Chemoprevention of Skin Cancer with Dietary Phytochemicals

BuHyun Youn and Hee Jung Yang
Pusan National University
Republic of Korea

1. Introduction

Cancer is responsible for a major cause of death in human. It is calculated that more than 11 million people are diagnosed with cancer worldwide (Jemal et al., 2009). Cancer arises through accumulation of multiple genetic alterations. In skin, UV radiation-induced gene mutations have been considered as a driving force of the skin carcinogenesis. Over the past 30 years, ozone depletion has induced increase in the level of UV-B radiation at the earth's surface. As a result, incidence of the skin cancer has been significantly increased, and it is recognized as a serious public health issue. Many researchers have studied mechanisms of UV-B radiation-induced skin cancer and strategies for skin cancer prevention and treatment. Among the various cancer therapies, chemoprevention is a pharmacological approach using natural, synthetic or biological agents that can prevent, inhibit and reverse the carcinogenic progression. Especially, dietary natural products in chemoprevention have been appreciated as credible components for the management of cancer. Epidemiological studies including more than 250 populations indicated that people who take five different kinds of fruits and vegetables a day showed about 50% decrease in cancer incidence and development than not or less eating plant foods. Based on accumulated researches, dietary plants have been believed to outstanding sources of the cancer preventive substances, and received considerable attention due to their various biological effects – anti-oxidant, anti-inflammatory and anti-carcinogenic functions. Therefore, chemoprevention by dietary phytochemicals has been regarded as a new, safety and efficiency strategy for cancer treatment.

This chapter gives a useful overview of recent studies in chemoprevention of skin cancer with dietary phytochemicals, and especially, focuses on UV-B radiation as a major factor of skin cancer and summarizes the UV-B radiation-induced skin carcinogenic mechanism.

2. Ultraviolet (UV) radiation-induced skin cancer and chemoprevention with dietary phytochemicals

Currently, skin cancer occurs at a rate of one in every six Americans (18%), and constitutes more than 30% of all newly diagnosed cancer patients in the world (Gloster et al., 1996; Aziz et al., 2005). The incidence and mortality in the skin cancer have rapidly increased worldwide because of an increase in the level of UV radiation at the earth's surface due to ozone depletion. The new strategies for skin cancer prevention and treatment are demanded, and chemoprevention has come to the fore.

2.1 Skin cancer

Epidemiological researches on the relation between diseases and death have demonstrated a significant death rate decrease in stroke, heart and infectious diseases within the United States, however, cancer mortality rate has not been changed in last 50 years (Aggarwal & Shishodia, 2006). In spite of a better understanding of the cancer mechanism and improvement of medical and pharmacological technology, the efficiency of cancer treatment has not progressed. In various types of cancer, especially, skin cancer has recognized a serious public health issue because of rapid increase of incidence, morbidity and mortality (Katiyar, 2011). There are over one million patients per year diagnosed skin cancer in the United States, and these account for 40% of all new cases of cancer diagnosed (Gloster et al., 1996; Johnson et al., 1998). Magnitude of the skin cancer is closely associated with exposure to UV radiation. Indeed, the high incidence of skin cancer is reported in some countries of the world such as Australia (particularly in Queensland) indicating serious destruction of ozone layer (Diepgen & Mahler, 2002).

Depending on the cellular origin, skin cancer is divided into two major categories – melanomas (melanocytic) and non-melanoma (epithelial) skin cancers (NMSCs), and NMSCs are subdivided into basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). Although both BCCs (the most common types of skin cancer, 80%) and SCCs are derived from the basal layer of the epidermis of the skin, BCCs and SCCs have a different feature – BCCs are characterized by slow growth and rare metastasis, whereas, SCCs have strong invasive and metastasis ability. Melanomas account for only 4% of skin cancer, but it is the main cause of death in patients with skin cancer (Marks, 1995).

2.1.1 UV radiation as a major risk factor for skin damages

Although various physical, chemical and environmental factors contribute to initiation and development of skin disorders – premature skin aging, wrinkling, scaling, dryness, mottled pigment abnormalities and skin cancer, UV radiation exerts the most detrimental effect in skin (Nichol & Katiyar, 2010; Katiyar, 2011).

Among invisible radiation emitted from the sun, UV radiation is classified into three categories according to its wavelength: UV-A (315-380 nm), UV-B (280-315 nm), and UV-C (190-280 nm) (Tyrrell, 1994). Because stratospheric ozone layer completely absorbs UV-C and mostly absorbs UV-B radiation, it has been considered that UV radiation reaching the surface of the earth is composed with 10% of the UV-B and 90% of the UV-A radiation. However, recently, the proportion of UV-B radiation at the surface of the earth has gradually increased due to depletion of the ozone layer (Latonen & Laiho, 2005). Although UV-B radiation accounts for a minor part of the sunlight arriving to the surface of the earth, previous studies have suggested that UV-B radiation could have the most cytotoxic and mutagenic effect to induce skin damage including skin cancer (Ichihashi et al., 2003).

