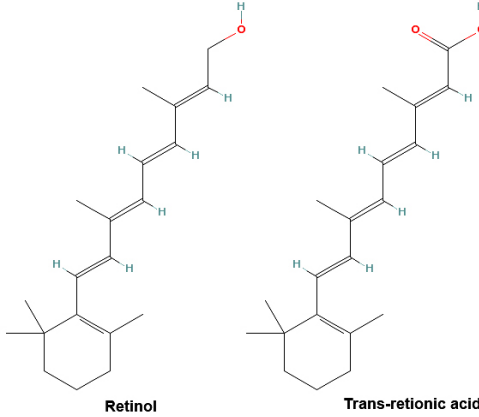
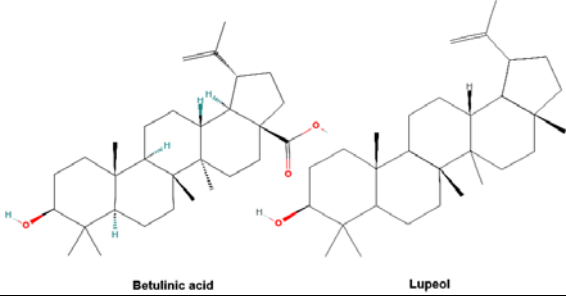
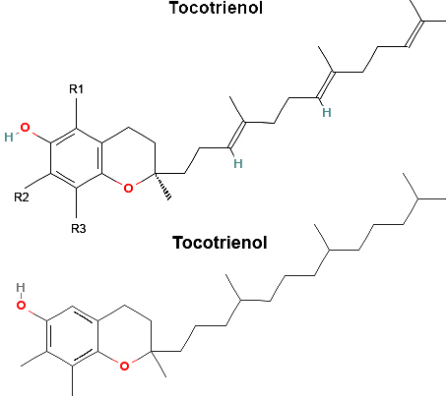
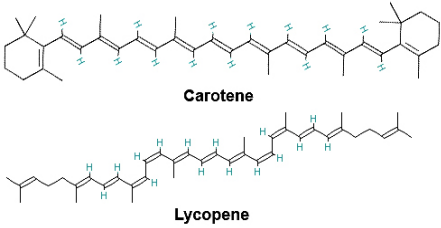
the Fas ligand and sensitized the cells to Fas-mediated apoptosis (57). Another recent study has demonstrated that perillyl alcohol can attenuate androgen receptor (AR)-mediated action in androgen sensitive prostate cancer cells by inhibiting AR gene expression and activation of c-Jun, which represses the expression and function of AR (58). Human phase I clinical trial results, for POH, used in the treatment of advanced malignancies in humans have been reported (59). Dosages ranging from 800-2400 mg/m<sup>2</sup>/dose were assayed for tolerability. The main toxicity was gastrointestinal and included nausea and vomiting, anorexia, unpleasant taste, satiety, and eructation. The main metabolites were perillic acid and dihydroperillic acid. The evidence of the POH efficacy in prostate cancer patients has been reported. POH was administered orally to patients with metastatic androgen-independent prostate cancer at 1200 mg/m<sup>2</sup>/dose four times daily and continued until disease progression or development of unacceptable toxicity. The disease was shown to stabilize for 6 months, although no objective tumor response was observed (60).

