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Bioactive Food Components for Melanoma: An Overview

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1. Introduction

The skin being the largest organ in the body accounts for the most common cancer in humans. Skin cancer is typically of three types, basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. Despite accounting for only 4% of all cases, melanoma is the most deadly skin cancer, resulting in over 79% of skin cancer related deaths [1, 2]. In the year 2011 in the United States melanoma is thought to cause 70,230 cases (40,010 in men and 30,220 in women) with 8,790 deaths (5,750 in men and 3,040 in women) associated with the disease [3]. The median age at diagnosis is between 45 and 55, although 25% of cases occur in individuals before age 40. It is the second most common cancer in women between the ages of 20 and 35, and the leading cause of cancer death in women ages 25 to 30.

There are multiple risk factors that contribute to the escalating incidences of melanomas in humans (Table 1). Among all, ultraviolet (UV)-radiation emitted from the sun is the main contributing factor towards the development of melanomas. It is well documented that UV-radiation is absorbed by the chromophores such as DNA, RNA, protein and melanin in the skin [4]. This UV absorption in the skin results in different photochemical reactions and the secondary interactions involving ROS (reactive oxygen species) result in damaging effects. UV irradiation of the skin causes erythema, edema, hyperplasia, hyperpigmentation, sunburn cells, immunosuppression, photoaging and photocarcinogenesis [5, 6]. UV irradiation to skin also has direct effects on biomolecules such as formation of cyclobutane pyrimidine dimers (CPDs), 8-hydroxy-2'-deoxyguanosine (8-OHdG), protein oxidation and generation of ROS [4, 7, 8].

Over the years, changes in lifestyle patterns have led to a significant increase in the amount of UV radiation that people receive, leading to a surge in the incidence of skin cancer and photoaging. Since these trends are likely to continue in the foreseeable future, the adverse effects of ultraviolet radiation have become a major human concern. One way of combating against the melanomas is through "chemoprevention" which is defined as the use of natural or synthetic agents to reverse, suppress or prevent premalignant lesions from progressing to

invasive cancers. Chemoprevention broadly is divided into 3 categories: (i) *primary*- preventing initial cancer in high risk individuals; (ii) *secondary*- preventing cancers in those with premalignant conditions; and (iii) *tertiary*- preventing second cancers in patients cured or an initial cancer [9, 10].

Ultraviolet (UV) radiation
UVA
UVB
Genetic syndromes
Xeroderma pigmentosum
Oculocutaneous albinism
Basal cell nevus syndrome
Ionizing radiation
X-rays
Other risk factors
Artificial UV radiation (tanning)
Skin color (having fair skin, especially with blue or hazel eyes)
History of lesions
Chronically injured or non-healing wounds
Working outdoors
Increasing age

Table 1. Risk factors for melanomas [Reviewed in [136-142]]

In recent years, natural agents have gained considerable attention because of their skin photoprotective effects [11, 12]. Nutritional agents with potential antioxidant, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties, and that have the ability to exert striking inhibitory effects on diverse cellular and molecular events are gaining considerable attention for the prevention of UV-induced skin damage [11-13]. Botanical anti-oxidants have also been shown to reduce the incidence of ROS-mediated photocarcinogenic and photoaging. This has generated a great interest in using botanical supplements rich in anti-oxidants to delay photocarcinogenesis and prevent photoaging. This chapter presents an overview of selected few botanical agents and their protective properties of the skin against melanoma.

2. Tea polyphenols

Tea, derived from the plant *Camellia sinensis*, is the most popular beverage consumed by two-thirds of the world's population. It is processed in different ways in different parts of the world to give green, black or oolong tea. "Black tea" is fully fermented, "oolong tea" is partially fermented and "green tea" is strained and not fermented. For the preparation of green tea, the young leaves are steamed to inactivate the enzymes thereby preserving as much as 90% of the polyphenols contained in fresh leaves from being degraded [14].

The most studied formulation of tea is the green tea. Green tea contains characteristic polyphenolic conpounds, (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC). A typical tea beverage (1 g leaf per 200 mL water in a 3 minute brew) usually contains 250-300 mg tea solids comprised of 30-40% catechins and 3-

6% caffeine [14]. Green tea is considered a dietary source of anti-oxidants nutrients like polyphenols (catechin and gallic acid), carotenoids, tocopherols, ascorbic acid and certain phytochemical compounds. They may also function indirectly as anti-oxidants through inhibition of the redox-sensitive transcription factors, inhibition of pro-oxidant enzymes, such as inducible nitric oxide synthase, lipoxygenases, cyclooxygenases, and xanthine oxidase and induction of anti-oxidant enzymes, such as glutathione-S-transferases and superoxide dismutases [15].

