INTRODUCTION

The skin is the most vital and largest organ in the human body. Skin is responsible for sense of touch. Skin is primarily composed of two layers: epidermis, the outer layer, and dermis, the inner layer. Skin primarily protects the human body from the damage caused by the external environmental agents such as UV rays, pathogens, and pollutants. In addition, vitamin D, a fat-soluble vitamin, is synthesized in the skin by the action of UV rays emitted by the sunlight. Apart
from beneficial effects, UV rays emitted by the sunlight are associated with several adverse effects. For example, UV rays emitted by the sunlight are responsible for causing skin cancer. According to the National Cancer Institute, skin cancer is the most common type of cancer in the United States, affecting approximately one million Americans every year [National Cancer Institute 2005]. UV rays have a wavelength ranging from 200 to 400 nm. UV rays based on their wavelengths are further classified into UV-A rays (320−400 nm), UV-B rays (280−320 nm), and UV-C rays (200−280 nm) [Katiyar 2007]. Sunlight primarily constitutes UV-A rays, to which we are mainly exposed, have a greater ability to penetrate the cutaneous layers, and are responsible for skin wrinkle, aging, and immune suppression [Katiyar 2007]. UV-B rays are mutagens and are shown to be responsible for melanoma (skin cancer that is formed in melanocytes) and non-melanoma types (skin cancer that is formed in basal cells and squamous cells) of skin cancers [Urbach 1978]. In addition, they are also responsible for erythema, sunburns, and immune suppression. UV-A and UV-B rays are responsible for about 90% of the estimated skin damage [Guercio-Hauer, MacFarlane, and Deleo 1994]. UV-C rays can potentially cause skin cancer and immunosuppression. Fortunately, we are not exposed to UV-C rays because the stratospheric ozone layer above the earth’s surface blocks these rays [Katiyar 2007].

The unique nature of the skin facilitates permeation of various hydrophobic drugs. The delivery of the drug through the skin is referred to as topical drug delivery. Skin formulations are classified as creams, gels, lotions, and ointments. In addition, drugs are also delivered through the skin using patches, and this method of drug administration is referred to as transdermal drug delivery. Although the topical and transdermal drug delivery systems are extensively used in the treatment of various skin diseases, certain kinds of skin diseases are treated orally or systemically.

Skin infections have caused significant mortality and morbidity ever since the origination of the human race. In ancient times, many cultures have applied natural products such as soybean, curd, cheese, honey, and moldy bread to counteract skin infections. A wide variety of nutraceuticals, including, but not limited to, carotenoids, melatonin, proanthocyanidins, curcumin, ferulic acid, tea, linoleic acid, gingerol, curry leaf, CoQ10, and silymarin, have been claimed to have beneficial effects in various skin diseases or disorders, such as melanoma and non-melanoma cancers, age-related skin diseases, acne, psoriasis, skin rash, inflammation, and immunomodulation. In addition, nutraceuticals are also used in skin care to improve skin texture, glow, and smoothness.

**CAROTENOIDS**

Carotenoids, such as beta-carotene, lutein, lycopene, and zeaxanthin, either alone or in combination, are commonly used as nutraceuticals in skin healthcare. In a recent study, it was shown that supplementation of carotenoid mixture containing lycopene (3 mg/day), lutein (3 mg/day), and beta-carotene (4.8 mg/day), along with α-tocopherol (10 mg/day) and selenium (75 μg/day), for a period of 12 weeks has
improved skin density, thickness, scaling, smoothness, and wrinkling [Heinrich et al. 2006].

Prolonged exposure to UV rays significantly reduces the skin and plasma levels of carotenoids. It is evident that carotenoids exhibit in vitro antioxidant properties by scavenging reactive oxygen species. On the contrary, carotenoids at high concentrations under in vitro conditions possess pro-oxidant properties [Young and Lowe 2001; Eichler, Sies, and Stahl 2002; Offord et al. 2002]. Therefore, the dosage of carotenoids is very critical in achieving the beneficial effects.

A meta-analysis of effectiveness of beta-carotene in protection against sunburn supported that supplementation of beta-carotene protects the skin against sunburn in a time-dependent manner [Kopcke and Krutman 2008]. In a placebo-controlled, parallel study, it was found that supplementation of beta-carotene at 24 mg/day or carotenoid mix of beta-carotene, lutein, and lycopene at 8 mg/day each for 12 weeks significantly attenuated the UV-B-induced erythema in humans [Heinrich et al. 2003]. In another study, it was demonstrated that chronically UV-B-irradiated hairless mice when supplemented with lutein/zeaxanthin reduced the tumor volume size and decreased the multiplicity when compared with the animals fed with normal diet [Astner et al. 2007]. Therefore, from the above studies, it is evident that supplementation of dietary carotenoids has a positive effect on the skin health.

