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Antioxidant Defense and UV-Induced Melanogenesis: Implications for Melanoma Prevention

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1. Introduction

Ultraviolet radiation (UVR) has been implicated as a major environmental factor in the pathogenesis of photoaging and skin cancers including melanoma. Hypermelanosis induced by UVR has been previously suggested to associate with melanomageneis, although the role of UVR in the development of melanoma is complicated since melanogenesis may depend on several factors such as skin type, genetic influence, the extent of sun exposure (e.g., intensity, timing and duration of UVR) and types of moles representing disturbed melanin synthesis (Parvel et al., 2004; Rass & Reichrath, 2008; Tran et al., 2008). Melanin has been well recognized for its photoprotective properties, although melanogenic intermediates can be phototoxic and UVR-dependent elevated melanogenesis could thus be biologically harmful, genotoxic and contributed to melanoma initiation, especially in lightly pigmented individuals (Brenner & Hearing, 2008; Smit et al., 2008; Takeuchi et al., 2004; Yamaguchi et al., 2006). The desire to have fair or tanned skin depends on different cultures. The use of whitening agents has been growing in the Eastern culture, whereas having tanned skin is favorable and attractive in the Western culture that makes artificial tanning products become increasingly popular. Various factors including endocrine and environmental factors, in particular UVR, affect melanogenesis, mainly regulated by tyrosinase in melanocytes and/ or melanoma cells, in response to physiological and pathological changes (H.Y. Park et al., 2009; Slominski et al., 2004).

This chapter focuses on the role of UV-induced oxidative stress in association with melanogenesis, which can be modulated by antioxidant defenses. Several studies have supported the relationship between UVR-mediated melanogenesis and oxidative stress, which takes place when there is increased production of reactive oxygen species (ROS) and/ or reactive nitrogen species (RNS) as well as antioxidant network impairment (Baldea et al., 2009; H.T. Wang et al., 2010). Therefore, improving antioxidant defense capacity to cope with oxidative insults may be beneficial in attenuation of abnormal production of melanin that could have a biological significance for the skin in protecting against photodamage. Whereas hyperpigmentation mediated by UV irradiation could reflect a sign of defensive response of the skin to stress, alteration in melanin synthesis may be implicated in skin damage and probably melanomagenesis, particularly in individuals with fair skin. Therefore, understanding the mechanisms by which antioxidants may modulate UVR-

induced melanogenesis is of significance in order to develop effective antimelanogenic agents, which may be therapeutically useful for melanoma prevention.

2. UV-induced melanogenesis and melanomagenesis

Recently, the incidence of various diseases and disorders of the skin related to solar radiation continues to grow. Acute and chronic exposure of the skin to UVR can induce various cellular and biological changes including sunburn cell formation, DNA damage, loss of cell homeostasis and function, abnormal pigmentation, immunosuppression and inflammation responsible for several skin problems, particularly photoaging and skin cancers including non-melanoma and melanoma, the most aggressive type of skin cancer (Afaq & Mukhtar, 2001; Scharffetter-Kochanek et al., 2000). Skin can be exposed to both UVB (290-320 nm) and UVA (320-400 nm) radiation exhibiting various detrimental effects on the skin by triggering cellular and molecular responses that are responsible for damage of epidermis composed of keratinocytes, melanocytes and Langerhans cells as well as dermis consisting of fibroblasts and other skin components, especially extracellular matrix including collagen and elastin (Pinnell, 2003). The acute effects of UVR cause keratinocyte toxicity or sunburn, DNA damage and altered melanin synthesis. The chronic effects of UVR result in accumulation of degraded collagen and abnormal elastin that could contribute to photoaging as well as mutagenesis leading to photocarcinogenesis including melanomagenesis (von Thaler et al., 2010). UVB radiation is considered as the "burning ray" and makes up 4-5% of UV light reaching to the earth and more than 90% of solar radiation that reaches us is UVA. UVA reaches the earth's surface to the greater extent than UVB and the longer wavelength of UVA makes it penetrate deeper through the epidermal layer, reaching the dermis, whereas UVB, which has a shorter wavelength, is more energetic and mutagenic than UVA (Bennett, 2008). The biological effects of UVB and UVA on the skin are different. UVB radiation preferentially results in direct DNA damage, which happens when DNA directly absorbs the UVB photon, to produce DNA photoproducts, typically cyclobutane pyrimidine dimers (CPD) and 6,4-photoproducts implicated in genotoxicity (Seite et al., 2010). However, UVA has no direct influence on DNA as the absorption of UVA photons by chromophores in the skin cells can induce generation of ROS, e.g., singlet oxygen and hydrogen peroxide (H_2O_2), which in turn damages DNA through formation of mutagenic oxidative DNA products such as 8-hydroxydeoxyguanosine (8-OHdG), single-strand breaks in DNA and DNA-protein crosslinks (Pfeifer et al., 2005). Fortunately, the cells including melanocytes have many DNA repair systems including nucleotide excision repair (NER), a vital repair mechanism for photodamaged skin, that remove various types of DNA lesions induced by UVR. However, when the repair mechanisms are not capable of restoring genomic integrity, mutations can occur and lead to the development of skin cancer (Gaddameedhi et al., 2010).

Experimental and epidemiological studies have indicated that UVB capable of generating photoproducts might be the primary cause for non-melanoma skin cancer and UVA-mediated oxidative damage may be a possible risk factor of malignant melanoma (Bennett, 2008; Rass & Reichrath, 2008). In addition, UVA-dependent indirect DNA damage via oxidative stress in melanocytes has been postulated to be involved in the development of malignant melanoma via different mechanisms (Pavel et al., 2004). UVA radiation was observed to contribute more to the generation of photoproducts-related oxidative damage of DNA including CPD than UVB (Besaratinia et al., 2005). The ROS/ RNS primarily generated