The activity of tea polyphenols on the inhibition of skin tumorigenesis has been studied in depth. Studies have shown that green tea polyphenols (GTP) have a significant inhibitory effect on tumor induction in a chemically induced initiation-promotion mouse model [16]. EGCG significantly inhibited the binding of ^{3}H-labelled polycyclic aromatic hydrocarbons to epidermal DNA. Topical application of EGCG resulted in significant inhibition in TPA-mediated induction of epidermal ornithine decarboxylase (ODC) activity. The application of EGCG before challenge with DMBA also resulted in significant inhibition both in percentage of mice with tumors and the number of tumors per mouse compared with non-EGCG-pretreated mice [17].

Oral consumption or topical application of brewed green tea or green tea extracts showed meaningful protection against ultraviolet or chemically induced carcinogenesis in mice. Oral consumption of brewed green tea at concentrations similar to human consumption (1.5-2.5%) significantly inhibited UVB or TPA-induced tumorigenesis [18, 19]. Mechanistically, oral consumption of GTP resulted in decreased UVB-induced ODC and carboxylase (COX) activities [20]. Oral administration or intra-peritoneal injection of GTP achieved similar effects to inhibit the growth of UV-induced skin papillomas [18] or TPA-induced COX2 in rodent models [21]. EGCG treatment was found to result in a dose-dependent decrease in the viability and growth of A-375 amelanotic malignant melanoma and Hs-294T metastatic melanoma cell lines [22]. Oral administration of GTP was found to reduce UVB-induced tumor incidence, tumor multiplicity and growth in SKH-1 mice. Reduced expression of matrix metalloproteinase (MMP)-2 and MMP-9, vascular endothelial growth factor (VEGF) and proliferating cell nuclear antigen (PCNA) was also observed [23]. Furthermore, oral administration of green tea to UV-pretreated high risk mice for 23 weeks inhibited skin tumorigenesis [24]. Pretreatment of SKH-1 hairless mice with green tea for 2 weeks enhances UV-induced increase in epidermal p53, p21 (WAF1/CIP1) and apoptotic sunburns in the epidermis [25]. Furthermore, mice treated with green tea during chronic UVB irradiation changed the mutation profile of the p53 gene in early mutant p53 positive epidermal patches [26].

3. Curcumin

Curcumin (diferuloylmethane) is a yellow substance extracted from the root of the turmeric plant *Curcuma longa* which belongs to the *Zingiberaceae* family. Curcumin has been used for centuries in indigenous medicine for the treatment of a variety of inflammatory and other diseases, and was shown for the first time in 1988, to have antimutagenic activity using the Ames *Salmonella* test [27]. It has a wide range of pharmacological activities including anti-inflammatory, anti-cancer, anti-oxidant, wound healing and anti-microbial effects [28], as well as several documented clinical applications referenced to its anti-inflammatory and anti-oxidant properties. Curcumin is also a potent scavenger of a variety of reactive oxygen species (ROS) such as superoxide anion radicals, hydroxyl radicals, and nitrogen dioxide

radicals. The molecular basis of anti-carcinogenic and chemopreventive effects of curcumin is attributed to its effect on several targets including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators and other cellular signaling molecules [29]. Curcumin is able to block multiple targets conferring protective effects against oxidative stress and inflammation and has proven useful in photoaging skin and photocarcinogenesis [30]. It was shown to induce apoptosis and cell cycle arrest in melanoma cells, associated with down-regulation of iNOS, the catalytic subunit of DNA-dependent protein kinase, and up-regulation of p53, p21(CIP1), p27(KIP1) and Chk-2 [31] and its apoptosis inducible ability has also been associated to the Fas receptor/caspase-8 pathway, independent of p53. It has been shown to down regulate the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β, and to inhibit the activation of transcription factors NF-κB, and activator protein-1 (AP-1), which regulate the genes for pro-inflammatory mediators and protective anti-oxidant genes [32].

Curcumin also suppresses the apoptotic inhibitor XIAP, decreases NF-κB downstream target genes such as COX-2 and cyclin D1 expression and blocks it cell survival pathway and selectively induced apoptosis in melanoma cells but not in normal melanocytes [33, 34]. It was shown to inhibit proteasomal activity, inhibit Ca^{2+}-adenosine triphosphatase (ATP) pump leading to accumulation of cytosolic calcium which then activates caspases, cleave p23 and downregulate the antiapoptotic Mcl-1 protein and thus inducing ER stress in melanoma cells [35]. The antiproliferative and proapoptotic effects induced by curcumin are shown to be independent of the B-Raf/ERK MAPK and the AKT pathway [36]. In spite the proapoptotic effects, curcumin has reportedly been associated with the inhibition of the ability of IFN-alpha, IFN-gamma, and IL-2 to phosphorylate STAT1 and STAT5 proteins [37], suggesting the possibility of it to adversely affect immune effector cells responses to clinically relevant cytokines with antitumor properties [36].