### 6.2. Diterpenes

Among diterpenes, vitamin A or retinol is the most important compound which is found in animals. The term retinoids refers to all analogs of retinol. Retinoids, a class of over 3000 natural derivatives and synthetic analogs of vitamin A, are powerful modulators of epithelial carcinogenesis (61). About 1500 different retinoids have been synthesized by modifying the ring structure, the side chain, or the terminal group of the molecule in attempts to obtain greater anti-carcinogenic activity and less toxicity. The naturally occurring retinoids include: retinol, the alcohol of vitamin A, retinoic acid, the carboxylic acid, retinal, the aldehyde, and 13-cis-retinoic acid, an isomer of retinoic acid. Retinoids, including vitamin A (retinol) and its active metabolite, retinoic acid play important roles in inhibiting cell proliferation, and promoting morphogenesis and differentiation (62, 63). Retinoids may be particularly effective in reversing pre-malignant epithelial lesions in the lung, skin, head and neck (64). Considerable interest has developed in the application of retinoids as chemopreventive agents for human cancer (65, 66). Most actions of retinoids are believed to be mediated by its nuclear receptors, which function as ligand-activated transcription factors (67). There are two types of retinoid receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Heterodimers of the RARs and RXRs bind to a specific DNA promoter sequence, termed the retinoic acid response element, and regulate gene transcription (68, 69). RXRs can also form homodimers and activate the retinoid X response element or form heterodimers with other members of the steroid receptor superfamily, thus serving in multiple regulatory functions in different signaling pathways (70). Retinoids provide resistance to chemical carcinogenic challenge, while vitamin A deficiency results in increased sensitivity to induce cancer (71). Vitamin A deficiency in humans has been associated with an increased incidence of cancer of anatomical sites (72). A low intake of vitamin A in cohort studies was also associated with an increased risk of cancer in the prostate (73, 74). Numerous studies have also shown that retinoids can prevent or reduce the incidence of

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**Table1.** Dietary terpenoids tested in prostate cancer

Terpenoids	Chemical Structure	Source	Ref
<b>Monoterpenes</b> D-limonene Perillyl Alcohol	 <p>D-Limonene</p> <p>Perillyl Alcohol</p>	Lemons, oranges, grapefruit, caraway, bergamot, peppermint, spearmint, dill, tomatoes	42
<b>Diterpenes</b> Retinol Trans-retinoic acid	 <p>Retinol</p> <p>Trans-retinoic acid</p>	Carrot, spinach, pumpkin, broccoli, mango, papaya, cherry, tomato, corn, orange, cabbage, watermelon, lettuce	61-63
<b>Triterpenoids</b> Betulinic Acid Lupeol	 <p>Betulinic acid</p> <p>Lupeol</p>	Olive, mango, strawberry, grapes, figs	88, 89, 93, 99
<b>Terpenoid</b> Chromanols Tocotrienols Tocopherols	 <p>Tocotrienol</p> <p>Tocotrienol</p> <p>Tocopherol</p>	Almonds, peanut oil, walnuts, palm oil	100, 108, 110
<b>Carotenoids</b> Carotene Lycopene	 <p>Carotene</p> <p>Lycopene</p>	Tomatoes, orange, carrot, peas, sprouts, green beans, corn	125, 128

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prostate cancer in various animal models. For example, both the synthetic retinoid N-(4-hydroxyphenyl) retinamide (4-HPR) and 9-cis RA have been shown to prevent cancer in animal models of prostatic carcinogenesis (75). In human prostate cancer cell lines, RXR $\alpha$  protein was decreased relative to noncancer prostate cell lines, and a reduction of cell growth or increased susceptibility to apoptosis was demonstrated with increases in the level of RXR $\alpha$  in RXR $\alpha$ -transduced prostate cancer cells (76). In a variety of studies using cultured human prostatic cancer cells, retinoids have been shown to inhibit tumor cell growth. For instance, the growth of the androgen-sensitive LNCaP cell line (77) and androgen-independent prostatic cancer cell lines (78), as well as primary cultures from prostatic adenocarcinoma, can be inhibited by retinoids. Retinoids can also inhibit the ability of these tumor cells to invade the extra-cellular matrix and induce apoptosis (79, 80). The mechanisms by which RA can induce growth inhibition of prostate cancer cell lines are unclear, but studies have implicated apoptosis, activation of retinoblastoma protein, and modulation of androgen receptor pathways (79-81). It has also been shown recently that the Bcl-2 protein is down-regulated by RA in prostatic cancer cells (82). The synthetic retinoid, fenretinide has been studied extensively as a chemopreventive agent against prostate cancer and exhibited chemopreventive activity (83). Retinoids used in clinical therapies exhibit potential toxicity (84, 85). All-trans-retinoic acids are relatively non-toxic with few serious adverse reactions compared to anticancer chemotherapy drugs; however, it does share adverse effects common to other retinoids (84-86).