by UVA radiation can cause direct deleterious chemical modifications to cellular components including lipids, proteins and, especially DNA, which can eventually initiate melanomagenesis (Cotter et al., 2007). A disturbance in the antioxidant network and an accumulation of oxidative products were also demonstrated in skin tissues of melanoma skin cancer and in melanocytes from atypical nevi (Sander et al., 2003; Smit et al., 2008). Moreover, the presence of high levels of RNS, in particular nitric oxide (NO), and nitrosative products in cutaneous melanoma has been observed to be correlated with poor prognosis of patients and contributed to melanoma invasiveness (Chin & Deen, 2010). Thus, excessive ROS/ RNS-mediated imbalanced redox state and oxidative damage to the biomolecules of melanocytes might play a role in the pathogenesis of malignant melanoma by disturbing cellular machinery that further impairs cellular homeostasis and function involving differentiation, proliferation and malignant transformation of melanocytes (Campos et al., 2007; Kadekaro et al., 2005). Ultimately, UVR can initiate melanomagenesis via various pathways including mutagenicity of DNA photoproducts and interference in cell signaling that subsequently affects melanocyte apoptosis, proliferation, differentiation and functions including the regulation of melanogenesis (von Thaler et al., 2010; Wittgen & van Kempen, 2007). It has been proposed that UVR-dependent disrupted synthesis of melanin, known to be photoprotective or phototoxic, is regarded as an indirect effect of UVR responsible for melanomagenesis, although the connection between melanin production and the development of melanoma is poorly understood. UVR-mediated abnormality of melanogenic responses may result in cytotoxicity and mutagenicity, particularly in lightly pigmented melanocytes, that could contribute to malignant transformation of melanocytes (Baldea et al., 2009; Marrot et al., 2005; Riley, 2003; Slominski et al, 2004). Development of melanoma could also be associated with aggravation of melanogenesis in the melanocytes having disrupted melanosomes leading to leakage of melanin, which can further damage the cells through oxidative products (Gidanian et al., 2008; Sarangarajan & Apte, 2006). The melanin was demonstrated to significantly augment process of UVA-generated ROS and oxidative DNA damage probably responsible for melanomagenesis in Xeroderma pigmentosum patients, which exhibited impaired NER (H.T. Wang et al., 2010). Higher levels of oxidative DNA products including 8-OHdG induced by UVA exposure also correlated to the melanin contents in the human melanoma cells (Kvam & Tyrrell, 1999). Furthermore, alteration in melanogenic mechanisms in congenital melanocytic nevi was suggested to be accountable for melanoma promotion via aggravation of oxidative stress in melanocytes (Dessars et al., 2009). Hence, attenuation of abnormal melanin production, which could yield damaging effect on the skin, may have a dermatological significance for individuals with high melanoma risk. Targeting strategy for prevention of UVR-induced melanomagenesis therefore may include development of effective antimelanogenic agents and elucidating the antioxidant mechanisms in regulation of melanogenesis is of importance.

3. Melanogenesis and oxidative stress

3.1 Melanin synthesis: The role of UVR

Skin color is attributed to the type, amount and distribution of melanin in the skin. Besides the influence of melanin on the skin color, it also plays a pivotal role in protecting the skin against harmful UVR (Westerhof, 2006). Melanocytes located at the epidermis-dermis junction are dendritic cells with dendrites extending outward from the cell body and the

dendritic processes of differentiated melanocytes are interspersed between neighbouring keratinocytes, forming the so-called epidermal melanin unit (Fig. 1). The melanogenic process takes place within melanosome, which are specialized membrane-bound cytoplasmic organelles, in melanocytes. Melanocytes synthesize melanin in melanosome before passing the melanosomes to the surrounding keratinocytes (Seiberg, 2001).