2.2 UV-B radiation-induced cellular mechanisms in skin

UV-B radiation can cross the whole epidermis layer and portion of the dermis compartment in skin. UV-B radiation can induce both direct and indirect adverse biological effects including induction of DNA damage, oxidative stress, inflammation, immunosuppression, alterations in the extracellular matrix (ECM) and premature aging of the skin (Mukhtar & Elmets, 1996; Latonen & Laiho, 2005), which together perform critical functions in the generation and maintenance of UV-induced carcinogenesis (Hruza & Pentland, 1993). Actually, it is experimentally demonstrated that UV-B radiation can act as a strong carcinogen in mouse skin

models, indicating that UV-B radiation can affect tumor initiation, promotion and progression in skin carcinogenesis (Aziz et al., 2004; Armstrong & Kricker, 2001).

Previous studies have suggested that the most important effect on UV-B radiation is DNA damage. UV-B radiation can provoke DNA single (or double) strand breaks and indirect DNA damage through reactive oxygen species (ROS) production. DNA damage activates (oxidative) stress signal transduction and DNA checkpoint signaling, and also induces cell cycle arrest, DNA repair and apoptosis. Although skin has an elaborate defense mechanism to protect the skin from the radiation-induced cellular damages, chronic exposure to UV-B radiation attenuates the cutaneous defense processes leading to initiation and development of skin cancer (Nichols & Katiyar, 2010). Especially, failure of DNA repair is regarded as a crucial factor of UV-B radiation-induced skin cancer.

2.2.1 Direct DNA damage by UV-B radiation

Cells include photosensitive molecules called chromophores, which, upon receiving photons in UV radiation, transfer electrons to a higher energy state. Moreover, the chromophore could transmit its excited energy to other molecules, therefore, chromophore can induce the chain reactions. The major cellular chromophore for UV-B radiation has been demonstrated to DNA. Due to the aromatic rings in DNA bases, DNA efficiently and directly absorbs UV-B radiation. On the other hands, although UV-A radiation is the most abundant (90%) light at the surface of the earth and has cytotoxic effects, UV-A radiation exhibits gentle extent of the DNA damage than UV-B radiation, because DNA is not a suitable chromophore for UV-A radiation (Tyrrell, 1994). The most typical types of UV-B radiation-induced DNA damage are production of abnormal DNA adducts – cyclobutane pyrimidine dimers (CPDs) and (6-4) photoproducts ((6-4) PPs), which cross-link adjacent DNA bases. Also, UV-B radiation could generate DNA double (or single) strand breaks and DNA-protein cross-links. CDPs and (6-4) PPs change the DNA structure through helix-distorting and induce mutations in the epidermal cells, causing to the tumor initiation and development (Ravanat et al., 2001). The occurrence of (6-4) PPs by UV-B radiation is 5-10 fold less than appearance of CPDs (Eveno et al., 1995). Part of CPDs, thymine-cytosine (TC) and cytosine-cytosine (CC) dimers are represented to be the most common mutation type, and TC→TT and CC→TT mutations in p53 tumor suppressor gene are repeatedly seen in the UV-B radiation-induced cancer cells (Ichihashi et al., 2003). Consequentially, distortions of the DNA helix due to UV-B radiation-induced abnormal DNA adducts can stop RNA polymerase (pol) and inhibit elongation along DNA during the transcription. Therefore, UV-B radiation could influence normal mammalian gene expression and function (Tornaletti & Hanawalt, 1999).

2.2.2 Indirect DNA damage by UV-B radiation

UV-B radiation-induced ROS induction results in oxidative damage to the DNA bases, lipid peroxidation and additional types of DNA damage (Kielbassa et al., 1997). Electron transfer and singlet molecular oxygen production induced by UV-B radiation mark guanine base and accelerate generation of 8-hydroxydeoxyguanosine (8-OHdG) in the DNA strand (Cadet et al., 2000). 8-OHdG has been represented to be a typical maker of oxidative stress because it is produced by ROS such as peroxynitrite, .OH radical and singlet oxygen. Also, 8-OHdG is a miscoding lesion inducing G to T transversion (de Gruijl et al., 2001).

UV-B radiation causes various types of DNA damage – protein-DNA cross-links, DNA double (single) strand breaks and thymine glycol (Ichihashi et al., 2003). Although skin cells

possess the defense machinery against oxidative stresses by means of the cooperation of chemical and enzymatic anti-oxidant components, repeated exposure to UV-B radiation could induce crucial uncorrectable oxidative damage to DNA. Excessive amounts of UV-B radiation can cause the degeneration of inner and outer cell membranes and suppression of macromolecular synthesis (proteins and lipids) inducing abnormal cellular metabolism (Latonen & Laiho, 2005). Moreover, UV-B radiation is well known to up-regulate gene expression through many intracellular signal transduction pathways, which may contribute to initiation and development of skin cancer. UV-B radiation is proved to suppress immune reaction and to induce tolerance to antigens. These biological effects of UV-B radiation had been proven in experimental animal models (de Gruijl et al., 2001).