Moreover, curcumin was also reported to cause cell death in 8 melanoma cell lines, four with wild type and four with mutant p53. In highly metastatic murine melanoma cells B16F10 as well as other cells, it significantly inhibited the activity of MMP2 , collagenase and focal adhesion kinase (FAK), important components of the intracellular signaling pathway, meanwhile it enhanced the expression of anti-metastatic proteins such as tissue inhibitor metalloproteinase-2, nonmetastatic gene 23, and E-cadherin [38, 39]. Curcumin-treated B16F10 cells formed eight fold fewer lung metastasis in C57Black 6 mice [39], and showed a dose dependent reduction in their binding affinity to extracellular matrix (ECM) protein including fibronectin, vitronectin and collage IV and a reduced α5β1 and α5β3 integrin receptors expression in the cell adhesion assays. In stimulated melanoma cells, curcumin has been shown to suppress melanogenesis by down regulating melanogenesis related proteins such as MITF, tyrosinase and tyrosinase-related proteins 1 and 2 [40]. Interestingly, its antimetastatic effects has been linked to the modulation of the expression of integrin receptors, collagenase activity, tissue inhibitor metalloproteinase (TIMP)-2, nonmetastatic gene 23 (Nm23) and E-cadherin [38], [39].

In resistant cases, a two hit combination of curcumin and other factors has been shown to enhance curcumin induced effects on melanoma cells in cell culture models. Small inhibitory RNA silencing of ABCA1 gene was shown to sensitize melanoma cells to the apoptotic effect of curcumin most likely due to a reduced basal levels of active NFκB as well as a reduction of P65 expression [41]. Moreover, C6 ceramide was shown to sensitize melanoma cells to curcumin-induced cell death and apoptosis by partially increasing the

intrinsic apoptotic pathway [42]. More recently, it has been shown that a combination of curcumin and tamoxifen concomitantly induced apoptosis and autophagy in melanoma cells without affecting non-cancerous cells [43].

Recent advances in view of selecting new antitumor agents with more potent and selective growth inhibitory activity has revolutionized the synthesis and testing of several analogous "curcumin-like" compounds. For instance the compound α,β-unsaturated ketone D6 was shown to be more effective in inhibiting melanoma growth when compared to curcumin [44]. Synthetic curcuminoid derivatives have been analyzed *in vivo* to test their inhibitory role to tumor-specific angiogenesis such that in mice injected with melanoma cells an intraperitoneal administration of tetrahydro curcumin, salicyl curcumin and curcumin III reduced the number of induced tumor-directed capillaries. Moreover, these curcuminoids have been shown to reduce serum Nitric Oxide (NO) and tumor-necrosis factor (TNF)-α levels in treated animals, perhaps by decreasing the production by activated macrophages [45]. A small molecule FLLL32, an analog of curcumin and STAT3-specific inhibitor for melanoma therapy was shown to induce caspase-dependent apoptosis in cells through reduced STAT3 phosphorylation and retained the cellular response to cytokines with antitumor activity, and most remarkably did not reduce the function or viability of normal donor immune cells. FLLL32 has also been shown to inhibit IL-6-induced STAT3 phosphorylation without reducing signaling due to IFN-γ and IL-2 [37, 46].

Despite the highly recognized chemotherapeutic potential of curcumin, its poor solubility to water and fast degradation has significantly hindered its clinical application. However, amphiphilic block copolymer micelles of poly(ethylene oxide)-b-poly(epsilon-caprolactone) used as solubilization and stabilization vehicles, were able to effectively solubilize curcumin, protect the degradation of encapsulated curcumin and control it release over several days [47]. A combination of curcumin and catechin was shown to inhibit the melanoma cell invasion by inhibiting MMPs, thus inhibiting lung metastasis [48]. Curcumin also was shown to inhibit the phosphorylation of Src kinase and STAT3 partly by downregulating PRL-3 and preventing melanoma cells from invading the draining lymph nodes [49]. In Mice, curcumin was reported to decrease the induction of epidermal ODC activity, epidermal cyclooxygenase and lipoxygenase enzyme levels, epidermal glutathione content, oxidation of DNA bases, and the number of tumors per mouse and tumor volume per mouse. Topical application of curcumin together with TPA was shown to induce epidermal hyperplasia and *c-Jun* and *c-Fos* expression in CD-1 mice [50]. Curcumin treatment successfully reduced the number and volume of tumors when given in diet to animals in which skin tumors had been inhibited with DMBA and promoted with TPA. The dietary consumption of curcumin resulted in decreased expression of proto-oncogenes, *ras* and *fos*, in the skin tissue [51, 52]. Topical application of curcumin together with TPA twice weekly for 18 weeks markedly inhibited TPA-induced tumor promotion [53]. Topical application on the dorsal side of the skin with curcumin before TPA exposure inhibited TPA-induced expression of c-fos, c-jun and c-myc [54]. Currently, several clinical trials are investigating the effect of curcumin in diverse cancerous and non-cancerous conditions but without any of them evaluating its effects against melanoma in human populations.