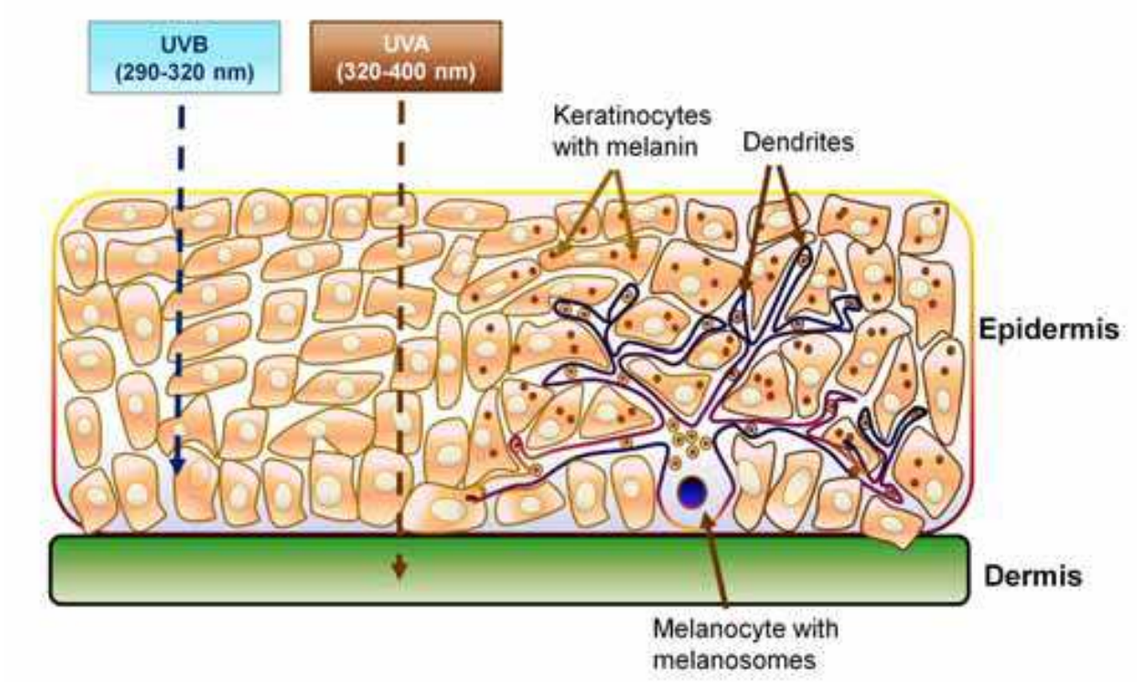

Fig. 1. Epidermal melanin unit

Melanin is synthesized by tyrosinase, a copper-containing metalloglycoprotein and the rate-limiting enzyme, capable of utilizing L-tyrosine, dihydroxyphenylalanine (L-DOPA) and 5,6-dihydroxyindole as substrates. In addition, other enzymes including the tyrosinase related proteins (TRP-1) and dopachrome tautomerase, also known as TRP-2, are responsible for melanogenesis. Melanogenesis is based on the enzymatic conversion of the amino acid tyrosine, through a series of intermediates, to melanin pigments (Ando et al., 2007). Firstly, L-tyrosine is hydroxylated to form L-DOPA. Subsequently, L-DOPA is oxidized to L-DOPAquinone, which will be further processed into either eumelanin (black or brown pigment) or pheomelanin (yellow or red pigment) (Costin & Hearing, 2007). The DOPAquinone produced generally form eumelanin through spontaneous reactions involving cyclization, decarboxylation, oxidation and polymerization. However, TRP-2 can generate 5,6-dihydroxyindole-2-carboxylic acid (DHICA) from DOPAchrome and TRP-1 catalyzes the oxidation of DHICA to indole-5,6-quinone carboxylic acid. In the absence of thiols, DOPAquinone is immediately converted to DOPAchrome and leads to eumelanin production. However, when glutatione (GSH) and cysteine are present, they can react with DOAPquinone intermediates to divert melanin pigment synthesis from eumelanin to pheomelanin through cysteinylDOPA (Ito & Wakamatsu, 2008) (Fig. 2). Besides enzymatic reactions, melanogenic pathway also involves non-enzymatic reactions by evolution of *o*-quinones, generated enzymatically by the action of tyrosinase, to produce several unstable

intermediates, which polymerize to render melanins. A series of both enzymatic and non-enzymatic reactions in eumelanin and pheomelanin synthesis has been observed to subsequently result in H_2O_2 formation (Munoz-Munoz et al., 2009).

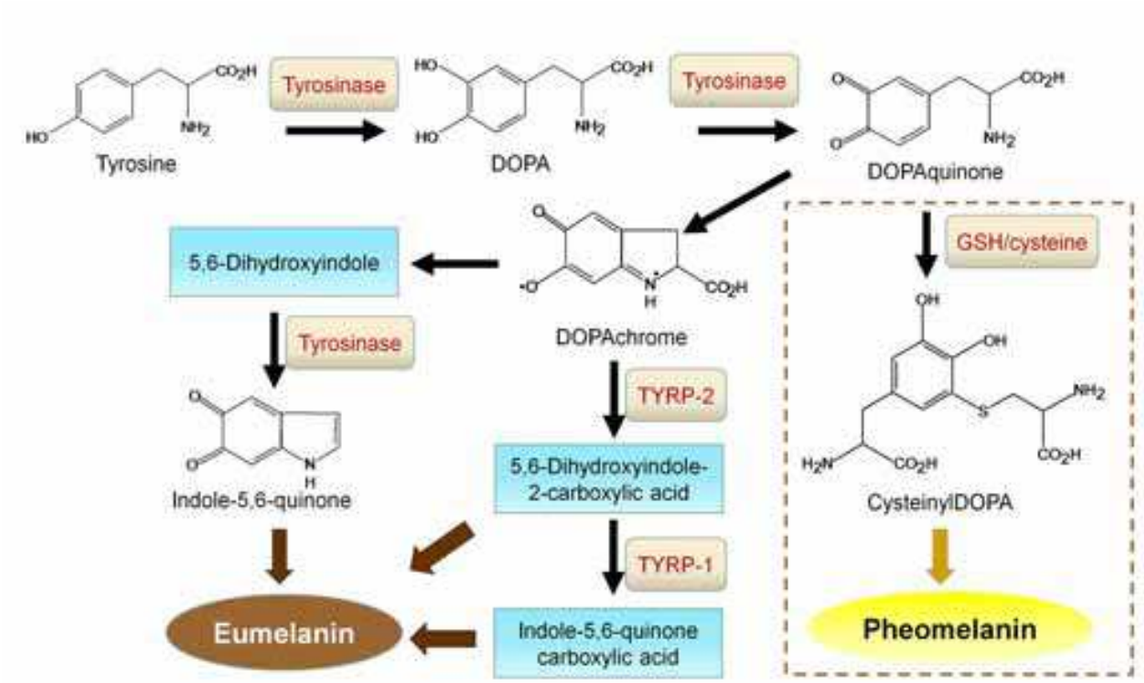

Fig. 2. Melanin synthesis pathway

Generally, variations of the skin or hair color are attributed to the composition of the mixed type of pheomelanin and eumelanin. Disturbance in melanin production can cause esthetic problems including skin hypopigmentary disorders, such as vitiligo, and hyperpigmentary disorders, such as melasma, freckles and postinflammatory hyperpigmentation, that may affect the quality of life of the patients (Halder & Nootheti, 2003). Environmental factors (e.g., UVR and drugs) and endogenous factors (e.g., hormone and age) can mediate the stimulation of melanin production through various signal pathways, which influence tyrosinase regulation. UV can aggravate melanin production in melanocytes either by directly affecting melanocytes or inducing keratinocytes to release signal molecules such as α-melanocyte-stimulating hormone (α-MSH), prostaglandin E_2 (PGE_2), adenocorticotropic hormone (ACTH) and endotholin-1, which can upregulate tyrosinase mRNA (Abdel-Malek et al., 1995; H.Y. Park et al., 2009). Important signaling pathways controlling melanogenesis include melanocortin-1 receptor (MC1R), microphthalmia-associated transcription factor (MITF), cyclic 3'-5'-cyclic adenosine monophosphate (cAMP), mitogen-activated protein kinases (MAPK) and adenyl cyclase. In particular, MC1R-MITF signaling is critical to melanocyte viability and function. Binding of melanogenic proteins or signal molecules, especially α-MSH, to MC1R in melanocytes leads to MITF induction, which subsequently activates transcription of the tyrosinase gene involved in melanin synthesis (Cui et al., 2007).

The roles of UV-mediated oxidative stress implicated in melanogenesis in relation to melanoma are the primary focus of this chapter. An increase in pigmentation is a hallmark

