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Evolving the Art of Essential Oil Mastery

Melanoma and Photoaging: Botanical Suppression of UV Damage

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Recent interest has been given to topical and dietary botanical extracts, terpenoids, and phenolic compounds for the prevention of photocarcinogenesis and photoaging. A wide variety of botanicals and their compounds have been reported to possess substantial anticarcinogenic and antimutagenic activities because of their antioxidant and antiinflammatory properties.[1]

Solar UV exposure is well known for its harmful effects on human health, including sunburn, melanoma, basal and squamous cell cancers, immune suppression, photoaging and hyperpigmentation. Skin cancer is the most common form of cancer in the US with over one million new cases reported each year.[2] The incidence of both non-melanoma and melanoma skin cancers has been increasing over the past decades. The World Health Organization reports there are currently between 2 and 3 million non-melanoma skin cancers and 132,000 melanoma skin cancers that occur globally each year.[3]

Excessive exposure to UV radiation (UVR) results in photoaging of the skin, specifically fine lines, wrinkles, leathery texture, broken blood vessels and hyperpigmentation, or age spots. Though sun exposure is not the only cause of aging and damage to the skin, it is one of the major preventable factors of premature aging.

Sun protection is now a common concern for many. Advice from the medical community, reasonable - along with fear based - reporting through the media, and an over-abundance of sun paranoia, has assisted in producing a plethora of products claiming to contain UV and sun protection, building this into a multi-billion dollar industry.

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[1] Baliga, M. S., & Katiyar, S. K. (2006). Chemoprevention of photocarcinogenesis by selected dietary botanicals. Photochem Photobiol Sci., 5(2):243-53.

[2] Skin Cancer Foundation. Retrieved November 10, 2008 from http://www.skincancer.org/?gclid=COzmwtLxjZcCFQquGgodUhRwSA

[3] World Health Organiztion. Retrieved November 10, 2008 from http://www.who.int/uv/faq/skincancer/en/index1.html

Pathogenesis of skin cancers

The sun's ultraviolet radiation has been implicated in numerous studies as a tumor initiator, tumor promoter and a carcinogen that can lead to melanoma and nonmelanoma skin cancers. Reactive oxygen species (ROS), induced by high dosages of UV irradiation, is believed to be a leading cause in skin cancers. ROS plays a role in tissue damage, increased production of ROS and may decrease the efficiency of the antioxidant defense system.[4] ROS, or oxidative stress, is known to cause cellular damage and other biochemical alterations such as inflammation, lipid and protein oxidation, DNA damage and certain enzyme activation or inactivation.[5] UV-B radiation causes mutations in DNA gene coding for proteins that lead to persistent disturbances passed onto daughter cells and the corrupted regulation of cell cycling, differentiation and apoptosis, that are found in skin cancers.[6]

Pathogenesis of photoaging

The key feature in premature aging of the skin is reduction of type-I procollagen from exposure to solar UV irradiation. UVR impairs transforming growth factor (TGF)-ß/Smad pathway, a major regulator of type-I procollagen, by the down-regulation of TGF-ß type II receptor (TßRII). This down-regulation of TßRII reduces expression of type I procollagen and is a critical molecular mechanism in the pathophysiology of photoaging.[7] Infiltrating neutrophils are white blood cells triggered as an immune response to exposure to UV-A and UV-B rays. These neutrophils, as a source of the active enzymes, elastase

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[4] Leboit, P. E., Burg, G., & Weedon, D., (Ed.). (2006). Pathology and Genetics of Skin Tumours. IARC, Lyon, France; pg 11

[5] Vayalil1, P. K., Elmets, C. A., & Katiyartarget, S. K. (2003). Treatment of green tea polyphenols in hydrophilic cream prevents UVB-induced oxidation of lipids and proteins, depletion of antioxidant enzymes and phosphorylation of MAPK proteins in SKH-1 hairless mouse skin. Carcinogenesis vol.24 no.5 pp.927±936

[6] de Gruijl, F. R., van Kranen, H. J., & Mullenders, L. (2001). UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. Journal of Photochemistry and Photobiology B: Biology Volume 63, Issues 1-3, Pages 19-27