4. Genistein

Genistein (4', 5, 7-trihydroxyisoflavone) is a widely distributed isoflavone primarily present in soy, *Ginkgo biloba* extract, oregano and sage [55, 56]. It was first isolated from soybean in

1931 [57]. Increasing incidence has accumulated that genistein shows preventive and therapeutic use for cancers, osteoporosis and cardiovascular disease in both humans and animals. Genistein is a potent inhibitor of cytochrome P450-medicated activation of benz-a-pyrene [58]. In an *in vitro* setting, genistein inhibits the activities of tyrosine protein kinase, topoisomerase II and ribosomal S6 kinase [59, 60]. Genistein has been reported to inhibit the growth of ras-transfected NIH3T3 cells without affecting the growth of normal cells [61]. Genistein can modulate the inflammatory responses that are commonly involved in the promotional stage of carcinogenesis [62]. It displays many anticancer properties which includes suppressing the growth of a variety of human gastrointestinal cancer cell lines, induction of differentiation of leukemia cells, and inhibition of endothelial cell angiogenesis relevant to tumor metastasis [63].

Genistein treatment in human NCTC 2544 keratinocytes prevented UV-induced enhancement of STAT1 (signal transducer and activator 1) thereby limiting lipid peroxidation [64]. Genistein inhibited UV-induced DNA damage as evaluated with the formation of pyrimidine dimers [65]. A dose-dependent inhibition of UVB-induced pyrimidine dimer formation was observed relative to increasing genistein concentrations [65]. Genistein substantially inhibits skin carcinogenesis and cutaneous aging induced by UV in mice and photodamage in humans [66]. Topical application of genistein before UVB radiation reduced the expression of c-fos and c-jun in the SENCAR mouse skin in a dose dependent manner [67]. Two promotion studies using DMBA and TPA protocol were conducted using CD-1 and SENCAR mice. Both these studies consistently showed that genistein substantially inhibited TPA-promoted skin tumorigenesis by reducing the tumor multiplicity. Genistein also inhibited DMBA-induced bulky DNA adduct formation and substantially suppressed TPA-stimulated H_2O_2 inflammatory responses and ODC activity in mouse skin [68].

5. Fisetin

Fisetin (3,7,3′,4′-tetrahydroxyflavone) is a flavonol, a structurally distinct chemical substance that belongs to the flavonoid group of polyphenols together with quercetin, myricetin and kaempferol with a chemical formula described earlier by the Austrian chemist Josef Herzig in 1891. It can be found in various plants, fruits and vegetables including apples, onions, persimmons and strawberries, where it functions as coloring agent [69], and was originally identified as an oxidative stress-induced nerve cell death inhibiting compound [70]. It has also been shown to possess neurotropic effects, promoting nerve cell differentiation and to enhance learning and memory in mice upon oral administration [71, 72]. In addition to its direct antioxidant and anti-inflammatory activities, fisetin can increase the intracellular levels of glutathione, and can as well reduce the production of lipid peroxides and their pro-inflammatory by products [73]. In addition to its neuroprotective and anti-ageing effects, recent data suggests that fisetin possess anticancer properties, and have been shown to induce apoptosis in diverse cancer cell lines [73]. A more recent report showed that fisetin treatment of human melanoma cells resulted in decreased cell viability and disruption of Wnt/β-catenin signaling associated with reduction of Wnt protein and its co-receptors expression, parallel by an increase expression of two endogenous Wnt inhibitor proteins, increased cytosolic levels of Axin and β-TrCP and decreased phosphorylation of GSK3-β [74]. An intraperitoneal administration of fisetin to mice was shown to significantly inhibit human melanoma tumor development and suggested that this "nontargeted therapies" is

promising to be effectively developed as a therapy armamater against melanoma since targeted therapies do not tar*get al*l of the pathways required for melanoma growth [74].

6. Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene), a polyphenolic flavonoid belonging to the stilbene family of phytoalexins, is found in grapes, nuts, berries and red wine. Resveratrol has been reported to exhibit a wide range of biological and pharmacological properties. Several plants including grapevine synthesize resveratrol when attacked by fungal pathogens [75]. Epidemiological studies indicate that the French have relatively lower risk of cardiovascular disease despite consuming a diet rich in fat. In reality, the high concentration of resveratrol in red wine consumed by the French is frequently cited to account for the "French Paradox" [5]. There have been extensive studies demonstrating that resveratrol possesses an ability to intervene in multistep carcinogenesis. In addition, resveratrol may be beneficial in the control of artherosclerosis, heart disease, arthritis or autoimmune disease. According to a study by Pezzerto *et al*. [76] resveratrol significantly reduced the number of tumors per mouse in a two-stage skin carcinogenesis model. In the *in vivo* assay, resveratrol offered a 60% reduction in DMBA and TPA-induced skin papillomas in mouse at 20 weeks [77]. Single topical application of resveratrol to SKH-1 hairless mice resulted in significant inhibition of UVB-mediated increase in skin edema. Resveratrol treatment to mouse skin also resulted in significant inhibition of UVB-mediated induction of COX and decreased ODC activity. It was also observed that resveratrol inhibited UVB-mediated increased level of lipid peroxidation which is a biomarker of oxidative stress [78]. Further, topical application of resveratrol to SKH-1 hairless mouse skin prior to UVB-radiation resulted in the inhibition of UVB-induced cellular proliferation, phosphorylation of surviving and upregulation of apoptotic factors (Smac and Diablo). The anti-proliferative effects of resveratrol might be mediated via modulation in the expression and function of cell cycle regulatory proteins like cyclin D1 and D2, cdk 2, 4, 6 and p21 and maybe associated with the inhibition of the MAPK pathway [79]. In normal human epidermal keratinocytes, resveratrol blocked UVB-mediated activation of NF-κB in a dose- and time- dependent fashion. Resveratrol treatment in these cells also inhibited UVB-mediated phosphorylation and degradation of IκBα and activation of IKKα [80]. Studies have demonstrated that topical application of resveratrol resulted in the inhibition of UVB-induced tumor incidence and a delay in the onset of skin tumorigenesis [81].

7. Pomegranate

The pomegranate (*Punica granatum*) fruit has been used for centuries in ancient cultures for its medicinal purposes. Pomegranate is a rich source of two types of phenolic compounds: anthocyanins (delphinidn-3-glycoside, delphinidin-3,5-diglycoside, pelargonidin-3-glycoside, pelargonidin-3,5-diglycoside, cyanidin-3-glycoside, cyanidin-3,5-diglycoside) and hydrolysable tannins. The other flavonoids present in pomegranate are quercetin, kaempherol and luteolin glycosides [82]. Pomegranate possesses strong anti-oxidant, anti-inflammatory and anti-cancer properties [58, 83]. Pomegranate juice shows potent anti-oxidant propterties that can be attributed to its high content of polyphenols (ellagic acid, EA), anthocyanins and other flavonoids [83].

Studies have demonstrated that treatment of NHEK with pomegranate fruit extract (PFE) prior to UVB-exposure inhibited UVB-mediated phosphorylation of ERK1/2, JNK1/2 and p38 proteins in a dose- and time- dependent manner [84]. The treatment also resulted in inhibition of UVB-mediated degradation and phosphorylation of IκBα, activation of IKK, nuclear translocation and phosphorylation of NF-κB/p65 at Ser 536 [84]. Another study has reported that PFE treatment of NHEK inhibited UVA-mediated phosphorylation of STAT-3, AKT and ERK1/2 [85]. Topical application of PFE resulted in inhibition of TPA-induced tumor promotion in DMBA-initiated CD-1 mice. Mice pretreated with PFE showed reduced tumor incidence and lower tumor burden when compared to mice that did not receive PFE [86]. Treatment of HaCaT cells with PFE prior to UVB-exposure protected cells from UVB mediated decrease in cell viability, inhibited UVB-mediated decrease in endogenous glutathione levels, lipid peroxidation and expression of MMP-2 & MMP-9 [87].
Delphinidin, a major anthocyanin present in pomegranate, protected NHEK from UVB-mediated decrease in cell death [88]. The study reported an induction of apoptosis, a decrease in PCNA, activation of caspases and an increase in PARP expression [88]. Topical application of delphinidin to SKH-1 hairless mice inhibited UVB-mediated apoptosis and markers of DNA damage such as CPDs and 8-OHdG. Oral feeding of PFE to SKH-1 mice inhibited single UVB exposure mediated epidermal hyperplasia, infiltration of leucocytes, generation of hydrogen peroxide and lipid peroxidation [89]. PFE consumption further protects mouse skin against the adverse effects of UVB radiation by modulating UVB-induced signaling pathways such as NF-κB, MAPKs, c-Jun [86]. Topical and oral administration of pomegranate to humans was shown to augment the protective effects of sunscreens and afforded protection from UVB. A double blind, placebo-controlled clinical trial indicated that oral intake of PFE inhibited UV-induced pigmentation in the human skin [90].