of biological response of melanocytes to UVR. Immediate responses to UVR mediated preferentially by UVA include the tanning, which occurs as a result of photooxidation of melanin, increased dendrite formation and subsequent induction of melanosome transfer from melanocytes to keratinocytes (Maeda & Hatao, 2004). For the delayed response, pigmentation can be generated by both UVB and UVA radiation and correlated to proliferation of melanocytes, increased transfer of melanosomes to keratinocytes and elevated synthesis of melanin. An induction of melanogenesis in response to UVR also depends on different melanocyte cell types, e.g., lightly-pigmented or darkly-pigmented cells (Kadekaro et al., 2003). Melanogenesis has long been recognized to serve as a major defense mechanism to protect the skin against damaging effects of UVR as both eumelanin and pheomelanin can absorb UVR and have antioxidant properties capable of limiting the penetration of UVR into the skin (Meredith & Sarna, 2006). Detrimental effects of UVR on DNA damage and the repair mechanisms could interfere with cellular signals and subsequently stimulate melanogenic response (Eller et al., 1996). Nevertheless, the protective roles of melanin against UVR-mediated skin damage are controversial. It was previously demonstrated that exposures of UVA-mediated skin pigmentation, which occurred as a result of photooxidation of melanin without increased melanin synthesis, failed to provide photoprotective effect on the skin against UVR including UVB radiation (Miyamura et al., 2011; Ou-Yang et al., 2004). The photoprotective properties of melanin are complex and possibly depend on several factors including type of melanins (eumelanin or pheomelain) and UV rays (UVA or UVB) (Miller & Tsao, 2010; Pfeifer et al., 2005). When eumelanin present in almost every type of human skin serves as a UV filter and ROS scavenger to neutralize the toxic intermediates, pheomelanin prevalent in fair-skinned individuals with red hair has been shown to be a photosensitizer aggravating ROS formation after UVR (Takeuchi et al., 2004). Melanocytes produce varying ratios of eumelanin or pheomelanin that affect skin colors in different human populations and also have an influence involving the interplay between genetic factors and UV exposure on susceptibility to melanomagenesis (Scherer & Kumar, 2010). The possible contribution of oxidative stress to the development of melanoma involve several mechanisms and probably associates with melanogenesis since pheomelanin and eumelanin could lead to photogeneration of ROS and serve as a potential source of H_2O_2 (Nofsinger et al., 2002). As reported by epidemiological studies, incidence of melanoma is different with regard to the variety of ethnicity or skin color (Sneyd & Cox, 2009; Veierod et al., 2003). Researchers have thus been attempting to gain insight into the genetic and biochemical factors responsible for melanomagenesis and postulated that UV exposure and pigmentary characteristics may link to melanoma risk (Barsh & Attardi, 2007). The risk observed to be greater for red-haired women could be attributed to genetic influence and sun exposure. Higher sensitivity of the skin to sun exposure appears to be correlated with red hair, which is more common in fair-skinned populations (Veierod et al., 2003). Previous studies suggested that UVR-mediated stimulation of pheomelanin production in association with redox imbalance in lightly pigmented skin could be accountable for melanomagenesis (Meredith & Sarna, 2006; Pavel et al., 2004; Smit et al., 2008). Moreover, in lightly pigmented melanocytes with increased melanogenesis, UVA radiation was observed to trigger greater DNA and membrane damage. Pheomelanin was regarded as a photosensitizer aggravating UVA-mediated DNA damage and cytotoxicity that would explain higher susceptibility of light-skinned individuals to melanomagenesis induced by UVR (H.Z. Hill & G.J. Hill, 2000; Kvam & Tyrrell, 1999; Wenczl et al., 1998).

3.2 The association of melanogenesis and oxidative stress

The production of melanin, primarily pheomelanin, upon UVR results in continuous generation of ROS including H_2O_2, hydroxyl radicals and superoxide radical ($O_2^{\bullet -}$) in melanocytes (Lin & Fisher, 2007; Mastore et al., 2005). In addition, oxidative intermediates including reactive quinones, which are cytotoxic to proteins and DNA in the cells, are generated during melanogenesis (Ito & Wakamatsu, 2008; Wenczl et al., 1998). An accumulation of H_2O_2 in normal melanocytes is found to be in direct proportion with the synthesis of melanin. While melanin can yield photoprotective effect, this situation is complex because its antioxidant or pro-oxidant property appears to rely on the redox state in the melanocytes (Sarangarajan & Apte, 2006). When the process of melanin production itself can be a crucial source of ROS, on the other hand, the presence of ROS can give rise to abnormal melanogenesis including overproduction of melanin. Previous studies have reported that enhanced ROS/ RNS formation induced by UVR was correlated to elevation of melanogenesis possibly through upregulation of tyrosinase activity, protein and mRNA in melanocytes and/ or melanoma cells (Dong et al., 2010; Horikoshi et al., 2000; Mastore et al., 2005; Yap et al., 2010). In addition, UVA-induced upregulation of heme oxygenase-1 (HO-1) mRNA, a known stress-response gene normally expressed under photooxidative stress, has been shown to associate with stimulation of melanin synthesis in melanocytes (Marrot et al., 2005). Formation of H_2O_2 or NO and oxidative damage was also found to mediate the promotion of melanin production in melanocytes through activating α-MSH/ MC1R or MITF signaling pathway, which is crucial for melanogenic process (Chou et al., 2010; Dong et al., 2010).

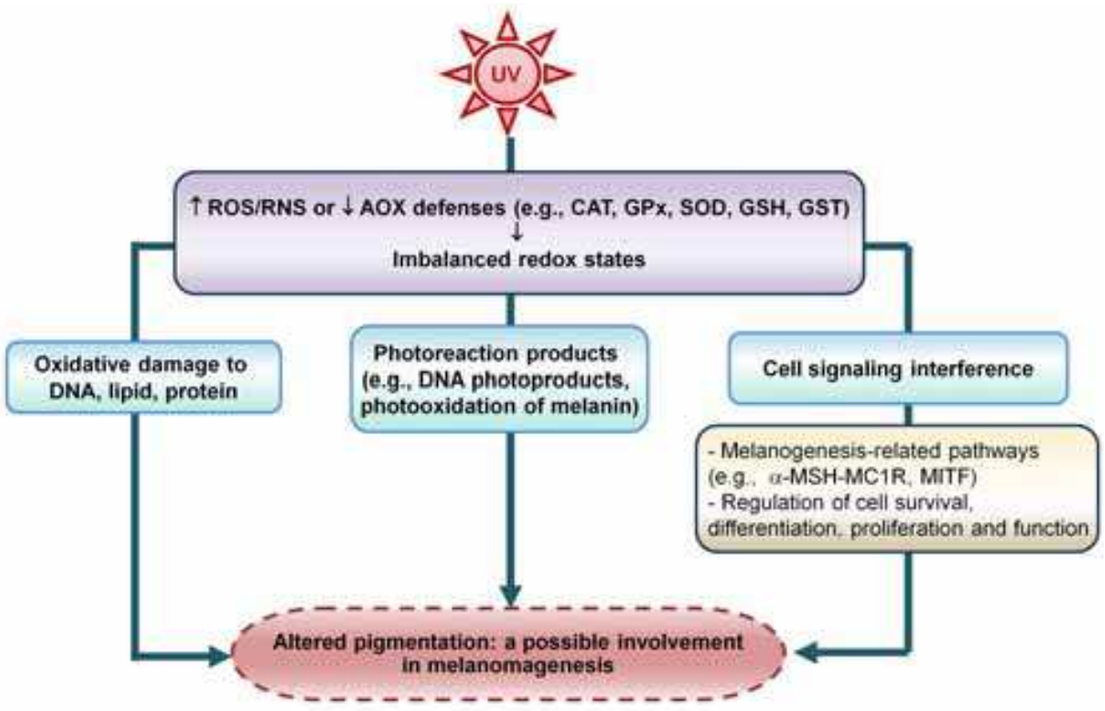

Fig. 3. UVR-induced oxidative stress and alteration in pigmentation

ROS/ RNS generation resulting in melanogenesis could occur either as a direct or indirect response of the skin cells to UVR. Directly, UVB and UVA radiation can interact with