2.2.3 Repair mechanism of UV-B radiation-induced DNA damage

The repair process of UV-B radiation-induced DNA lesions occurs immediately after irradiation. Also, the cellular defensive events such as cell cycle arrest or apoptosis simultaneously proceed (Decraene et al., 2001). In skin, the UV-B radiation mediated–cellular photoprotective events are associated with paracrine regulation, ECM alteration, initiation of inflammation, and pigmentation (Clydesdale, 2001).

The predominant UV-B radiation-induced DNA damage is represented as pyrimidine dimers which induce helix-distorting lesion, and it is repaired by nucleotide excision repair (NER) process in mammalian cells (de Gruij et al., 2001). NER is a complicated process which is required 20-30 proteins (e.g., Xeroderma pigmentosum (XP): XPA - G) having specific functions such as recognition and incision of the DNA lesion (Friedberg, 2003). The NER repair complex is recruited to the DNA lesion and causes to regional unwinding around the damaged site by the DNA helicase activity of TFIIH (transcription factor II H). Then, the damaged DNA site is incised at almost 15 nucleotides from both sides of the bulge and is deleted. Incised DNA strand is sealed by new oligonucleotide synthesis and ligation through the reaction of DNA endonuclease, polymerase and ligase (Friedberg, 2001). NER pathways are divided into 2 subcategories – transcription-coupled repair (TCR) and global genomic repair (GGR). TCR is rapidly activated process in a gene-dependent manner, and it can repair the only template strand having transcriptional activity. While, GGR occurs more slowly than TCR and it can repair damaging sites from both non-transcribed genomic DNA and non-transcribed strand of expressed gene. Cell survival and proliferation are mainly regulated through TCR rather than GGR, however, genomic integrity and instability are controlled more by GGR (Hanawalt, 2002). Furthermore, GGR is initiated by the XPC-HR23B protein complex identifying the UV-B radiation-caused DNA lesion, and TCR is raised by pol II complex stopping at the DNA damage sites (Tornaletti & Hanawalt, 1999).

Although the DNA repair mechanisms are exquisitely regulated, deficiency in DNA repair often occurs, and unrepaired DNA damage could trigger in a mutations within the next cell division. Typical DNA polymerase cannot bypass the DNA lesion, however, a specific DNA polymerase can sometimes bypass the DNA lesion. Therefore mutations occasionally present, and the unrepaired DNA mutations are often misinterpreted during the DNA replication (Latonen & Laiho, 2005). Consequentially, failure of repair process in UV radiation-induced DNA damage could be regarded as a major cause one of the skin cancer.

2.3 UV-B radiation-induced skin carcinogenesis

The skin is the largest organ composing a body surface area, and it protects internal body organs as a first defense barrier against harmful influences of environmental and xenobiotic

stimuli. Exposure to UV-B radiation could induce initiation of skin cancer and repeated exposure to UV-B radiation accelerates skin carcinogenesis through depleting cutaneous defense mechanisms (Nichols & Katiyar, 2010).

Photocarcinogenesis in skin is progressed through complex and multiple steps – tumor initiation, promotion and progression (Digiovanni, 1992). Tumor initiation is rapidly induced by exposure to carcinogenic agents (e.g., UV radiation, the best known carcinogenic agent in skin cancer) and associated with irreversible genetic alterations that modify the response of basal (stem) cells in the epidermis. Unlike initiation process within just few days, tumor promotion requires long time more than 10 years. And it is reversible event that relates clonal expansion of initiated cells under the repeated radiation exposure to induce a benign tumor. In tumor progression stage, the final step of carcinogenesis, transformation of the benign tumor to an invasive and metastatic malignant tumor is promoted through additional genotoxic UV-B radiation (Surh, 2003). In other words, the incidence of skin cancer is closely associated with sun exposure – total quantity and time exposed to sun, and type of sun light (de Gruijl et al., 2001). If radiation-induced abnormal DNA adducts are not repaired, the significant mutations could be accumulated through the replication of DNA including the abnormal DNA adducts. The initiation of skin carcinogenesis has some connection with pivotal gene mutations in proto-oncogenes or tumor suppressor genes, and the *TP53* tumor suppressor gene has been reported as representative example in repeated sun-exposed skin (Brash et al., 1991). UV-B radiation-mediated gene alteration events occur in the basal cells in the epidermis, and could induce initiated cells (Zhang et al., 2001). Then, repeated UV-B irradiation could accelerate the proliferation of the initiated cells and generate a benign tumor. The driving force in tumor promotion is regarded as modification in gene expression. Researches in various skin cell lines have established certain signal molecules that are activated by UV-B radiation. These signaling molecules contain epidermal growth factor receptors (EGFR), mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3-kinase (PI3K), cyclooxygenase-2 (COX-2) and various transcription factors (AP-1, CREB and NF-κB) (Wan et al., 2001). In tumor progression stage, there are associated with further gene alterations, including changes of gene copy number, gene mutations and gene re-arrangements that take place in the progression of benign to malignant skin tumors (Zoumpourlis et al., 2003)**.**