8. Lupeol

Lupeol, a triterpene found in fruits such as olives, mango, strawberry, grapes, figs and in medicinal plants like ginseng, shea butter plant, *Tamarindus indica*, *Bombax ceiba* [91] and has been used by native people in North America, Latin America, Japan, China, Africa and the Caribbean islands [92-97]. Lupeol has been demonstrated to inhibit various pharmacological activities under *in vitro* and *in vivo* conditions. These include its beneficial activity against inflammation, cancer, arthritis, diabetes, heart disease, renal- and hepatic toxicity [94, 98-107]. Topical application of lupeol alleviated TPA-induced inflammation in the ear mouse model [98] and decreased the expression of myeloperoxidase, a neutrophil specific marker, resulting in reduced infiltration into inflamed tissues [98]. Lupeol was found to reduce infiltration in mouse model of arthritis, an inflammation associated disease [108]. This beneficial effect was shown to be associated with the potential of lupeol to modulate the immune system. Lupeol was reported to suppress CD4+ and CD8+ T cell counts resulting in reduced cytokine expression (IL-2, IL-4,IFN-gamma) [109].
Epidemiological data suggests that the content of phytosterols (like lupeol) in the diet is associated with a reduction in common cancers including cancer of breast, prostate and colon [110, 111]. Tumorigenic animal models suggest that phytosterols modulate host systems potentially enabling more robust anti-tumor responses such as enhancing immune recognition of tumor cells, altering hormone-dependent growth of endocrine tumors, and modulating sterol biosynthesis [91, 111]. Mutation that occurs through DNA strand breaks

have been shown to form the precursor of cancer development [112-115]. An accumulation of these mutations transform neoplastic cells into malignant carcinomas. Lupeol was reported to exhibit strong anti-mutagenic activity under *in vitro* and *in vivo* systems [102, 116]. A study demonstrated that topical application of lupeol prevents DMBA-induced DNA strand breaks in murine skin [102]. Recently, lupeol was shown to inhibit benz-a-pyrene induced genotoxicity in mouse models [117].

There is increasing evidence that lupel inhibits tumor promotion in two stage skin carcinogenesis in mouse model [103]. Topical application of lupeol for 28 weeks was shown to significantly decrease tumor burden and tumor multiplicity [103]. The anti-tumor effects were observed to be associated with the potential of lupeol to modulate signaling pathways like NF-κB and phosphatidylinositol-3-kinase (PI3K)/Akt, that play an important role in tumorigenesis [103]. Lupeol was shown to significantly inhibit NF-ΚB translocation to the nucleus and its DNA-binding activity in a mouse model of skin tumorigenesis [103]. Lupeol was also observed to inhibit ODC activity, an important biomarker of tumor promotion [103, 118]. Lupeol was also shown to inhibit growth of highly metastatic tumors of human melanoma origin by modulating the expression of BCl-2 and Bax proteins [104]. A recent study demonstrated that lupeol significantly inhibits the growth of metastatic melanoma cells that harbor constitutive activation of Wnt/β-catenin signaling [119].

9. Silymarin

Silymarin refers to three mixtures of flavonoids including silybin, silydianin and silychristin, a flavanolignan, isolated from the fruits and seeds of the plant milk thistle (*Silybum marianum* L. Gaertn.) which are protective against photocarcinogenesis. Mouse models studies elucidated that silymarin possess antioxidant, anti-inflammatory and immunomodulatory properties responsible for its efficacy against photocarcinogenesis [120, 121]. Using UV-irradiated human melanoma cells silymarin was shown to protect against UV-induced apoptosis as well as modulation of the cell cycle with increase in the G2/M phase [120]. Silymarin's potential to reduce UV-induced apoptosis is partially through activation of human deacetylase SIRT1 as well as by activation of the AKT and MAPK pathways [122]. An unclear knowledge of whether the protective effects of silymarin in melanoma cells is beneficial to melanoma prevention still lingers, but it was shown to enhanced the cytotoxic effect of anti-Fas agonistic antibody on human melanoma cells [123]. A more recent report showed that silybinin, a major active constituent of silymarin, prevented mitomycin C-induced apoptosis in human melanoma cells through suppression of the mitochondria-mediated intrinsic but not the extrinsic apoptosis pathway [124]. However, further studies are required to delineate the role of silymarin in the prevention of melanoma carcinogenesis.