[7] Quan, T., He, T., Kang, S., Voorhees, J. J., & Fisher, G. J. (2004). Solar Ultraviolet Irradiation Reduces Collagen in Photoaged Human Skin by Blocking Transforming Growth Factor-ß Type II Receptor/Smad Signaling. American Journal of Pathology, 165:741-751.

and matrix metallo proteinases-1 and -9, play a primary role in the initial steps of photoaging and are responsible for the breakdown of the extracellular matrix.[8] The unifying pathogenic agents for these changes are UV-generated ROS, which deplete and damage non-enzymatic and enzymatic antioxidant defense systems of the skin.[9] Solar UV stimulation of melanocytes is responsible for hyperpigmentation, the concentrated accumulation of melanin in spots on the skin.

Protection and reversal of solar UV damage and carcinogenesis

Over the counter sunscreen use is the most widespread approach to chemoprevention and protection from photoaging. Though useful, sunscreens are not adequate and fail in the prevention of solar UV induced skin cancer and photoaging.[10] This may be due to improper use, incomplete spectral protection and potential toxicity. Common sunscreens are designed to protect against sun damage by either reflecting or scattering UVR (titanium dioxide and zinc oxide) or by absorbing the UV rays (oxybenzone and the methoxycinnimates).

Novel strategies have been presented to reduce the occurrence of skin cancer and delay the process of photoaging through photochemoprevention via use of botanical antioxidants present in the common diet.[11] Antioxidants are capable of preventing UVR-induced skin cancer through their capability to quench ROS and inhibit many UVR-

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[8] Rijken, F., Kiekens, R. C. M., van den Worm, Lee, P. L., van Weelden, H., & Bruijnzeel, P. L. B. (2006). Pathophysiology of photoaging of human skin: focus on neutrophils. Photochem. Photobiol. Sci., 5, 184 – 189.

[9] Wlaschek, M., Tantcheva-Poór, I., Naderi, L., Ma, W., Schneider, L. A., Razi-Wolf, Z., Schüller, J., & Scharffetter-Kochanek, K. (2001). Solar UV irradiation and dermal photoaging. Journal of Photochemistry and Photobiology B: Biology, 63(1-3):41-51.

[10] Kiefer, D. (2007, June). What's Missing From Your Sunscreen?. LE Magazine. Retrieved on November 15, 2008 from http://www.lef.org/magazine/mag2007/jun2007_report_sunscreen_02.htm

[11] Afaq, F., & Mukhtar H., (2006). Botanical antioxidants in the prevention of photocarcinogenesis and photoaging. Exp Dermatol., 15(9):678-84.

induced signal transduction pathways.[12] Skin care products with botanical antioxidants are growing in popularity, though there is little acknowledgement of their use as sun protective agents.

Essential oils and their compounds showing UV and chemopreventitive properties

Several essential oils, along with compounds extracted from the oils, have been studied and documented for use in chemoprevention and prevention from photoaging. The cell regenerative and other skin healing properties of essential oils is well known and has helped to make aromatherapy a popular practice in esthetics and spa. The essential oil antioxidant and anti-inflammatory properties have only recently been promoted for their protection from photoaging - or as more superficially stated, for their "anti-aging" benefits - but have had very little attention for their use in skin cancer prevention. Following is a list of essential oils and compounds that have been researched and documented for their success in prevention and suppression of skin cancers and photoaging.

alpha-Santalol and sandalwood oil
Sandalwood oil in its whole extract was used in topical application for 20 weeks and decreased incidence of multiplicity of skin papillomas and inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced epidermal ornithine decarboxylase (ODC) activity, a prominent event in skin cancer, and DNA synthesis in CD-1 female mice.[13] The study implicated alpha-santalol as the active compound. In a study employing human epidermoid carcinoma A431 cells it was assessed that treatment with alpha-santalol at concentrations of 25-75 microM resulted in a concentration and a time-

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[12] F'guyer, S., Afaq, F., & Mukhtar, H. (2003). Photochemoprevention of skin cancer by botanical agents.; Photodermatol Photoimmunol Photomed., 9(2):56-72.