**LUPEOL**

Lupeol is a naturally occurring pentacyclic triterpine of plant origin present in several common fruits and vegetables, such as mangoes, figs, strawberries, and olives [Saleem et al. 2004]. It was demonstrated that lupeol, when administered topically at a dose level of 0.75 and 1.5 mg/animal 1 h before benzoyl peroxide, a free radical generator, treatment attenuated the early responses of tumors induced by benzoyl peroxide in mice skin [Sultana et al. 2003]. In another study, it was demonstrated that topical application of lupeol (1−2 mg/mouse) 30 min before the 12-0-tetradecanoyl-phorbol-13-acetate (TPA) (3.2 nmol/mouse) resulted in inhibition of TPA-induced skin cancer in CD-1 mice model [Saleem et al. 2004]. Recent studies suggest that lupeol has protective effects on 7,12-dimethylbenz[a]anthracene (DMBA)-induced DNA alkylation damage in mice skin. This particular study also implies the potential use of lupeol as a chemotherapeutic agent because DNA alkylation damage can lead to cancer and other genetic diseases [Nigam, Prasad, and Shukla 2007]. In addition, it is also observed that, when lupeol (and its natural and semi-synthetic derivatives) is administered topically, it exhibits anti-inflammatory properties with improved keratinocyte proliferation [Nikiema et al. 2001].

**MELATONIN**

Melatonin is a naturally occurring hormone secreted by the pineal gland. Melatonin (N-acetyl-5-methoxytryptamine) is biosynthesized by a series of reactions
from indole amino acid tryptophan [Yu, Tsin, and Reiter 1992]. Melatonin is a highly potent antioxidant that acts by scavenging hydroxyl and lipid peroxidyl free radicals [Reiter et al. 1995]. Several studies investigated the photoprotective effects of melatonin in humans. The topical application of melatonin solution resulted in attenuation of UV-induced erythema in a dose-dependent manner [Bangha, Elsner, and Kistler 1997]. Interestingly, more pronounced results were obtained when melatonin was formulated in combination with vitamin C and vitamin E [Dreher et al. 1998].

Recently, Maldonado et al. [2007] reviewed the use of melatonin as a potential pharmacological support against thermal injury. It is evident that thermal injury results in lymphocytopenia and sleep deficiencies. It is believed that melatonin ameliorates burn injuries by inhibiting the proinflammatory cytokines and improving the sleep mechanisms.

It is evident from the body of research material published to date that melatonin exhibits tumorostatic properties, which includes melanomas and tumors of cutaneous origin [Cos and Sanchez-Barcelo 2000]. In a mice study, melatonin reduced the number of papillomas during the initiation as well as promotion stages of tumor induced by benzo[a]pyrene. This study also found that mice treated with melatonin prevent the binding benzo[a]pyrene and its metabolites to DNA [Kumar and Das 2000].

PROANTHOCYANIDINS

Oligomeric proanthocyanidins, when administered as a dietary supplement before UV radiation followed by topical application in the form of a lotion or a cream (Anthogenol), has attenuated the inflammation and improved the hydration properties of the skin in humans [Hughes-Formella, Wunderlich, and Williams 2007]. It was shown that supplementation of grape seed proanthocyanidins (GSPs) in the diet (0.2 and 0.5 % weight/weight [w/w]) to mice protected its skin from UV-B-induced oxidative stress by inhibiting mitogen-activated protein kinase and NF-κB cellular signal pathways [Sharma, Meeran, and Katiyar 2007]. In another study, the dietary supplementation of GSPs in mice attenuated UV-B-induced immunosuppression by inhibiting immunosuppressive cytokine IL-10 and inducing immunostimulatory cytokine IL-12 production [Sharma and Katiyar 2006].