10. Other multifaceted food bioactive agents

It has become clear that plants and phytosynthetic agents possess a broad spectrum of targeted and non-targeted potential drug compounds for cancer prevention and therapy. The anticancer properties of other fruits and vegetables are partly related to their isoprenoid constituents. A report showed that isoprenoids extracted from different plants possesses variable degrees of potency in suppressing the growth and proliferation of melanoma and other cancer cells [125]. Perillyl alcohol, derived from essential oils of lavendin, peppermint

and other diverse plants, is known to inhibit melanoma cell growth [125], but only few reports examined their efficacy in melanoma in situ. In a recent report topical perillyl alcohol was demonstrated to delay melanoma tumors appearance in TPras transgenic mice [126]. However, only a modest protective effect was detected in sun-burned skin subjects in a double-blind, randomized, phase II trial of topical perillyl alcohol possibly as a result of inadequate delivery through the epidermis [127].
Other bioactive agents such as garlic extract [128], exo-biopolymer from rice bran [129], and isothiocyanates extract of wasabi [130], as well as flavonoids such as hesperitin, naringenin [131] and chrysin derived from acacia honey [132] have been evaluated for their cytotoxic effect on melanoma cells. A limited number of studies have been effectuated on these compounds with several of them appearing as potential agents against melanoma, but the exact knowledge regarding their active excipient as well as their mechanistic potentials requires extensive *in vitro* cell culture and *in vivo* animal model studies to elucidate.

11. Nanotechnology for melanoma

There are several issues in the effective prevention and therapy of melanoma which include development of novel agents, determination of optimal therapeutic combinations and effective delivery of agents to the tumor. The optimal agent delivery, which is the most important issue, is essential to improve drug concentrations, reduce side effects, and lower effective doses for better efficacy of the agents. We recently employed the use of nanotechnology to improve the outcome of chemopreventive intervention and coined the term 'nanochemoprevention' [119]. Utilization of nanotechnology for the development of efficient anticancer drug delivery system is one of the most recent advancement in medical science. The structure and tunable surface functionality of nanoparticulate system allows it to encapsulate/conjugate single or multiple entities either in the core or on the surface, rendering them ideal carriers for various anticancer drugs. Further, most drugs have poor solubility and low bioavailability, and are formulated with undesirable solvents, and, the use of nanocarriers, allows for the preparation of low water soluble cancer medications as solid or liquid formulations.
For melanoma research, utilization of nanotechnology is a relatively new and rapidly developing field with constant research going on all around the world. So far no natural agents have been nanoformulated but constant work is going on and nanotechnology is being actively utilized in melanoma research. In one of the first study in the field, Banciu *et al*. [133] evaluated the inhibitory effects of glucocorticoids (GC) encapsulated in long-circulating liposomes (LCL-PLP) (LCL-GC). The effects of all LCL-GC on the production of angiogenic/inflammatory factors *in vivo* in the B16.F10 murine melanoma model as well as on the viability and proliferation of tumor cells and endothelial cells *in vitro* were investigated. The results showed that all four selected LCL-GC formulations inhibit tumor growth, albeit to different degrees. The differences in antitumor activity of LCL-GC correlate with their efficacy to suppress tumor angiogenesis and inflammation. The *in vitro* results presented suggested that LCL-BUP has strong cytotoxic effects on B16.F10 melanoma cells and the anti-proliferative effects of all LCL-GC towards angiogenic endothelial cells play a role in their antitumor activity.
Tran *et al*. [134] discussed some promising new nanotechnology based therapies under development for the treatment of melanoma. This article summarized the utilization of liposomes for effective therapy of melanoma. A recent study demonstrated that the delivery

of doxorubicin using a nanotechnology-based platform significantly reduces the systemic toxicity of the drug, keeping unchanged its therapeutic efficacy in a mouse melanoma tumor model. Single-walled carbon nanotubes were used to conjugate a doxorubicin prodrug. The CNT-doxorubicin conjugate (CNT-Dox) induced time-dependent cell death in B16-F10 melanoma cells *in vitro*. The nanoparticle was rapidly internalized into the lysosome of melanoma cells and was retained in the subcellular compartment for over 24 h. In an *in vivo* melanoma model, treatment with the nanotube-doxorubicin conjugate abrogated tumor growth without the systemic side-effects associated with free doxorubicin. High-resolution photoacoustic tomography (PAT) with extraordinarily optical absorbing gold nanocages (AuNCs) was utilized in a study [135]. When bioconjugated with [Nle(4),D-Phe(7)]-alpha-melanocyte-stimulating hormone, the AuNCs served as a novel contrast agent for *in vivo* molecular PAT of melanomas with both exquisite sensitivity and high specificity. The bioconjugated AuNCs enhanced contrast approximately 300% more than the control, PEGylated AuNCs. A study optimized the antitumoral effects of direct electric current (DC) with poly(ε-caprolactone) (PCL) nanoparticles loaded with the amino acid tyrosine. The authors observed that the *in vitro* cytotoxicity of DC was significantly increased when associated with L-tyrosine-loaded NPs, using a murine multidrug-resistant melanoma cell line model. More studies involving nanotechnology are certainly required to be utilized in melanoma research that will open new avenues for prevention and therapy of melanoma. Studies involving nanoformulation of bioactive food components will be a welcome addition where nanotechnology could be involved to improve pharmacokinetics and reduce side effects associated with drugs.