2.4 Chemoprevention of skin cancer

Skin cancer arises primarily from sun-exposed body site and is intimately associated with repeated sun exposure (Kwa et al., 1992). Thus, an approach aimed at preventing or protecting from UV-B radiation-induced cellular damages has considered as an effective strategy for the management of skin cancer (Aziz et al., 2005). Fundamental and primary prevention of skin cancer is an attempt to minimize the exposure to the sun through use of sunscreens or protective clothing, and these approaches could clearly be helpful at decreasing the risk of skin cancer. However, due to several causes, these primary prevention methods have shown limited success (Bode & Dong, 2000). Therefore, new strategies for skin cancer prevention and treatment are demanded, and chemoprevention has come to the fore. The term of 'chemoprevention' was first mentioned by Michael Sporn in the mid-1970's to depict the strategy of blocking or retarding the initiation of pre-malignant tumors with non-toxic chemical resources – natural, synthetic, or biological agents (Surh, 2003).

2.4.1 Chemoprevention with dietary phytochemicals

Since 1999, chemoprevention has been in spotlight as a new anti-cancer strategy, and various review articles focusing on the subjects, principles, mechanisms and prospects of chemoprevention have been pouring (Bode & Dong, 2000).

Chemopreventive agents have been reported to interfere with a multistep of the carcinogenesis such as tumor initiation, promotion and progression. Chemopreventive agents are classified into two major categories – blocking agents and suppressing agents. Blocking agents inhibit the carcinogens from interaction with target molecules, metabolic activation or subsequently interaction with important cellular molecules – DNA, RNA and proteins. Also, blocking agents suppress carcinogen activation and promote detoxification. Whereas, suppressing agents prevent the tumor promotion and progression. They are closely associated with apoptosis, cell-cycle, cell proliferation, differentiation, DNA repair, expression and activation of oncogenes (or tumor suppressor genes), angiogenesis and metastasis in initiated cells (Wattenberg, 1985).

Plants including vegetables, fruits, seeds, nuts, flowers, and bark, have been used as a source of traditional medicines throughout history and utilized as a basis for various pharmaceutical drugs today. Plants include macronutrients – protein, fat, carbohydrate, and micronutrients – dietary fiber, vitamins, and minerals. Also, they contain non-nutritive components like polyphenols, terpenes and alkaloids that could serve considerable health advantages beyond the basic nutrition (Aggarwal & Shishodia, 2006). These non-nutritive compounds in plants are named phytochemicals ('phyto' is derived from the Greek term signifying 'plant') and are reported to have substantial biological properties such as anti-carcinogenic and anti-mutagenic effects (Surh, 2003). The NCI (National Cancer Institute) identified approximately thirty five plant-based foods that show anti-cancer properties. These contain chilli peppers, grape, turmeric, green tea, soybean, ginger, cabbage, apple, onion, tomato and garlic etc. Hundreds of phytochemicals have been identified as potential chemopreventive agent: allicin, anethol, capsaicin, catechins, curcumin, diallyl sulfide, dietary fiber, diosgenin, ellagic acid, eugenol, evodiamine, genistein, gingerol, indole-3-carbinol, isoflavones, lutein, lycopene, phytosterols, resveratrol, S-allyl cysteine, saponins, selenium, silymarin, ursolic acid and β-carotene etc. (Nichols & Katiyar, 2010).

Actually, epidemiological studies have indicated that populations (206 human and 22 animals) that consume a great quantity of the vegetables and fruits, have lower risk of the colon, endometrium, esophagus, lung, oral cavity, pancreas, pharynx and stomach cancer (Steinmetz & Potter, 1996). Moreover, experimentally, numerous cell culture and animal model researches have been demonstrated that various phytochemicals can suppress the inflammatory processes that induce to transformation, hyperproliferation, and initiation of carcinogenesis. Their inhibitory effects could suppress the final steps of carcinogenesis such as angiogenesis and metastasis (Saunders & Wallace, 2010). In addition to their biological functions, especially, plant-based natural products are thought to be safe (having little or no toxicity) chemopreventive agents, because natural compounds are contained in generally consumed foods and beverages (Bode & Dong, 2000).

2.4.2 Biological properties of dietary phytochemicals

During the last several centuries, the intake of dietary phytochemicals through plant food has been related to health advantages such as a photoprotection of the skin. Previous studies have demonstrated that various dietary phytochemicals possess the sunscreen ability, anti-inflammatory, anti-cancer, anti-oxidant and anti-bacterial effects.