### 6.3. Triterpenoids

Triterpenoids form a group of natural substances which includes steroids and consequently sterols (87-89). Squalene is the immediate biological precursor of all triterpenoids. The large groups of steroids including sterols are present in very small amounts in bacteria but at large amounts in plants and animals while the hopanoids are very abundant in prokaryotes where they replace cholesterol (89). Triterpenoids have shown to possess anti-inflammatory and anti-carcinogenic properties (90, 91). Lup-20(29)-en-3 $\beta$ -ol (Lupeol), a triterpene found in fruits such as olive, mango, strawberry, grapes and figs, in many vegetables and in several medicinal plants, is used in the treatment of various ailments worldwide by native people (92, 93). Lupeol possesses strong antioxidant, anti-inflammatory, anti-arthritic, anti-mutagenic, and anti-malarial activity *in vitro* and *in vivo* systems acts as a potent inhibitor of protein kinases and serine proteases, and inhibits the activity of DNA topoisomerases II, a target for anticancer chemotherapy (92-96). It has been shown that Lupeol activates Fas receptor-mediated apoptotic machinery of LNCaP cells and inhibits the tumorigenesis of prostate cancer cells in animal model. A striking observation on the effect of Lupeol was that prostate cancer cells were highly sensitive to Lupeol-mediated loss of viability, and no such effect was observed in normal human prostate epithelial cells (97).

Betulinic acid is a pentacyclic triterpene isolated from the stem bark of *Betula alba*, and the studies show

that betulinic acid decreases the expression of VEGF and anti-apoptotic protein survivin in both prostate LNCaP cells and tumors (98). Studies from our laboratory has shown that betulinic acid selectively inhibit the proliferation of human prostate cancer LNCaP, DU-145 and PC-3 cells and effectively induces apoptosis associated with the cleavage of PARP and shift in Bax:Bcl-2 ratio in favor of cell death (99).

### 6.4. Terpenoid Chromanols

Tocotrienols and tocopherols (vitamin E) are terpenoid chromanols, tocotrienols possess the ability to stimulate the killing of cancer cells selectively through apoptosis in order to reduce cancer cell proliferation, while leaving normal cells unaffected (100). One of the mechanisms by which tocotrienols are thought to suppress cancer is related to the isoprenoid side-chain that makes them different from tocopherols (101). Isoprenoids are plant compounds that have shown to suppress the initiation, growth and progression of prostate cancer and many types of cancer in experimental studies (102, 103). They are common in almonds, peanut oil and walnuts, which may explain why diets rich in these foods have consistently been shown to reduce the incidence of cancer (104-107). Much of the broad involvement of vitamin E in human metabolism is due to its role as the body's primary lipid-soluble antioxidant. Tocopherols and tocotrienols are part of the body's highly effective defense system, without which life as we know it could not exist. This defense system consists of a network of antioxidants, interacting with and supporting each other. Antioxidants such as vitamin C, coenzyme Q10 and glutathione are needed for effective recycling of tocopherols and tocotrienols. The unique power of both tocopherols and tocotrienols is their ability to break the chain reaction of lipid peroxidation by neutralizing peroxy radicals to prevent the spread of free radical damage in cell membranes. Tocotrienols are more potent scavengers of the peroxy radical than  $\alpha$ -tocopherol and provide far better protection against lipid peroxidation (108, 109). Vitamin E is a generic term for at least eight structurally related molecules:  $\alpha$ -tocopherol ( $\alpha$ T),  $\beta$ -tocopherol,  $\gamma$ -tocotrienol ( $\gamma$ TE), and  $\delta$ -tocotrienol. Among them,  $\alpha$ T is the predominant form of vitamin E in plasma and tissues and is the form that has drawn most attention in the past. Benefit from  $\alpha$ T for cancer prevention has been suggested in some studies (110). Recently, studies have indicated that other forms of vitamin E appear to have unique properties that are not shared by  $\alpha$ T but may be important to human health (111). For instance,  $\gamma$ T, the major form of vitamin E in US diets, but not  $\alpha$ T, exhibits anti-inflammatory activities by inhibiting cyclooxygenase – catalyzed prostaglandin E2 formation in cell cultures and animals (112, 113).  $\gamma$ T, unlike  $\alpha$ T, is strongly nucleophilic and thus is more efficient than  $\alpha$ T in trapping reactive nitrogen species (114-116). Consistently, the administration of  $\gamma$ -enriched tocopherols significantly lowered C-reactive protein, a biomarker of inflammation, in haemodialysis patients (117). Recently, Helzlsouer *et al.* reported that men in the highest quintile of plasma concentration of  $\gamma$ T had a 5-fold reduced risk of prostate cancer compared with those in the lowest quintile. In the same study, significant protective effects of high concentrations of selenium and