12. Conclusions

With incessant efforts by the researchers worldwide, the prospect for the therapy of advanced melanoma has improved considerably and currently the future of this avenue is considered very optimistic. As described throughout this manuscript bioactive food components have great potential for melanoma therapy with each agent demonstrating multidimensional effects and targets as summarized under table 3. Although the preclinical data with these and other natural agents is encouraging, data from epidemiological studies is still needed to indicate a definite efficacy. Also, further understanding of the molecular and immunologic mechanisms that promote survival of melanoma tumor cells is needed. Several gene and protein modulation as depicted in table 2 could be targeted for better regulation of melanoma progression. Such information will undeniably lead to the development of better, more specific and less toxic agents. With careful planning and rational design of future human intervention trials and cohort studies natural agents could be easily exploited for betterment of patients with melanoma.

Another approach that seems promising is utilizing a combination of two or more bioactive food components. In contrast to the single agent approach, researchers should direct their attention upon different natural and synthetic products as a complex mixture, a cocktail approach, which together may have synergistic anti-cancer benefits. This approach could be exploited both *in vitro* and *in vivo* as well as in clinical and epidemiological studies. Since utilization of these bioactive food agents is relatively inexpensive, simple to use and possibly non-toxic, studies to assess its role in clinical melanoma is accessible and will be of interest. As many *in vitro* and *in vivo* studies assessing the role of dietary agents on melanoma have shown significant effects against multiple targets, an in-depth analysis of our approach with the chemopreventive cocktail is warranted.

Gene	Protein	References
Gene amplification		
MITF	Mitf	[142, 143]
BRAF	Braf	[143, 144]
c-MYC	c-Myc	[144-147]
HRAS	H-Ras	[148, 149]
CCND1	Cyclin D1	[150]
CDK4	Cdk4	[150]
CDH2	N-cadherin	[145, 151]
Gene losses		
ITGB3BP	beta 3 endonexin	[152]
CDKN2A	P16Ink4a/ p14Arf	[144, 150]
PTEN	Pten	[145, 150]

Table 2. Alterations involving known genes found in melanomas

Agent	Effects observed	References
Tea polyphenols	Inhibition of skin tumorigenesis	[16-19]
	Decreased UVB induced ODC, COX and tumorigenesis;	[20, 21, 23-25]
Curcumin	Inhibition of photoaging and photocarcinogenesis;	[30, 31]
	Modulation of multiple signaling pathways	[29, 32-34, 39, 48, 50, 54]
	Increase of intrinsic apoptotic pathway and/or autophagy	[42, 43]
Genistein	Inhibition of UV-induced effects *in vitro* Inhibition of inflammation and ODC activity	[64-66] [68]
Fisetin	Decreased cell viability and disruption of Wnt/β-catenin pathway	[74]
Resveratrol	Inhibition of skin tumorigenesis	[76, 77, 81]
	Decreased oxidative stress	[78]
Pomegranate	Modulation of multiple signaling pathways	[84-87]
	Inhibit UV-mediated apoptosis and DNA damage, photoprotection	[88, 89]
	Inhibit UV-induced pigmentation	[90]
Lupeol	Inhibit DMBA-induced DNA strand breaks and B(a)P induced genotoxicity	[102, 117]
	Inhibit tumor promotion, ODC activity etc.	[103, 104, 118]
Silymarin	Exhibit antioxidant, anti-inflammatory and immunomodulatory properties	[120, 121]

Table 3. Observed effects of various bioactive food components in skin cancer

13. Glossary

UVB	Ultraviolet B
ROS	reactive oxygen species
CPD	cyclobutane pyrimidine dimers
8-OHdG	8-hydroxy-2'-deoxyguanosine
EGCG	epigallocatechin-3-gallate
ECG	epicatechin-3-gallate
EC	Epicatechin
GTP	green tea polyphenols
TPA	12-O-tetradecanoyl-phorbol-13-acetate
ODC	ornithine decarboxylase
DMBA	7,12-dimethylbenz-a-anthracene
NF-ĸB	Nuclear factor-kappa B
TNF-α	tumor necrosis factor-alpha
XIAP	X-linked inhibitor of apoptosis
MMP	matrix metalloproteinase
TIMP	tissue inhibitor metalloproteinase
MT1-MMP	membrane type 1-matrix metalloproteinase
FAK	Focal Adhesion Kinase
Nm23	Non-metastatic 23
STAT1	signal transducer activator 1
NHEK	Normal Human Epidermal Keratinocyte

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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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