chromophores and melanin in the melanocytes to generate ROS such as H_2O_2 and $O_2^{\bullet-}$ capable of upregulating tyrosinase to promote melanin formation ((Takeuchi et al., 2004; Xiao et al., 2007). Indirectly, UVB and UVA exposure generates ROS and NO through inflammatory and immune responses of keratinocytes to produce various mediators such as α-MSH, cytokines and growth factors. Furthermore, UVA radiation is suggested to exert an influence on melanogenesis preferentially associated with oxidative stress. Previous *in vitro* and *in vivo* studies have reported that UVR-induced ROS/ RNS generation could not only interfere with melanogenesis but also contribute to melanocyte proliferation and transformation, which ultimately leads to melanomagenesis (Horikoshi et al., 2000; Weller, 2003). Fig. 3 shows possible mechanisms by which UVR-induced redox imbalance contributes to altered pigmentation probably involved in melanomagenesis. Thus, antioxidant defenses might play a beneficial role in controlling detrimental effect of excessive melanin induced by oxidant formation.

4. Antioxidant defense system and melanogenesis

During the process of melanogenesis induced by UVR, oxidative insults responsible for melanocyte damage can be generated by various sources including reactive intermediates, particularly H_2O_2, produced during melanogenic process and photochemical reactions of melanin as well as melanin intermediates possessing oxidant properties (Sarangarajan & Apte, 2006). Endogenous antioxidants have been widely recognized to function as an important defense system to prevent skin damage from the hazardous effects of UVR. The abilities of various antioxidants to preserve redox balance could also be crucial for the homeostasis of the skin cells including melanocytes, which are continuously exposed to an oxidative environment (Meyskens et al., 2001). They include enzymatic antioxidants (e.g., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase and thioredoxin reductase) and non-enzymatic antioxidants or low molecular weight antioxidants (ascorbate or vitamin C, GSH and α-tocopherol) (Hanada et al., 1997; Pinnell, 2003). SOD converts $O_2^{\bullet-}$ into H_2O_2 as well as CAT and GPx degrades H_2O_2 into water. Enzymatic and non-enzymatic antioxidants work in a complex network to maintain a redox balance by several mechanisms such as neutralization of oxidants, inhibition of oxidative damage and regulation of transcription factors involved in cell homeostasis and function (Wood & Schallreuter, 2008). As far as a relationship between UVR-mediated oxidative stress and melanogenesis is concerned, it is significant to understand the photoprotective effects of antioxidant defenses, which may be beneficial for the prevention of melanomagenesis.

4.1 Antioxidant defenses: Their protective role against photooxidative stress

Since UVR-mediated ROS production has been postulated to contribute to enhanced melanogenesis possibly regarded an adaptive response to oxidative stress, eliminating excessive ROS production and/ or potentiating the capacity of endogenous antioxidants may be the potential therapeutic strategies for photodamaged skin and, maybe, melanoma development induced by UVR. Major endogenous antioxidants of the skin include GSH, a ubiquitous thiol antioxidant, which potentially maintains redox balance and serves as a substrate for GPx or glutathione-S-transferase (GST), and antioxidant enzymes including CAT and GPx that are primarily involved in the neutralization of H_2O_2, a byproduct of melanogenic process (Campos et al., 2007; Masaki et al., 1998). UVR could result in

deficiency in antioxidant defenses in association with melanocyte damage and disturbance of melanin synthesis (Kvam & Dahle, 2003; Maresca et al, 2008). Additionally, phase II detoxification enzymes, e.g., GST and NAD(P)H quinone oxidoreductase (NQO) and γ-glutamylcysteine synthetase (GCS), a rate-limiting enzyme in GSH synthesis, serve as an important antioxidant enzymes of the skin and play a vital role in protection against cell damage by facilitating the elimination of various xenobiotics including chemicals, drugs and pollutants that generate ROS as by-products from the body (Afaq & Mukhtar, 2001; Kokot et al., 2009). Thiol antioxidants, GSH and cysteine involved in a step in pheomelanin synthesis, are capable of protecting melanocytes against unfavorable effects of the reactive species and GSH is also responsible for the conjugation reaction catalyzed by GST to convert a xenobiotic to a non-toxic metabolite (Cotter et al., 2007; Degl'Innocenti et al., 1999; E.S. Park et al., 2007). GST can act as detoxifying antioxidants by catalyzing conjugation reaction of GSH with toxic substrates including quinones and oxidative products as well as by scavenging H_2O_2 occurred during formation of eumelanin and pheomelanin (Meysken et al., 2001). Therefore, detoxification enzymes are essential for the skin in protecting against photooxidative stress. UVR was observed to affect molecular regulation of detoxifying enzymes including GST, NQO and GCS in the skin cells through the transcription factor NF-E2-related factor 2 (Nrf2) (Kannan & Jaiswal, 2006). Nrf2 has been identified to be involved in the human skin adaption to the environmental stress including UVR through the antioxidant response element (ARE), a *cis*-acting enhancer sequence, which transcriptionally regulates the genes encoding phase II enzymes to protect against oxidative damage by maintaining the cellular redox status (Y. Liu et al., 2011; Marrot et al., 2008; Schafer et al., 2010). It has been demonstrated that inhibition of tyrosinase involved in upregulation of GSH detoxification systems including GSH content and GPx and GST activities was able to suppress tumor promotion in mouse skin (Nakamura et al., 2000). Moreover, an influence of GST variations (e.g., GST deficiency) on melanoma risk has been previously discussed (Mossner et al., 2007). Further studies are needed in order to explore whether compounds capable of upregulating various antioxidant defenses including detoxification enzymes could be developed as chemopreventive agents against skin cancers including melanoma.