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$\alpha$ T were observed only when  $\gamma$ T concentrations were high (118). Consistently,  $\gamma$ T and its metabolite, 2,7,8-trimethyl-2-( $\beta$ -carboxyethyl-6-hydroxychroman), is more potent than  $\alpha$ T in inhibiting prostate cancer cell growth by the down regulation of cyclins (119, 120).  $\gamma$ T dose-dependently inhibited proliferation of prostate cancer LNCaP and PC-3 cells but had no effect on prostate epithelial PrEC cells.  $\gamma$ T and its combination with  $\delta$ T induced apoptosis in LNCaP by interrupting *de novo* synthesis of sphingolipids (120). More recently our laboratory has demonstrated that tocotrienol-rich fraction of palm oil is capable of selectively inhibiting cellular proliferation and accelerating apoptotic events in prostate cancer LNCaP, DU145 and PC-3 cells, in comparison to normal human prostate epithelial PrEC and virally transformed normal human prostate epithelial PZ-HPV-7 cells (121). The tocotrienol-rich fraction offers significant promise as a chemopreventive and/or therapeutic agent against prostate cancer and it is becoming clear that individual vitamin E forms possess different chemical and biological activities and have distinct tissue distribution (122, 123). Combinations of different form of vitamin E may be superior to each alone. Growing evidence implies that selenium and vitamin E may decrease the risk of prostate cancer. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a randomized prospective double-blind study designed to determine whether selenium and vitamin E decrease the risk of prostate cancer in healthy men. A total of 32,400 men are planned to be randomized in SELECT. SELECT is the second large-scale, population based, phase III, randomized controlled trial which directly test the effect of these agents alone and combination on the incidence of prostate cancer in North American males study of chemoprevention for prostate cancer with final results anticipated in 2013 (124).

### 6.5. Carotenoids

Carotenoid group include beta-carotene, alpha-carotene, lycopene, lutein, astaxanthin, cryptoxanthin and zeaxanthin (125). Carotenoids belong to the category of tetraterpenoids, derived from a 40-carbon polyene chain, which could be considered the backbone of the molecule. The hydrocarbon carotenoids are known as carotenes, while oxygenated derivatives of these hydrocarbons are known as xanthophylls. Beta-carotene is a tetraterpenoid distributed widely throughout the plant kingdom and is the predominant pigment in orange-flashed melon (*Cucumis melo* L) varieties (126). Interest in beta-carotene as a potential anti-cancer agent established in the 1980s from the results of both case-control and cohort studies showing a consistent association for foods high in beta-carotene and reduced risk of prostate cancer (127). They possess antioxidant action as one of the mechanism for their cancer preventive effects. Tomatoes are the major source of lycopene commercially. Although lycopene is the most abundant carotenoids in tomatoes, they also contain other potentially beneficial carotenoids such as alpha-carotene, beta-carotene, lutein, phytoene, and phytofluene (128). Studies confirmed that increased serum levels of lycopene, the carotenoid pigment present in large amounts of tomatoes, were more highly correlated to decreased prostate cancer risk than were levels of other circulating,