Dietary administration of GSPs (0.2 and 0.5 % w/w) to hairless mice inhibited tumor incidence, tumor multiplicity, and tumor size in UV-B-induced initiation and promotion stages of mouse photocarcinogenesis [Mittal, Elmets, and Katiyar 2003]. In addition, it was also shown that dietary GSPs prevented the progression of UV-B-induced papillomas to carcinomas [Mittal, Elmets, and Katiyar 2003]. However, in a double-blind, placebo-controlled, randomized Phase II trial involving 66 volunteers, oral supplementation of GSP extract (100 mg three times a day) had no significant effect in patients with breast induration after radiotherapy for breast cancer [Brooker et al. 2006].
CURCUMIN

Curcumin is a yellow-colored phenolic compound obtained from turmeric. Turmeric is commonly used as a spice and coloring agent in many Asian foods for centuries. There are several reports that have demonstrated curcumin as an anti-inflammatory and antioxidant agent. In the past few years, there has been considerable interest in identifying the cellular and molecular mechanisms by which the isolates of turmeric cures the skin ailments. In a review, it was summarized that curcumin exhibits anti-inflammatory properties probably by inhibiting COX2 lipoxygenase, and iNOS [Srinivasan, Sudheer, and Menon 2007]. Because inflammation is closely associated with the tumor promotion, several studies have also demonstrated the beneficial effects of curcumin in attenuating tumor promotion.

One study found that topical application of curcumin inhibited benzo[α]pyrene-initiated and TPA-induced tumors in mouse skin in a dose-dependent manner [Huang et al. 1988]. The in vitro studies have shown that curcumin reduces human epidermal keratinocytes differentiation and proliferation and enhances apoptosis [Balasubramanian and Eckert 2007]. In another study, it was observed that curcumin at micromolar concentrations induces apoptosis and reduces proliferation in melanoma cells by suppressing nuclear factor κB inhibitor kinase and nuclear transcription factor NF-κB [Siwak et al. 2005].

In a randomized, controlled study in rats, it was found that oral administration of curcumin before and after the skin burns reduced the progression of unburned skin interspaces into full necrosis [Singer et al. 2007]. The oral administration of curcumin before γ-radiation has expedited the wound healing in mice by enhancing wound contraction and increasing the synthesis of collagen, hexosamine, NO, DNA, proliferation of fibroblasts, and vasculature [Jagetia and Rajanikant 2004]. Therefore, curcumin may be potentially used in the skin burn treatment and wound healing.

FERULIC ACID

Ferulic acid is a phenolic compound present in high concentrations in leaves, fruits, and vegetables. It possesses potent antioxidant properties, and the antioxidant potential of ferulic is explained by its unique structural characteristics. The phenoxy radical form of ferulic acid is resonance stabilized by the delocalization of electrons. Ferulic acid has been reported to scavenge hydroxyl, alkoxy, peroxyl, and superoxide free radicals [Srinivasa, Sudheer, and Menon 2007].

Topical formulation of ferulic acid (0.5%), L-ascorbic acid (15%), and α-tocopherol (1%) has been shown to reduce skin erythema and sunburn cell formation [Lin et al. 2005]. This formulation has effectively reduced oxidative stress and thymidine dimer formation induced by UV radiation [Lin et al. 2005]. An in vitro study has shown that addition of ferulic acid at concentrations ranging from 1 to 10 μg/ml to human lymphocytes 30 min before UV-B irradiation has inhibited UV-B-induced lipid peroxidation and oxidative stress in a dose-dependent manner [Prasad et al.
In another study, it was shown that topical application of ferulic acid inhibited TPA-induced skin tumor formation [Huang et al. 1988].

**TEA**

Tea is obtained by the fermentation of fresh leaves of the plant *Camellia sinensis*. Polyphenols are the major constituents of the tea. During the past decade, several tests were conducted to evaluate the effect of black and green tea constituents on the skin health.

EGCG is one of the main constituents of green tea. In rats, the topical application of EGCG (2%) hydrophilic ointment 30 min before UV-A exposure has decreased skin damage caused by UV-A rays. However, the application of EGCG 30 min after the UV-A exposure has resulted in no beneficial effects [Sevin et al. 2007].

In an *in vivo* study, the aqueous extracts of black tea were formulated as a gel and tested for protection against a broad range of UV radiation (200–400 nm). In the subjects receiving black tea gel, no erythema was observed, indicating the potential application of black tea in sunscreens [Turkoglu and Cigirgil 2007].

A randomized, double-blind, three-arm parallel-group, vehicle-controlled, clinical study was conducted using Polyphenon E (MediGene AG, Munich, Germany), a proprietary extract of green tea leaves, for the treatment of extragenital and perianal warts. The topical application of Polyphenon E 10 and 15% ointment for 16 weeks has resulted in complete clearance of warts in 51 and 53% of the patients, respectively [Stockfleth et al. 2008].

