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DIETARY PHYTOCHEMICALS AS PROMISING PREVENTIVE MEASURES FOR SKIN CANCER

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ABSTRACT

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 [1, 2]. 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 be 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, safe and efficient strategy for cancer treatment. This article 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.

Key words: Skin cancer, UV radiation, Chemoprevention, Phytochemicals.

INTRODUCTION

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 [3]. Inspite 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 [4]. There are over one million patients per year diagnosed with skin cancer in the United States, and these account for 40% of all new cases of cancer diagnosed [1, 5]. 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 [6]. 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 [7].

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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 [4, 8]. 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) [9]. 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 [10]. 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 [11].

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 [10, 12], which together perform critical functions in the generation and maintenance of UV-induced carcinogenesis [13]. Actually, it has been 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 [14,15].

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 by depleting cutaneous defense mechanisms [8]. Photocarcinogenesis in skin is progressed through complex and multiple steps – tumor initiation, promotion and progression [16]. 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.

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 [17]. 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 [18]. 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 [19].

UV-B radiation-mediated gene alteration events occur in the basal cells in the epidermis, and could induce initiated cells [20]. Then, repeated UV-B irradiation could accelerate the proliferation of the initiated cells and generate a benign tumor. Modification in gene expression is regarded as the driving force in tumor promotion. 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) [21]. In tumor progression stage, these 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 [22].

Chemoprevention of skin cancer with dietary phytochemicals

Skin cancer arises primarily from sun-exposed body site and is intimately associated with repeated sun exposure [23]. Thus, an approach aimed at preventing or protecting from UV-B radiation-induced cellular damages has been considered as an effective strategy for the management of skin cancer [2]. 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 [24]. Therefore, new strategies for skin cancer prevention and treatment are demanded, and chemoprevention has come to the fore. The term ‘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 [17].

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 chemo-prevention have been pouring [24]. 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. However, 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 [25].

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 [3]. 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 anticarcinogenic and anti-mutagenic effects [17].

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. [8]. 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 [26].

Moreover, experimentally, numerous cell culture and animal model researches have been demonstrated that various phytochemicals can suppress the inflammatory processes that induce transformation, hyper-proliferation, and initiation of carcinogenesis. Their inhibitory effects could suppress the final steps of carcinogenesis such as angiogenesis and metastasis [27]. 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 [24].

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, antiinflammatory, 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 [8].

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 [12]. 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 [28] and COX-2 expression has been related to the pathological inflammation and cancer. A number of researches have suggested that COX-2 over expression is closely associated with UV-B radiation-induced skin cancer - premalignant lesions, BCCs and SCCs [29]. Curcumin, green tea extract, gingerol, resveratrol 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

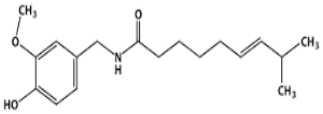
The skin has well-regulated anti-oxidant defense system against UV-B radiation-induced oxidative stresses. But, repeated and excessive exposure to UV-B radiation cannot handle cutaneous anti-oxidant capacity. UV-B radiation is reported to induce excessive production of ROS resulting in the oxidative 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 [30]. Some botanical phytochemicals (e.g., Caffeic acid phenethyl ester (CAPE), curcumin, green tea extracts, genistein, gingerol, quercetin and resveratol) are suggested to play role in protecting the anti-oxidant system of skin and preventing from skin carcinogenesis [31].

PHYTO-CHEMICALS USEFUL TO TREAT SKIN CANCER

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 [32, 33].

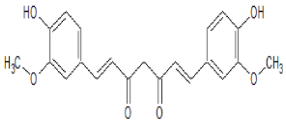
Chillies



Capsaicin

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 [34]. Topical administration of curcumin has been reported 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 [35]. Also, curcumin tends to attenuate the induction of ornithine decarboxylase (ODC) in mouse skin [36] 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 [37]. These researches suggest that curcumin could be beneficial chemopreventive agent against the skin cancer [31].