diet derived carotenoids (129). It has been shown that lycopene is one of the most potent natural antioxidant. A case-control study indicated that the consumption of tomato products reduces the risk of prostate cancer and lycopene is one of the compounds in raw and processed tomato products that may contribute to a reduced risk of prostate cancer, other carotenoids and phytochemicals in tomato products may be synergistically responsible for the health benefits (130, 131). One 6-year, prospective, epidemiological study of approximately 47,000 men, the Health Professional Follow-up study (HPFS), concluded that 2 to 4 servings per week of raw tomatoes significantly reduced the risk of prostate cancer by 26% compared to no servings per week. Additionally, eating tomato products such as pizza and tomato sauce 2-4 times per week significantly reduced the risk by 15% and 34%, respectively, compared to not eating these foods (132). A clinical trial of 26 prostate cancer patients demonstrated supplementation with a tomato oleoresin extract (as Lyc-O-Mato, from LycoRed-Biodar, New York), which contained 30 mg of lycopene, reduced tumor size and made less involvement of surgical margins and/or extra prostate tissues with cancer less than in the control group (133). It has been suggested that the antioxidant carotenoid and that the free radical scavenging activity of these compounds may protect cells against oxidative mutagenesis. Another clinical study which randomly assigned 32 prostate cancer patients to a tomato-based diet for three weeks, noted those in the treatment group had a 15.5% reduction in prostate specific antigen (PSA, a marker of prostate cancer), as well as reductions of several other markers for prostate cancer (134). Although the role of all carotenoids in humans has yet to be fully determined, 25 carotenoids and 9 metabolites have been identified and characterized in human serum and other organs including prostate (135). Tomato and its products contain primarily all-trans-lycopene (79-91%); however, cis-lycopene accounts for 79-88% of total lycopene in malignant and benign prostate tissues (136). *In vitro* experimentation demonstrated that *cis* lycopene is absorbed more readily than all-trans-lycopene. The role of *cis* versus *trans* lycopene in human physiology has not yet been determined (135, 136). Two other studies concluded that dietary intervention and supplementation with 15 mg lycopene and smaller quantities of other tomato carotenoids, including phytoene, phytofluene,  $\zeta$ -carotene, and  $\gamma$ -carotene twice daily positively altered serum markers of prostate cancer progression (137, 138). Serum prostate specific antigen (PSA) levels, a marker of tumor activity, decreased in both trials, and tomato oleoresin supplementation altered biomarkers of cell growth and differentiation in the one study in which it was tested. Cancer cells show a decrease in cellular differentiation, and are sometimes 'revert back' to a more undifferentiated, embryonic-type cell. If tomato carotenoids can increase cellular differentiation, they may be important in the treatment of prostate cancer.

## 7. MODULATION OF INTERMEDIATE AND ENDPOINT BIOMARKERS BY TERPENOIDS

Study of markers of risk and surrogate end-point biomarkers holds great promise for cancer

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chemoprevention (139-141). The criteria for biomarker relevance are that they must be differentially expressed in normal and high-risk tissue, be closely linked to the casual pathway for cancer, be modified by the chemopreventive agent and with a shorter latency than cancer, and, finally, be assayed easily and with quantitative reliability. Alterations in the levels of prostate specific antigen (PSA) and the various grades of PIN are considered to be the primary intermediate biomarkers for evaluating the efficacy of an agent and for identifying appropriate cohorts for chemoprevention studies (142). Studies reported in literature have shown that terpenoids have potential to modify certain proteins and transcription factors which could be used as intermediate and endpoint markers to evaluate the efficacy of the test compound. For example, RXR $\alpha$  is the major component of retinoid action whose inactivation leads to the development of preneoplastic lesions in the prostate whereas chemopreventive responses including induction of apoptosis in prostate cancer cells by retinoic acids appear to be transcriptionally regulated by RAR $\beta$  (143). Further, it has been demonstrated that gap junctional intercellular communication and Cx43 expression levels could be useful intermediate endpoints in prostate cancer chemoprevention trials, because they are decreased in prostate cancer cells (144). Therefore, chemopreventive agents modulating Cx43 expression and/or gap junctional intercellular communication would be of great interest. Retinoids and carotenoids are potent regulators of Cx43 and gap junctional intercellular communication. In particular, lycopene increases gap junctional intercellular communication by increasing expression of the gap junctional gene, Cx43. This action correlates strongly with the ability of lycopene and other carotenoids to suppress neoplastic transformation in cell culture systems. Upon restoring the gap junction proteins, functional communication was restored in human prostatic carcinoma cell lines, increased normal differentiation, reduced proliferation, and suppressed tumorigenicity. In recent epidemiological studies, relatively high plasma IGF-1 and low IGFBP-3 levels have been independently associated with greater risk of prostate cancer (145). Recent data show that lycopene administration to humans with prostate cancer significantly reduces serum IGF-1 levels. Additionally, lycopene produces changes in the expression of many proteins in prostate cancer chemoprevention processes, e.g. cyclins, and phase II detoxification enzymes. Furthermore,  $\gamma$ -tocopherol ( $\gamma$ T), the major form of vitamin E in diets, exhibits anti-inflammatory activities by inhibiting cyclooxygenase catalyzed prostaglandin E<sub>2</sub> formation in cell cultures and animals (146).  $\gamma$ T is strongly nucleophilic and thus is more efficient in trapping reactive nitrogen species. Consistently, administration of  $\gamma$ -tocopherols significantly lowered C-reactive protein, a biomarker of inflammation in dialysis patients (147). Similarly, cell death induced by vitamin E forms is linked to *de novo* synthesis of sphingolipids. Ceramide is the common intermediate for the formation of complex sphingolipids, including sphingomyelin and glucosphingolipids. Recently, ceramide has been proposed as a mediator in regulating stress response, particularly during apoptosis (148). In addition, other sphingolipid intermediates, such as sphingosine, sphingosine-1-