Recently, it was reported that pretreatment with polymeric black tea polyphenolic fractions (PBP1–PBP5) or thearubigins has attenuated TPA-induced skin papillomas in mice. In this study, it was also found that PBP2 as the most potent polymeric phenolic fraction [Patel et al. 2008].

**FATTY ACIDS**

Studies have shown that fatty acids from animal and plant origins have a wide array of beneficial effects on skin health. Fish oils rich in omega-3 polyunsaturated fatty acids have been reported to significantly reduce the UV-B-induced erythema in humans [Orengo, Black, and Wolf 1992; Rhodes et al. 1994, 2003] and animals [Orengo et al. 1989]. EPA and DHA, the two omega-3 polyunsaturated fatty acids, were found to significantly inhibit the production of UV-B and TNF-α-induced IL-8, a proinflammatory cytokine, in keratinocytes [Storey et al. 2005]. In another study, EPA, when applied topically on human skin, reduced the UV-induced collagen and decreased the epidermal thickening. Therefore, EPA has potential application as photoprotective and anti-skin-aging agent [Kim et al. 2006].

A study was conducted in animals to determine whether the essential and nonessential fatty acids would affect the cutaneous wound healing after the surgery. Topical application of linolenic (omega-3), linoleic (omega-6), and oleic acids
(omega-9) modulated the wound-healing process. It was also found that the application of oleic acids resulted in faster recovery when compared with linolenic, linoleic acids, and control [Cardoso et al. 2004].

Dietary supplementation with 1.0 or 1.5% (w/w) CLA has significantly inhibited skin papillomas in mice when compared with a diet without CLA and 0.5% (w/w) CLA [Belury et al. 1996]. It is hypothesized that CLA reduces skin papillomas by modulating peroxisome proliferators-activated receptor -δ [Belury 2007], which plays a major role in inflammatory responses and apoptosis.

Many studies were conducted to determine the efficacy of primrose oil on inflammatory diseases such as atopic eczema and psoriasis [Wright and Burton 1982; Berth-Jones and Graham-Brown 1993; Williams 2003]. Primrose oil constitutes approximately 70% linoleic and 10% gamma-linolenic acids. One study had 99 patients with atopic dermatitis treated with primrose oil or placebo for 12 weeks, and significant clinical improvement was shown at high doses [Wright and Burton 1982]. Another study was conducted to investigate the effectiveness of evening primrose oil for atopic dermatitis. In this study, 123 patients with atopic dermatitis were treated with primrose oil, combination of primrose oil and fish oil, or a placebo for 16 weeks [Berth-Jones and Graham-Brown 1993]. However, the treatment with these oils did not result in reduction of the skin surface area affected by atopic dermatitis. To conclude, some of the studies have demonstrated the beneficial effects of primrose oil for atopic dermatitis [Wright and Burton 1982], whereas the others did not [Berth-Jones and Graham-Brown 1993]. Therefore, the usage of primrose oil for atopic dermatitis remains questionable.

Cocoa butter is a natural fatty acid extracted from cocoa bean. It is widely used in many topical products such as creams, soaps, ointments, and lotions. Cocoa butter acts as an emollient and alleviates dry skin, inflammation, and irritation.

**GINGER**

Ginger rhizome is obtained from *Zingiber officinale*. The ginger rhizome is commonly used throughout the world as a spice and flavoring agent. The topical application of ethanol extract of ginger on SENCAR mouse skin has resulted in the significant protection against TPA-induced skin tumor [Katiyar, Agarwal, and Mukhtar 1996]. Subsequently, [6]-gingerol was determined as the principal component that is responsible for tumor protection [Park et al. 1998]. Furthermore, the topical application of [6]-gingerol has resulted in inhibition of DMBA-induced skin papillomagenesis [Park et al. 1998]. In another study, it was demonstrated that topical application of [6]-gingerol (30 μM) before UV-B radiation has resulted in the induction of COX2 mRNA and protein and NF-κB translocation in a hairless mice. This study is of particular significance, implying the potential application of [6]-gingerol against UV-B-induced skin disorders [J. K. Kim et al. 2007].

Topical application of ginger dry extract (DE) and gingerols enriched dry extract (EDE) in mice in the form of solution have exhibited dose-dependent anti-inflammatory properties: ID$_{50}$ = 142 and 181 μg/cm [Minghetti et al. 2007]. However, the
increase in [6]-gingerol concentration in the extract did not result in improved activity. In addition, application of DE and EDE in the form of medicated plasters resulted in the reduction of inflammation in mice [Minghetti et al. 2007].