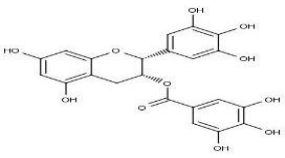
Turmeric



Curcumin

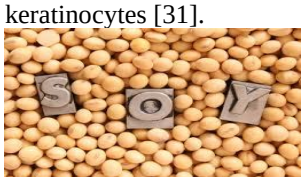
Epigallocatechin-3-gallate (EGCG) - a polyphenol compound mainly contained in green tea has anti-oxidant properties. It has been demonstrated to suppress UV-B radiation-induced malignant transformation in skin through the regulation of the activation of AP-1, NF-Kb and IKKα, phosphorylation and degradation of IκBα, activation of PI3K, STAT3, ERK, AKT and ERBB2 receptor, VEGF production, and cell cycle and apoptosis associating molecules [38]. As a potent anti-oxidant, EGCG can scavenge ROS, such as lipid free radicals, superoxide radical, hydroxyl radicals, hydrogen peroxide and singlet oxygen [39]. Moreover, EGCG suppresses UV-B radiation-induced skin tumor initiation and development through inhibition of AP-1 and NF-κB in SKH-1 hairless mouse skin [40].

Green tea

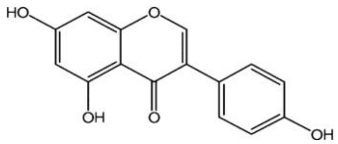


EGCG

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 [41]. Genistein has been known to have anti-oxidant and anti-carcinogenic properties in skin [42]. Also, genistein down regulates the UV-B radiation-mediated phosphorylation of tyrosine protein kinase (TPK) and PGE2 production in human epidermoid carcinoma A431 cells, and suppresses COX-2 expression in HaCaT keratinocytes [31].



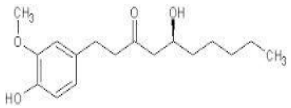
Soyabean



Genistein

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 ornithine decarboxylase (ODC) activity and TNF-α production and AP-1 activation in a two-stage mouse skin carcinogenesis model [32].

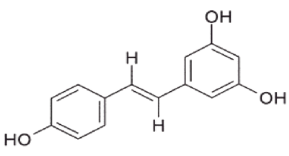
Ginger



Gingerol

Resveratrol- a phytoalexin that is mainly contained in grapes has anti-oxidant, antiinflammatory, anti-proliferative effects. Resveratrol is an ingredient of colored grapes, red wine 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 [43]. 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 [2]. Topical application of resveratrol inhibits UV-B radiation-induced skin tumor initiation, promotion and progression [8]. 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. Resveratrol presents effective chemoprevention properties based on anti-oxidant, anti-inflammatory in three major stages of skin carcinogenesis [44].

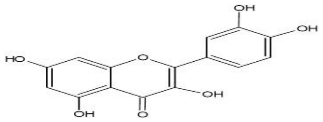
Grapes



Resveratrol

Quercetin - as the most abundant flavonol compound, quercetin is found plentifully in apples, red wine, tea and particularly onions [45, 46, 47]. 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 [48]. Also, it has wide range of effects including anti-inflammatory and anti-cancer properties [49]. 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 antioxidant systems – glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase activities, against UV radiation damage [50]. Oral administration of quercetin prevented UV-B radiation-mediated immunosuppression in SKH-1 hairless mice [51, 52].

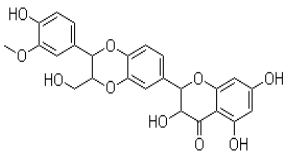
Apples



Quercetin

Silymarin – a polyphenolic flavonoid isolated from milk thistle plant has anti-oxidant and anti-carcinogenic effects in mouse models [53]. 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 down regulation of extracellular signal regulated protein kinase (ERK) and up regulation of stress-activated protein kinase/Jun NH(2)-terminal kinase (SAPK/JNK1/2) and p38 in human epidermoid carcinoma A431 cells [54]. Silymarin is reported to protect skin against photocarcinogenesis in mice. Silymarin shows significant inhibition against UVB- induced skin edema, skin sunburn, cell apoptosis, depletion of catalase activity, induction of COX-2 and ODC activities, and ODC mRNA expression [55]. 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 [31, 56].

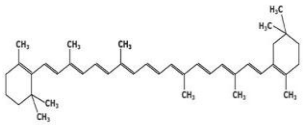
Artichoke



Silymarin

β-Carotene- this compound is carotenoid in nature, widely found in carrots. This is believed that it is able to induce apoptosis in melanoma cells in vitro by activating caspases cascade. β-carotene exerts its anti-carcinogenic action by inducing the regulation of Bcl-2 and caspases-3, which stimulates apoptosis.