Sunscreen effects of phytochemicals - Most of the natural products have different colored pigments – typically yellow, red or purple, and can absorb UV radiation. Accordingly, the natural phytochemicals can block the penetration of the UV radiation into the skin. Actually, the entire UV-B radiation and part of the UV-C and UV-A radiation are absorbed by phytochemicals having the pigment. This sunscreen ability of natural products can reduce inflammation, oxidative stress and DNA damaging effects by UV-B radiation in the skin. However, sunscreen effects account for only a part of various photoprotective effects in dietary phytochemicals (Nichols & Katiyar, 2010).

Anti-inflammatory effects of phytochemicals - UV-B radiation-induced erythema, edema and hyperproliferattive epithelial responses are known to representative inflammatory markers, and play important functions in skin tumor promotion (Mukhtar & Elmets, 1996). UV-B radiation-induced COX-2 expression and prostaglandin (PG) generation are specific responses of keratinocytes (mainly localized in epidermis) in both acute and chronic irradiation. COX-2 is a rate-limiting inflammatory enzyme for the production of PG metabolites from arachidonic acid (Langenbach et al., 1999), and COX-2 expression has been related to the pathological inflammation and cancer. A number of researches have suggested that COX-2 overexpression is closely associated with UV-B radiation-induced skin cancer - premalignant lesions, BCCs and SCCs (Buckman et al., 1998). Curcumin, green tea extract, gingerol, resveratol and basil based-ulsoric acid are reported to have anti-inflammatory effects through inhibiting of the inflammatory COX-2 enzyme.

Anti-oxidant effects of phytochemicals - The skin has well-regulated anti-oxidant defense system against UV-B radiation-induced oxidative stresses. But, repeated and excessive exposure to UV-B radiation cannot handle cutaneous anti-oxidant capacity. UV-B radiation is reported to induce excessive production of ROS resulting in the oxidative stress and depletion of anti-oxidant defense enzymes (superoxide dismutase, catalase, thioredoxin reductase and glutathione reductase). The strategies targeted at counteracting ROS generation and anti-oxidant defense enzymes could be helpful for the skin cancer prevention (Afaq et al, 2002). Some botanical phytochemicals (e.g., Caffeic acid phenethyl ester (CAPE), curcumin, green tea extracts, genistein, gingerol, quercetin and resveratol) are suggested to carry out the role in protecting the anti-oxidant system of skin and preventing skin carcinogenesis (F'guyer et al., 2003).

Based on previous researches of biological properties of the natural products, there has been considerable attention in the use of various phytochemicals for prevention and treatment of skin cancer.

2.4.3 Molecular targets of dietary phytochemicals in skin

Extracellular stimuli (e.g., UV-B radiation)-induced signal transduction is transmitted from the plasma membrane (receptors) into the cell and then, an intracellular chain of signaling molecules stimulates complex cellular responses. Also, skin carcinogenesis is associated with many functional genes regulating important cellular functions (e.g., intracellular, cell-surface, or extracellular function). All signal transduction pathways relating skin carcinogenesis are prime targets for chemopreventive agents (Bode & Dong, 2000). However, although considerable research has been done in explaining the mechanisms of carcinogenesis, further investigations are demanded to verify molecular and cellular targets for effective use of chemopreventive agents. Exactly, identification of exact target molecules for phytochemicals in cellular reaction process is essential to apply dietary phytochemicals to safe and effective medical treatment.

Although chemoprevention with natural products has considerable advantages, the negative results obtained for phytochemicals on lung cancer prevention highlight the need

for caution in application of the potential chemopreventive agents before their mechanism of action is entirely comprehended (Omenn et al., 1996). This example suggests the need to verify carcinogenic mechanisms and molecular and cellular targets for effective use of potential chemopreventive substances.

Skin carcinogenesis is a multistage process that can be activated by UV radiation (especially, UV-B radiation). The alteration of the signaling molecules regulating cell proliferation, differentiation and death are associated with UV-B radiation-induced skin cancer (Nichols et al., 2010). UV-B radiation are known to modulate the transcription factors (e.g., AP-1, NF-kB, STAT3), anti-apoptotic proteins (e.g., Akt, Bcl-2, Bcl-XL), pro-apoptotic proteins (e.g., caspases, PARP), numerous protein kinases (e.g., AKT, ERK, IKK, JNK, PI3K, p38), cell cycle proteins (e.g., cyclins, cyclin-dependent kinases), cell adhesion molecules, inflammatory enzymes (e.g., COX-2 and 5-LOX), and growth factor signaling pathways (e.g., EGFR, TNF, IGF).

There is summarization of the photoprotective effects and target molecules in some selected representative dietary phytochemicals, such as capsaicin, curcumin, resveratol, green tea polyphenol – (epigallocatechin-3-gallate (EGCG)), silymarin, quercetin and genistein, on external stimuli (e.g., UV-B radiation)-induced skin inflammation, oxidative stress and DNA damage condition. It is based on previous laboratory researches utilizing animal models and skin cell lines and indicating skin cancer chemopreventive activities of these phytochemicals.