ALOE VERA

*Aloe vera* is a small plant containing succulent leaves. The aloe extracts are commonly used in a wide variety of formulations such as skin creams, lotions, gels, and ointments. Topical application of *A. vera* gel (97.5%) in humans has significantly attenuated UV-induced erythema after 48 h [Reuter et al. 2008]. In a double-blind, placebo-controlled study involving 60 patients suffering from slight to moderate chronic plaque-type psoriasis found that topical application of *A. vera* extract (0.5% extract) in a hydrophilic cream (three times per day, five consecutive days per week) significantly cured lesions, erythema, and infiltration when compared with the placebo [Syed et al. 1996].

In mice, the topical administration of aloe gel (1 ml/9 cm² per day) and/or oral administration of aloe leaf extract (1000 mg/kg/day) for 16 weeks resulted in decreased number and size of the skin papillomas induced by DMBA [Chaudhary, Saini, and Goyal 2007]. The topical (25% *A. vera* in Eucerin cream) and oral (100 mg/kg/day) administration of *A. vera* in mice has significantly reduced the wound diameter by 50.8 and 62.5%, respectively, compared with controls [Davis et al. 1989]. *A. vera* tends to have some beneficial effects in preventing skin reactions during radiation therapy [Olsen et al. 2001], burn wound healing [Maenthaisong et al. 2007], desquamation, and pain related to radiation therapy [Heggie et al. 2002]. However, additional studies are warranted to unequivocally establish these wide arrays of beneficial effects of *A. vera*.

CoQ₁₀

CoQ₁₀ is incorporated into a variety of skincare products because of its exceptional antioxidant properties. In an *in vitro* study involving human dermal fibroblasts, the combination of CoQ₁₀ and carotenoids have resulted in attenuation of inflammation induced by UV radiation [Fuller et al. 2006]. In another study, CoQ₁₀ nanoparticles were observed to attenuate the oxidative stress induced by UV-B-induced irradiation by increasing the manganese superoxide dismutase and glutathione peroxidase immunoreactivity and their protein levels in the hairless mouse skin [D. W. Kim et al. 2007].

SILYMARIN

Silymarin is the active constituent extracted from the fruits of *Silybum marianum* L. Gaertn. Chemically, silymarin is a mixture of flavolignanas primarily containing silybin
Topical application of silymarin at a dose of 9 mg/application before UV-B exposure has been shown to reduce the tumor incidence, tumor multiplication, and tumor growth in mice [Katiyar et al. 1997]. In subsequent mice studies, it was reported that topical application of silymarin attenuates UV-B-induced immunosuppression and oxidative stress [Katiyar 2002] primarily through the inhibition of infiltration CD11b+ cells, a major source of oxidative stress [Katiyar, Meleth, and Sharma 2008]. In addition, it was reported that topical application of silybin and 2,3-dehydrosilybin on human keratinocytes at a dose of 1–50 μmol/L suppressed UV-A-induced oxidative damage [Svobodova et al. 2007]. Administration of silymarin either locally or locally and systemically has significantly protected rats from burn-induced oxidative damage [Toklu et al. 2007]. Together, these results imply the potential application of silymarin as a therapeutic agent for the treatment of skin cancers and burns.

**CURRY LEAVES**

Curry leaves are obtained as fresh leaves from *Murraya koenigii*. Curry leaves are commonly used as flavoring agents in Indian food preparations. The topical application of 10 and 20% curry leaf extract has been shown to reduce 29.05 and 43.75 % of DMBA-induced skin carcinoma in Swiss mice [Dasgupta, Rao, and Yadava 2003]. However, the principal active constituent of curry leaf that is responsible for anticarcinogenic properties is yet to be determined.

**CONCLUSIONS**

Many experimental studies have found that nutraceuticals, irrespective of the mode of administration (i.e., topical, oral, or systemic), exert the beneficial effects in skin disorders. This has led to the extensive usage of dietary supplements for the prevention and treatment of skin diseases. However, there are several contradictory reports challenging the effectiveness of nutraceuticals, which mandate large clinical studies in humans to validate the usefulness of nutraceuticals for skin care. Furthermore, pharmacological investigations are necessary to explore the effectiveness of supplementation of nutraceuticals with commonly used dermatological agents. Several experimental studies have demonstrated that nutraceuticals are safer than or have fewer side effects than prescription medications. This holds true only when a specific nutraceutical is supplemented during a particular period. However, in a real case scenario, people may take several drugs along with nutraceuticals for skin care. Therefore, it is necessary to study drug-nutraceutical interactions to understand their safety.

**REFERENCES**


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