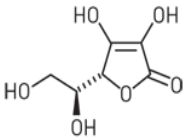
Carrots



β-carotene

Vitamin-C- also known as ascorbic acid, widely found in citrus fruits, possesses anti-carcinogenic and powerful anti-oxidant properties. Vitamin-C appears to act by inducing apoptosis and by inhibiting cell proliferation and cell growth. Apoptosis induction by vitamin-C is thought to occur by way of pro-oxidant activities that can be blocked by N-acetyl-L-cysteine, a potent anti-oxidant. It is thought that vitamin-C suppresses the expression of vascular endothelial growth factor (VEGF) in melanoma cells, thus enabling it to suppress angiogenic processes, which could result in tumor development.

Citrus fruit

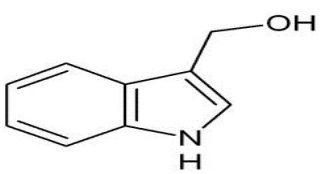


Vitamin C

Tea tree oil- it is terpenoid in nature and is extracted from *Melaleuca alternifolia*. Tea tree oil possesses various terpenoids as active constituents. Tea tree oil is believed to possess anti-cancer activity and is relatively safe if taken in low concentrations. Tea tree oil is effective against basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Tea tree oil in 10% dimethylsulfoxide results in a direct cytotoxic effect on tumor cells and induces local immune activation when applied topically. Tea tree oil could potentially be used to treat skin cancer.

Indole-3-carbinol- this compound is found relatively at high levels in cruciferous vegetables such as broccoli, cabbage, cauliflower and Brussels sprouts. Indole-3-carbinol is produced by the breakdown of the glucosinolate glucobrassicin. Indole-3-carbinol is the subject of on-going biomedical research into its possible anti-carcinogenic, anti-oxidant and anti-atherogenic effects. Indole-3-carbinol possesses ability to alter estrogen metabolism and other cellular effects. It generally blocks the initial stage of tumor development. It is believed that indole-3-carbinol decreases the tumor susceptibility by suppressing the alfatoxin-DNA binding.

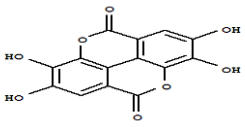
Cabbage



Indole-3-Carbinol

Ellagic acid- this compound is mostly found in raspberries, walnuts, pomegranate and strawberries. This compound possesses anti-viral and anti-bacterial properties. Ellagic acid inhibits the viral enzyme integrase, which is responsible for the replication of cells and also inhibits gyrase enzyme, which is responsible to support bacterial DNA for the induction of cell death. Ellagic acid also possesses anti-carcinogenic properties. Ellagic acid stimulates apoptosis. The American Cancer Society (ACS) has reported that ellagic acid is responsible to decrease the number of cancer cells and rate of cancer cell growth by preventing the destruction of p53 gene. The p53 gene is known as tumor suppressor gene. In human skin cells, ellagic acid protects against UV-B damage by blocking the production of matrix metalloproteinase enzyme that breaks down the collagen and reduce the expression of ICAM, a molecule involved with inflammation.

Pomegranate



Ellagic acid

CONCLUSION

From this review, it has been clear that naturally derived compounds are likely to gain utmost importance in future skin melanoma treatment.

This article has summarized some of essential phyto-chemicals which are believed to possess anti-cancer properties. The incidence of the skin cancer has accelerated worldwide because of an increase in the level of UV-B radiation at the earth surface due to depletion of ozone layer; therefore incidence of the skin cancer in the future might increases significantly. Therefore, prevention and treatment of skin cancer becomes crucial.

Among various options, chemoprevention by dietary phyto-chemicals has gained a considerable and significant interest. Especially, chemoprevention by using the natural products is considered to be an inexpensive, readily acceptable and accessible strategy for skin cancer management. Dietary phyto-chemicals could directly interact with intracellular signaling molecule in prevention and treatment of skin cancer. Thus, sufficient studies have demanded the application of dietary phyto-chemicals to clinical trials. Chemoprevention by phyto-chemicals has been regarded as a safe strategy (little or no adverse effect) and a realistic method for controlling the risk of skin cancer. Individuals need to modify their dietary habits and lifestyle in combination with a careful use of skin care products i.e. phyto-chemicals to prevent the skin from the harmful ultra-violet environment.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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