4.2 Antioxidant defenses: A target for development of antimelanogenic agents

While proper use of sunscreens has been widely recommended to protect against UVR-mediated skin damage leading to a variety of skin disorders including hyperpigmentation, their photoprotective effects could be insufficient when there is overproduction of ROS/ RNS. Attempts have thus been made to develop potential antimelanogenic agents from natural and synthetic compounds and to study the mechanisms by which they function. Several depigmenting agents are now available in oral and topical formulations. Kojic acid and arbutin, the well-known tyrosinase inhibitors, are usually used as standard skin whitening agents in several studies for testing candidate compounds and as ingredients in a variety of skin care products (Parvez et al., 2006). In general, agents exhibit depigmenting effects by acting at various levels of melanogenesis. Since tyrosinase is the rate-limiting enzyme for melanin synthesis, it thus has been the main target of drug designers for new depigmenting agents. Tyrosinase inhibitors can serve as competitive inhibitors of tyrosinase or non-competitive inhibitors (such as inhibitors of melanosome transport and inhibitors of non-enzymatic or oxidative reactions in the melanogenic pathway) (Briganti et al., 2003). Moreover, antimelanogenic agents that have traditionally been used for the treatment of hyperpigmentation include melanocytotoxic agents, e.g.,

hydroquinone and azelaic acid, which can be converted to cytotoxic species (Kasraee, 2002). Nevertheless, based on the findings that oxidative stress, which occurs through increased formation of ROS/ RNS, may be implicated in melanogenesis, agents that can remove oxidants or block the oxidative reactions should also have promising depigmenting properties. This gives a new direction for the search of potential depigmenting agents, and explains the connection between oxidative stress and various pigmentation disorders. Antimelanogenic effects of natural antioxidants (Table 1), phytochemicals (Table 2) and botanicals processing antioxidant properties (Table 3) have been intensively explored in a variety of preclinical *in vitro* cell culture and animal models as well as clinical trials (Gomez-Cordoves et al. 2001; Saikia et al. 2006). Phytochemicals including phenolics and essential oils, usually identified as active ingredients in botanicals, are capable of scavenging ROS/ RNS and inhibiting cellular oxidative stress and thus might be responsible for the pharmacological effects of the plant extracts (Verschooten et al. 2006; K.H. Wang, 2006).

Natural antioxidants	**Antimelanogenic actions**
Ascorbic acid and its derivatives e.g., magnesium L-ascorbyl-2-phosphate (VC-PMG), ascorbyl 2-phosphate 6 palmitate (APPS) and tetra-isopalmitoyl ascorbic acid (VC-IP)	Application of VC-PMG cream for 3 months reduced hyperpigmentation in some patients (Kameyama et al., 1996). APPS lotion applied for 4 weeks reduced perifollicular pigmentation in a randomized, single-blinded, placebo-controlled clinical trial (Inui & Itami, 2007). Topical application of VC-IP for 3 weeks suppressed UVB-induced pigmentation in subjects (Ochiai et al., 2006). Their actions may involve inhibitory effects on non-enzymatic or oxidative reactions in the melanogenic pathway (Ando et al., 2007).
Lipoic acid	Suppressed tyrosinase activity, protein and mRNA in B16 melanoma cells (J.H. Kim et al., 2008).
Tocopherol analogues and tocotrienols (e.g., γ- and δ- tocotrienols)	Hydrophilic γ-tocotrienol reduced UV-induced pigmentation in guinea pig skin via inhibition of tyrosinase activity (Kuwabara et al., 2006). Tocotrienols inhibited UVB-induced melanogenesis in different melanoma cells through downregulation of tyrosinase activity and protein (Yap et al., 2010). Their actions may be related to inhibition of oxidative reactions in the melanogeic process and of lipid peroxidation as well as promotion of GSH (Yamamura et al., 2002).
α-Tocopheylferulate (α-tocopherol linked to ferulic acid by an ester bond)	Suppressed tyrosinase activity at the post-translational level possibly via anti-oxidative action in normal human melanocytes (Funasaka et al., 2000).

Table 1. Studies on the antimelanogenic actions of natural antioxidants

Phytochemicals/sources	Antimelanogenic actions
Daidzein derivatives (e.g., 8-hydroxydaidzein)	Exhibited antityrosinase effect on B16 melanoma cells. Application of 8-hydroxydaidzein cream for 2 months provided whitening activity in human volunteers (Tai et al., 2009).
Gallic acid	Inhibited tyrosinase activity possibly via reduction of ROS formation and elevation of GSH/ GSSG ratio in B16 melanoma cells (Y. J. Kim, 2007)
Hydroxycinnamic acids (e.g., caffeic acid, ferulic acid and *p*-coumaric acid) from corn bran	Suppressed tyrosinase activity in B16 melanoma cells via free radical scavenging activity (S.W. Choi et al., 2007).
Luteolin	Suppressed tyrosinase activity via inhibiting ROS formation in B16 melanoma cells (M.Y. Choi et al., 2008).
Origanoside from *Origanum vulgare*	Downregulated tyrosinase activity as well as tyrosinase, MITF and TRP-2 proteins in B16 melanoma cells and reduced pigmentation in mice skin (Liang et al., 2010)
Proanthocyanidins from grape seed	Oral administration reduced UV-induced pigmentation of guinea pig skin. Their actions may involve ROS/ RNS scavenging activities as well as inhibition of oxidative damage of lipid and DNA (Yamakoshi et al., 2003).
Quercetin from rose hip (*Rosa canina L.*)	Downregulated tyrosinase activity and protein in B16 melanoma cells (Fujii & Saito, 2009)
Resveratrol from red wine	Downregulated tyrosinase at post-transcriptional level in human melanocytes (Newton et al., 2007)
Polyphenols such as epigallocatechin-3-gallate (EGCG)	Downregulated tyrosinase and MITF proteins in mouse melanocyte cell line (D.S. Kim et al., 2004)
Vanillin and vanillic acid from *Origanum vulgare*	Downregulated melanogenesis-related signaling including MITF, MC1R, tyrosinase, TRP-1 and TRP-2 via inhibiting ROS formation and lipid peroxidation in B16 melanoma cells (Chou et al., 2010)