Capsaicin - a pungent component of chilli peppers had been reported to work as a carcinogen in experimental animals due to its irritant effects. However, today, numerous studies have suggested that capsaicin has effects of chemoprevention and treatment in skin cancer through the regulation of the IκBα degradation, NF-κB activiation and translocation, AP-1 activation, pro-apoptosis proteins, generation of ROS and activation of JNK in dorsal skin of female ICR mice and mouse skin carcinogenesis model (Park et al.,1998; Han et al, 2001).

Curcumin - a yellow pigment that exists in the rhizome of turmeric is one of the most examined phytochemicals and owns powerful anti-inflammatory and anti-oxidant potential. Curcumin has been indicated to inhibit tumor promotion and progression in skin carcinogenesis through the regulation of the COX-2 expression, NF-κB and AP-1 activation, catalytic activity of ERK, caspase-mediated apoptosis and oxidative stresses in skin squamous carcinoma A431 cell line (Chan et al., 2003). Topical administration of the curcumin has been represented to enhance glutathione contents and glutathione-S-transferase (GST) activity, and suppresses lipid peroxidation and COX-2 activation in mouse skin and human IGR-39 melanoma cells (Iersel et al., 1996). Also, curcumin has been represented to attenuate the induction of ornithine decarboxylase (ODC) in mouse skin (Ishizaki et al, 1996) and to induce p53-associated apoptotic cell death through the blocking the NF-κB pathway and inhibiting the apoptotic inhibitor XIAP (X-linked inhibitor of apoptosis protein) in human basal carcinoma cells (Jee et al., 1998). These researches suggest that curcumin could be beneficial chemopreventive agent against the skin cancer (F'guyer et al., 2003).

Epigallocatechin-3-gallate (EGCG) - a polyphenol compound mainly contained in green tea has anti-oxidant properties. It has been demonstrated to suppress UV-B radiation-induced malignant transformation in skin through the regulation of the activation of AP-1, NF-κB and IKKα, phosphorylation and degradation of IκBα, activation of PI3K, STAT3, ERK, AKT and ERBB2 receptor, VEGF production, and cell cycle and apoptosis associating molecules (Afaq et al., 2003). As a potent anti-oxidant, EGCG can scavenge ROS, such as lipid free radicals, superoxide radical, hydroxyl radicals, hydrogen peroxide and singlet oxygen (Katiyar et al., 2000). Moreover, EGCG suppressed UV-B radiation-induced skin tumor initiation and development through inhibiting the AP-1 and NF-κB in SKH-1 hairless mouse skin (Mittal et al., 2003).

Fig. 1. Plant sources containing dietary chemopreventive phytochemicals

Genistein - a soy derived isoflavone has been mostly proven to contribute to the putative breast and prostate cancer preventive activity. In UV-B radiation-stimulated skin, it is reported that genistein suppresses NF-κB DNA binding and regulates to c-Jun and c-Fos in SENCAR mouse skin (Wang et al., 1998). Genistein has been known to have anti-oxidant and anti-carcinogenic properties in skin (Wei et al., 1998). Also, genistein downregulates the UV-B radiation-mediated phosphorylation of tyrosine protein kinase (TPK) and PGE$_2$ production in human epidermoid carcinoma A431 cells, and suppresses COX-2 expression in HaCaT keratinocytes (F'guyer et al., 2003).

Gingerol - a phenolic compound that takes charge of the spicy taste in ginger has been explained to prevent neoplastic transformation in skin carcinogenesis through the regulation of the ornithine decarboxylase (ODC) activity and TNF-α production and AP-1 activation in a two-stage mouse skin carcinogenesis model (Park et al., 1998).

Resveratol - a phytoalexin that is mainly contained in grapes has anti-oxidant, anti-inflammatory, anti-proliferative effects. Resveratol is an ingredient of red wine, colored grapes, peanuts and mulberries. Interest in red wine has been increased with so-called 'French paradox' - red wine has been presented to attenuate the mortality rates of cardiovascular diseases and some cancers (Kopp, 1998). The present study demonstrated that resveratrol conveys significant protection against UV-B radiation-induced skin carcinogenesis through modulation of the survivin and Smac/DIABLO in SKH-1 hairless mice (Aziz et al., 2005). Topical application of resveratrol inhibits UV-B radiation-induced skin tumor initiation, promotion and progression (Nichols & Katiyar, 2010). Resveratrol administration inhibits gene expression and catalytic activity of the COX-2, AP-1, MAPKs (ERK, JNK and p38), PKC and protein tyrosine kinases and activation of NF-κB through restriction of IKK phosphorylation. Resveratol presents effective chemoprevention properties based on anti-oxidant, anti-inflammatory in three major stages of skin carcinogenesis (Jang et al., 1997).