phosphate and dihydrosphingosine, have been shown to mediate cell survival (149). Vitamin E caused a large amount of dihydroceramide accumulation was observed before apoptosis, whereas total ceramide increased only when apoptosis was substantial. An increase in ceramide could be used as a potential biomarker for the vitamin E caused biological effects.

## 8. CONCLUSION

The future of terpenoid research remains open to innovation, with a specific need for emphasizing on important beneficial properties for human health. The biological role of terpenoids in the prevention and perhaps treatment of cancer and other chronic diseases are being studied and understood. Although the antioxidant properties of some terpenoids have been extensively studied, their role as an anticancer agent needs further investigation. The simple reason could be that tumors have many molecular targets, which function aberrantly, and therefore requires extensive research. The goal for the success of terpenoids in chemoprevention research is to evaluate bioavailability, metabolism, mechanism of action and safety of test agent in better devised tumor-specific risk model and/or high-risk cohorts, preclinical drug testing models (i.e. gene targeting/knockout models), and developing translational/mechanistic studies. Above all, diet modification, and food or nutritional extracts containing terpenoids with known anti-carcinogenic activity may be more acceptable to healthy populations with known genetic risk based upon gene-environment interactions. Because prostate carcinogenesis may span 20 years or more, clinicians and medical practitioners have potential opportunities to suppress the disease in its early, pre-malignant stages before clinical, invasive disease develops with various dietary terpenoid agents. Although some human clinical trials are beginning to be undertaken there is a great need for well designed human intervention studies that takes into consideration study designs including subject selection, endpoint measurement and the bioavailability of test agent in the target organs. Only through these measures we can increase our understanding and the important role played by dietary terpenoids with an attempt to make a meaningful impact in the prevention, treatment and increased survival of the patients at risk for prostate cancer.

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**Abbreviations:** DNA, Deoxyribonucleic acid; VEGF, vascular endothelial growth factor; HIF, hypoxia-inducing factor; MMPs, matrix metalloproteinases; uPa, urokinase-type plasminogen activator; IGF, insulin-like growth factor; COX, cyclooxygenase, EGFR, epidermal growth factor receptor; EC, epicatechin; EGC, epigallocatechin; ECG, epicatechin-3-gallate; EGCG, epigallocatechin-3-gallate; POH, perillyl alcohol; ERK, extracellular-regulated kinase; AR, androgen receptor; 4-HPR, N-(4-hydroxyphenyl) retinamide; RA, retinoic acid; PrEC, normal prostate epithelial cells; PARP, Poly (ADP-ribose) polymerase; T, tocopherol; TE, tocotrienol; SELECT, Selenium and Vitamin E Cancer Prevention Trial; Cx, connexin; PIN, prostatic intraepithelial neoplasia; PSA, prostate specific antigen; IGFBP, insulin-like growth factor binding protein

**Key Words:** Terpenoids; Cancer Chemoprevention; Biomarkers; Prostate Cancer, Neoplasia, Tumor, Review

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