Table 2. Studies on the antimelanogenic actions of phytochemicals

Since the skin is the body part that is most accessible to UVR, in order to prevent the cells from harm, the antioxidant defenses of the skin continuously respond to elevated levels of ROS and play an important role in prevention of UVR-induced biological response and damage of the skin cells including melanocytes. However, insufficient protection by antioxidant defense against photodamaged skin can happen due to the accumulation of

stress or oxidative insults induced by UVR. Moreover, antioxidant defenses might fail to neither prevent melanocyte damage nor abnormal pigmentation in relation of UVR-dependent oxidative damage. Recent studies have indicated the possible involvement of defect of antioxidant defenses in increased melanogenesis. UVA-mediated augmentation of melanogenesis was correlated to depletion of SOD and catalase activities and GSH content as well as aggravation of ROS production in lightly pigmented melanocytes (Baldea et al., 2009; Smit et al., 2008). On the other hand, promotion of antioxidant defenses such as GSH level and GPx activity and decrease in ROS/ RNS formation have been found to associate with reduction of melanogenesis by inhibiting tyrosinase activity in cultured melanoma cells and human melanocytes (Benathan, 1997; Y.J. Kim et al., 2008). Thus, exploring antimelanogenic effects of candidate antioxidants and underlying mechanisms involving modulation of antioxidant network could lead to the development of promising depigmenting agents.

Besides abilities of antioxidants to restore redox balance, they have also been found to regulate signaling pathways implicated in the regulation of melanogenesis include α-MSH/ MC1R pathway and MITF. Modulation of pigmentation by antioxidants has been proposed to be achieved through regulating MITF activity. Decrease in ROS levels and recovery of antioxidant defenses including GSH correlated with downregulation of MC1R, MITF and other melanogenesis related signaling pathways (e.g., cAMP, PKA or MAPK) that resulted in reduction of tyrosinase activity and melanin content (Chou et al., 2010; Yanase et al., 2001).

Indeed, the roles of antioxidants in mediating melanogenic signaling cascades are complex and further studies are needed in order to verify implication of antioxidant defenses for regulation of melanogenesis. As reported in many studies concerning depigmenting activity of natural antioxidants or phytochemicals/ botanicals possessing antioxidant properties (Table 1-3), they possibly provide antimelanogenic effects involving several mechanisms including (a) antioxidative actions or free radical scavenging activities capable of inhibiting non-enzymatic reactions in the melanogenic pathway and suppressing oxidative damage of biomolecules including DNA damage, (b) promotion of antioxidant defense capacity to maintain redox homeostasis (c) inhibition of tyrosinase at cellular or molecular levels and (d) regulation of melanogenic signaling cascades.

In addition, antioxidant combinations are suggested to have higher efficacy than single antioxidant that may be due to synergistic effects of the combined preparation (Bialy et al., 2002). Ascorbic acid is often combined with other antioxidants in several skin care formulations as it can recycle other antioxidants, such as α-tocopherol, from their radical forms and thus plays a vital role in the synergistic effects of antioxidant combinations. Tomato extract rich in carotenoids combined with vitamin C and vitamin E yielded protective effects against UVA-mediated hyperpigmentation and DNA damage in human melanocytes (Smit et al., 2004). An open pilot study reported that oral administration of vitamin C combined with bioflavonoids for 4 weeks improved progressive pigmented purpura (Reinhold et al., 1999). Therefore, a combination of depigmenting compounds that target different steps of melanogenic process and give synergistic effects would yield a greater effect and better outcome.

4.3 Antioxidant defenses: Implications for melanoma prevention

Melanin is crucial for skin homeostasis and its complex biosynthesis has a pivotal impact on the melanocyte biology. As discussed earlier, lightly pigmented melanocytes appear to be

Botanicals/their active ingredients	Antimelanogenic actions
Citrus hassaku fruit/ flavanone glycosides	Inhibited tyrosinase activity in B16 melanoma cells and protected against UVB-induced pigmentation in guinea pig skin via radical scavenging activity (Itoh et al., 2009)
Curcuma longa/ curcumin	Inhibited tyrosinase activity as well as melanogenesis-related signaling proteins such as MITF and TRP in B16F10 cells (Jang et al., 2009)
Pomegranate/ ellagic acid	Oral administration inhibited UV-induced pigmentation in guinea pig skin (Yoshimura et al., 2005).
Polypodium leucotomos/ hydroxycinnamic acids	Oral administration for 4 months reduced psoralen-UVA-mediated pigmentation and possibly prevented UVA-induced mitochondrial DNA damage of human skin (Middelkamp et al., 2004; Villa et al., 2010).
Pycnogenol® (French pine bark extract)/ proanthrocyanidins and hydroxycinnamic acids	Oral administration for 30 days reduced pigmentation in women with melasma (Ni et al., 2002) and its action in B16 melanoma cells involved the ROS/ RNS scavenging activity and upregulation of GSH (Y.J Kim et al., 2008).
Silymarin (milk thistle or *Silybum marianum* L.)	Downregulated tyrosinase protein in mouse melanocyte cell line (Choo et al., 2009).
Alpinia spp. (e.g., *A. officinarum*)	Downregulated TRP-1 and TRP-2 mRNA and MITF protein in B16 melanoma cells (Matsuda et al., 2009)
Chestnut flowers/ gallic acid and flavonoids	Downregulated tyrosinase, TRP-1 and TRP-2 proteins possibly via radical scavenging activity in human melanoma cells (Sapkota et al., 2010)
Oolong tea/ polyphenols e.g., EGCG, epicatechin-3-gallate and epicatechin	Oral administration inhibited UVB-induced pigmentation in guinea pig skin by suppression of tyrosinase protein and mRNA (Aoki et al., 2007).