Quercetin - as the most abundant flavonol compound, quercetin is found plentifully in red wine, apples, tea and particularly onions (Gossé et al., 2005; Jeong et al., 2009; Murakami et al., 2008). Quercetin has anti-oxidant property as a free radical scavenger and metal ion chelator and is believed to prevent the harmful effects of UV radiation or reduce the damage (Aherne & O' Brien, 2002). Also, it has wide range of effects including anti-inflammatory and anti-cancer properties (Pan & Ho, 2008). The major functions of quercetin are regulation of the cell cycle arrest and induction of caspase-dependent cell death, and the major target molecules are indicated to p53, Wnt/β-catenin and ODC. Quercetin can protect skin anti-oxidant systems – glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase activities, against UV radiation damage (Erden Inal et al., 2001). Oral administration of quercetin prevented UV-B radiation-mediated immunosuppression in SKH-1 hairless mice (Steerenberg et al., 1997; Svobodová et al., 2003)

Silymarin – a polyphenolic flavonoid isolated from milk thistle plant has anti-oxidant and anti-carcinogenic effects in mouse models (Berton et al., 1997). The exact molecular mechanism of the anti-carcinogenic effects of silymarin is still being examined. But, silymarin has been revealed to suppress UV radiation-induced NF-κB activation in human HaCaT keratinocytes. Also, treatment of the silymarin results in a significant downregulation of extracellular signalregulated protein kinase (ERK) and upregulation of stress-activated protein kinase/Jun NH(2)-terminal kinase (SAPK/JNK1/2) and p38 in human epidermoid carcinoma A431 cells (Singh et al., 2002). These results propose that silibinin could be possible underlying molecular events through inhibition of proliferation

and induction of apoptosis in epidermoid A431 cancer cells. Silymarin is reported to protect skin against photocarcinogenesis in mice. Silymarin shows significant inhibition against UV-B-induced skin edema, skin sunburn, cell apoptosis, depletion of catalase activity, induction of COX-2 and ODC activities, and ODC mRNA expression (Katiyar et al., 1997). These results suggest that silymarin gives substantial protection against UV-B radiation-induced cellular damage in mouse skin. Moreover, recent investigation shows that silymarin suppresses endogenous tumor promoter, tumor necrosis factor-alpha (TNF-α) – a central mediator in skin tumor promotion in mouse skin (Singh & Agarwal, 2002; F'guyer et al., 2003).

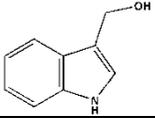| Molecular targets of representative dietary phytochemicals in skin		
Plant name	Active component	Molecular targets
Honey bee propopolis	Caffeic acid phenethyl ester (CAPE)	Bax↑, β-Catenin↓, Bcl-2↓, Bcl-xL↓, EGFR↓, PKC↓, ODC↓, Caspase-3↑ *↑: up-regulation *↓: down-regulation
Chilli peppers	Capsaicin	AP-1↓, Bcl-2↓, Bcl-xL↓, Cdc25↓, Cdk1↓, CIAP↓, NF-κB↓, Survivin ↓
Tumeric	Curcumin	Akt↓, AP-1↓, Bcl-2↓, Bcl-xL↓, COX-2↓, c-Fos↓, c-Jun↓, c-Myc↓, CyclinD1↓, EGFR↓, ICAM1↓, Bcl-2↓, Bcl-xL↓, IL-6↓, iNOS↓, Jak2↓, JNK↓, MMP9↓, NF-κB↓, PKA↓, PKC↓, p53↓, Src↓, TNF↓, VCAM1↓, 5-LOX↓
Green tea	Epigallocatechin-3-gallate (EGCG)	AP-1↓, Bcl-2↓, COX-2↓, c-Myc↓, IGF↓, IKKα↓, IL-6↓, iNOS↓, MAPKs↓, NF-κB↓, p21/WAF1↑, p53↑, VEGF↓, 5-LOX↓
Cloves	Eugenol	Caspase-3↓, NF-κB↓, PARP↓, p53↓
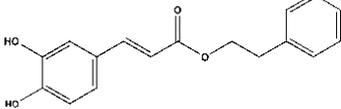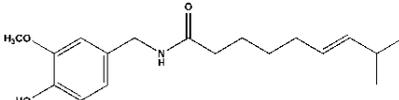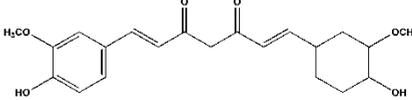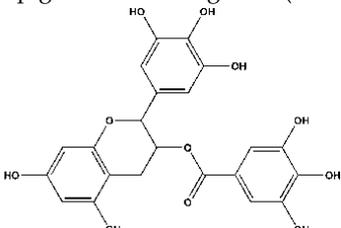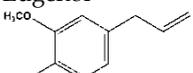
Molecular targets of representative dietary phytochemicals in skin		
Plant name	**Active component**	**Molecular targets**
Tetradium	Evodiamine 	Caspase-3,-8,-9↓, Cdc25↓, Cdk 2↓, CyclinA ↓, CyclinB1↓
Soybean	Genistein 	Caspase-12↓, Glutathione peroxidase↑, NF-κB↓, p21/WAF1↓
Ginger	Gingerol 	AP-1↓, COX-2↓, iNOS↓, NF-κB↓, ODC↓, TNF↓
Cabbage	Indole-3-carbinol 	Bcl-2↓, Bcl-xL↓, Cdc25↓, Cdk1↓, CIAP↓
Apple	Quercetin 	AP-1↓, IL-1,-6,-8↓, MAPKs↓, MMP-2,-3↓, NF-κB↓, PI3K↓, TNF↓, 5-LOX↓
Grape	Resveratol 	AP-1↓, COX-2↓, Cyclin D1↓, MAPKs ↓, 5-LOX↓, NF-κB↓, Survivin↓
Basil	Ursolic acid 	COX-2↓, Cyclin D1↓, NF-κB↓, MMP-9↓
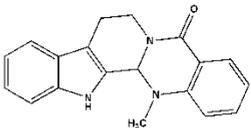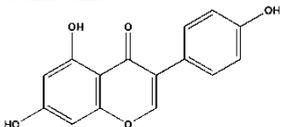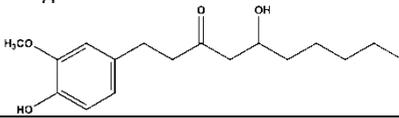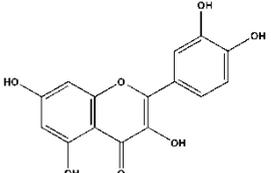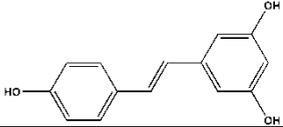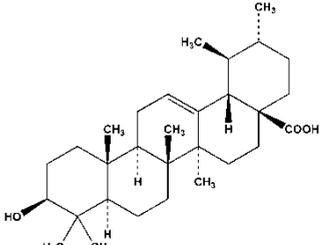
Table 1. Molecular targets of representative dietary phytochemicals