Table 3. Studies on the antimelanogenic actions of botanicals and the possible active ingredients

more susceptible to accumulate DNA damage in UVR-induced tanning, which may be reflected as a protective or stress response of the skin. Melanin in fair skin could be accountable for UVR-induced genotoxicity involving elevated ROS production that may lead to melanocyte transformation (Marrot et al., 2005). A disturbance of redox state, which can be mediated by melanogenesis, may subsequently affect cellular machinery involving differentiation and proliferation of melanocytes and/ or melanoma cells. Decreased activities of antioxidant enzymes (e.g., SOD) were observed to associate with melanoma cell proliferation (Bravard et al., 1999). Nevertheless, redox regulation in melanogenesis related to the pathogenesis of melanoma is complex and the modulation of melanocyte and

melanoma cell homeostasis by redox states remains controversial. Attenuation of ROS formation or upregulation of antioxidant defenses can either enhance or reduce melanogenesis in melanocytes as well as affect melanoma survival. Melanin is well recognized to have photoprotective properties against UVR-mediated melanocyte damage and could be beneficial for the prevention of melanomagenesis induced by UVR. Signaling pathways required for regulation of melanocyte homeostasis and pigmentation including α–MSH-MC1R and MITF were demonstrated to play an essential role in restoring DNA repair as well as in survival and transformation of melanocytes in response to increased intracellular ROS (Abdel-Malek et al., 2006; F. Liu et al, 2009). H_2O_2 also can cause an attenuation of melanin production and, on the other hand, increased melanogenesis associated with elevated activities of antioxidant enzymes including CAT in darkly pigmented melanocytes is more resistant to harmful effects of UVR (Maresca et al., 2008). Therefore, contribution of UV-mediated oxidative stress involved in disturbed melanin synthesis to the pathogenesis of malignant melanoma is complicated and different cell types of melanocytes and melanoma cells studied need to be taken into account. However, beneficial effects of antioxidants on individuals with melanoma susceptibility and under stress environment against development of melanoma seem warranted. As proposed by previous *in vitro* and *in vivo* studies that antioxidants could be useful as chemopreventive agents, antioxidants (e.g., N-acetylcysteine/ NAC) and phytochemicals (e.g., genistein) have been determined to exhibit inhibitory effects on UV-induced melanoma promotion through inhibition of oxidative DNA damage (Cotter et al., 2007; Russo et al., 2006). Oral administration of NAC may yield chemopreventive effects on patients having a high risk for melanoma since it could inhibit UV-induced oxidative stress and GSH depletion in melanocytic nevi (Goodson et al., 2009). Furthermore, phytochemicals (e.g., eugenol from clove oil) and botanicals (e.g., *P. leucotomos*) possessing antimelanogenic properties exhibited photoprotective effects against melanoma development via regulation of signaling cascades involving cell cycle and growth factor (Ghosh et al., 2005; Philip et al., 2009). Possible mechanisms by which augmentation of antioxidant capacity contributes to the protection against melanoma initiation include detoxification of carcinogens and reactive intermediates produced from UVR, inhibition of genotoxicity induced by photochemical reactions in melanogenic process and restoration of redox balance related to signaling cascades involved in cell growth and proliferation (Meyskens et al., 2001). The roles of antioxidants in the inhibition of melanomagenesis yet are controversial as phytochemicals possibly yield anticancer effects on melanoma through increased oxidative stress through aggravation of ROS levels and impairment of antioxidant defense system (e.g., GSH depletion), although they exhibited selective cancer cell toxicity, probably attributed to chemical structures of phytochemicals and differences in redox states and ROS levels between normal cells and cancer cells (Thanasamy et al., 2007).

While applications of sunscreens offer satisfactory effect against sunburn and squamous cell carcinoma, protection against melanoma is more complicated since some studies giving conflicting results on the effect of sunscreens against melanomagenesis (Lin & Fisher, 2007). Additionally, the protective effect of sunscreens against UVR-mediated skin damage appears to be insufficient that may be due to inadequate quantities applied and its ineffectiveness in quenching ROS generated in response to UVR. It is widely recommended that sufficient prevention from deleterious effects of UV radiation is beneficial and thus applying exogenous antioxidants to counteract oxidative stress and/ or promote antioxidant defense capacity may offer a potential pharmacological approach for the prevention of skin

cancers including melanoma. Moreover, the approach of applying antioxidants cannot be the sole strategy to prevent the adverse effects of UVR. Combined strategies including avoidance of excessive sun exposure, appropriate use of sunscreens and skin care products as well as modification of lifestyle and dietary habits are necessary and may yield benefit for prevention of UV-induced melanomagenesis.

This chapter focuses on the aspect of adverse effect of UVR and it is important to emphasize that the contribution of UV exposure to the development of melanoma depends on several factors. Therefore the benefits of moderate sun exposure, for example, UVB, an essential source of vitamin D, that have a remarkable impact on health should not be ignored.

5. Conclusion

While there is a rising demand for antimelanogenic agents and several promising natural compounds are under intensive development, they remain challenging because there is no entirely satisfactory outcome and many agents cause adverse effects. Since UVA irradiation-mediated disturbance in antioxidant defense system and redox state is postulated to play a vital role in melanogenesis, antioxidant-rich medicinal plants have therefore gained attention for their properties in regulating skin pigmentation. We have reported that a recovery of antioxidant defenses including increased CAT and GPx activity and GSH content by *Alpinia galanga* (AG) and *Curcuma aromatica* (CA) was able to counteract UVA-mediated increased melanogenesis through downregulation of tyrosinase in human G361 melanoma cells. Terpenoid derivatives including eugenol and curcuminoids identified in the rhizome extracts of AG and CA, respectively, could be active components responsible for their antimelanogenic effects (Panich et al, 2010). Elucidating the protective roles of phytochemicals and botanicals containing antioxidants against UVR-induced disrupted homeostasis including abnormal pigmentation could offer an approach for development of photoprotective agents that may provide not only cosmetic benefits but also promising interventions for melanoma prevention. Moreover, it is crucial to perform the studies of putative antimelanogenic agents using physiologically relevant skin models such as primary human melanocytes as melanocytes and melanoma cells have different redox states and might provide different responses of antioxidant defenses to UVR-mediated oxidative damage.

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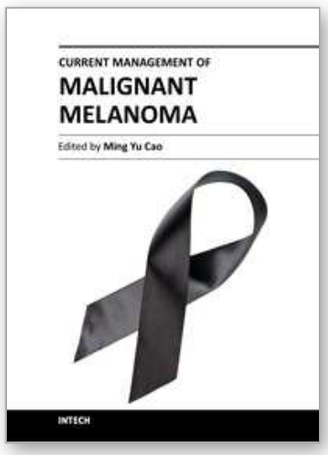

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Management of melanoma is challenging, especially for the late stage of the disease. Development of new therapies and optimizing current treatments are being pursued in attempt to further improve the survival rate. The book provides up-to-date knowledge and experience in early diagnosis, prevention and treatment of melanoma as well as current ongoing clinical studies on melanoma. The book also provides the most recent perspectives of research on the molecular basis of melanoma, such as melanoma associated genes and a possible link between stress and melanoma.

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