3. Conclusion

The incidence of the skin cancer has recently accelerated worldwide because of an increase in the level of UV-B radiation at the earth's surface due to ozone depletion. Since it is very difficult to restore the once destroyed ozone layer to its original condition, incidence of the skin cancer will be significantly increased in future. Therefore, prevention and treatment of skin cancer will be the important problem. Among diverse strategies, chemoprevention by dietary phytochemicals has attracted considerable interest and it is now being studied in detail. Especially, chemoprevention using the natural products is considered to be an inexpensive, readily acceptable and accessible strategy to cancer management.

Dietary phytochemicals could directly interact with intracellular signaling molecule in prevention and treatment of skin cancer. Mostly dietary phytochemicals have been reported that they could have duplicity - a certain compound can 'switch on' the target molecules and sometimes 'switch off' the target molecules depend on various factors. Therefore, it is essential to identify the target molecules in the signaling network that can be influenced by individual chemopreventive compounds to allow medical application. In many cases, the chemopreventive effects of dietary phytochemicals confirmed in cultured cells or tissues are only achievable at supraphysiological concentrations – these concentrations would not be aquired when the phytochemicals are tried as food intake.

Moreover, phenolic compounds – the most widely used phytochemicals are frequently shown as glycosides or are conjugated to glucuronide, sulfate and methyl groups after administration, which might have a lower bioavailablity. Both pharmacokinetic properties and bioavailability are pivotal problems in investigating the prevention and treatment of the cancer and should be evaluated cautiously before attempting medical trials with dietary phytochemicals. From the viewpoint of the delivery of the phytochemicals, the penetration of phytochemicals into the skin is somewhat limited.

Although sufficient studies are demanded to apply dietary phytochemicals to clinic trials, chemoprevention by phytochemicals has been regarded as a safe strategy (having little or no genotoxicity) and a realistic method for controlling the risk of the cancers. Also, unlike the carcinogenic environmental factors that are difficult to control, individuals can modify their dietary habits and lifestyle in combination with a careful use of skin care products to prevent the photodamaging effects in the skin.

In this chapter, UV radiation (especially, UV-B radiation) is focused as a major factor of skin cancer, and mechanisms of the UV radiation-induced skin cancer and information of the chemoprevention of dietary phytochemicals are summarized. These contents will be useful to understand the 'chemoprevention of skin cancer with dietary phytochemicals'**.**

4. Acknowledgment

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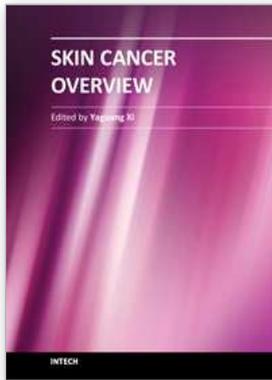
Skin Cancer Overview

Edited by Dr. Yaguang Xi

The book Skin Cancer Overview is divided into three sections to cover the most essential topics in skin cancer research: Etiology, Diagnosis and Treatment, and Prevention. Due to the complexity of skin cancer, this book attempts to not only provide the basic knowledge, but also present the novel trends of skin cancer research. All chapters were written by experts from around the world. It will be a good handbook for researchers with interests in skin cancer.

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