[13] Dwivedi, C., Guan, X., Harmsen, W. L., Voss, A. L., Goetz-Parten, D. E., Koopman, E. M., Johnson, K. M. Valluri,, H. B., & Matthees, D. P.; (2003). Chemopreventive Effects of a-Santalol on Skin Tumor Development in CD-1 and SENCAR Mice. Cancer Epidemiology, Biomarkers & Prevention, Vol. 12, 151–156

dependent decrease in cell number, which was largely due to cell apoptosis.[14] These, along with other findings, [15] [16] suggest that alpha-santalol, and the use of sandalwood essential oil, is a potential chemopreventative agent in UVB-induced skin tumor development.

Eugenol: 4-Allyl-2-methoxyphenol

4-Allyl-2-methoxyphenol (eugenol), a compound most commonly related to clove (*Eugenia caryophyllata*) essential oil, was found to be a potent inhibitor of melanoma cell proliferation. A 2004 published study showed that eugenol produced a significant tumor growth delay and an almost 40% decrease in tumor size. [17] Eugenol was well tolerated as determined by measurement of bodyweights. Examination of the mechanism of the antiproliferative action of eugenol in the human malignant melanoma cell line showed that it arrests cells in the S phase of the cell cycle. Eugenol induced apoptosis, with the results suggesting that eugenol could be developed as the gene coding E2F-targeted agent for melanoma treatment. The cytotocity of eugenol-related compounds is also related to

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[14] Kaur, M., Agarwal, C., Singh, R. P., Guan, X., Dwivedi, C., & Agarwal, R. (2005). Skin cancer chemopreventive agent, {alpha}-santalol, induces apoptotic death of human epidermoid carcinoma A431 cells via caspase activation together with dissipation of mitochondrial membrane potential and cytochrome c release. Carcinogenesis, 26(2): 369-80.

[15] Dwivedi, C., Valluri, H.B., Guan X, & Agarwal R. (2006). Chemopreventive effects of alpha-santalol on ultraviolet B radiation-induced skin tumor development in SKH-1 hairless mice. Carcinogeneisis, 27(9):1917-22.

[16] Arasada, B. L., Bommareddy, A., Zhang, X., Bremmon, K., & Dwivedi, C. (2008). Effects of alpha-santalol on proapoptotic caspases and p53 expression in UVB irradiated mouse skin; Anticancer Res., 28(1A):129-32.

[17] Ghosh, R., Nadiminty, N., Fitzpatrick, J. E., Alworth, W. L. Slaga, T. J., & Kumar, A. P. (2005). Eugenol Causes Melanoma Growth Suppression through Inhibition of E2F1 Transcriptional Activity; The Journal of Biological Chemistry, 280(7):5812–5819

its ability to efficiently scavenge ROS.[18]

Conifer: *Tetraclinis articulata*

In a study examining the cytotoxic effect of *Tetraclinis articulata* essential oil it was determined that the oil contains components that are effective at inducing apoptosis on a number of human cancer cell lines.[19] Melanoma, breast and ovarian cancer cells gave IC50s of around 80 micrograms/m. The authors recognized the advantages of using a mixture of monoterpenes (C10) as present in an essential oil over a single component. There are differing reports regarding composition of the essential oil of *Tetraclinis articulata*.[20] Many of the components distilled from the aerial parts and branches of trees from Morocco and Malta are those commonly found in other conifers, including alpha-pinene, limonene, camphor, borneol and bornyl acetate. These compounds occur in smaller, trace, amounts in the oil from Tunisia, which contains high amounts of camphene, Z-ß-ocimene.[21] Similar composition to the Tetraclinis species is found in other essential oils such as *Rosmarinus officinalis*, which has also been shown to have cancer chemopreventive properties.[22]

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[18] Fujisawa, S., Atsumi,T., Kadoma, Y., & Sakagami H. (2002) Antioxidant and prooxidant action of eugenol-related compounds and their cytotoxicity.; Toxicology, 177(1):39-54.

[19] Buhagiar, J. A., Podesta, M. T., Wilson, A. P., Micallef, M. J., Ali, S. (1999). The induction of apoptosis in human melanoma, breast and ovarian cancer cell lines using an essential oil extract from the conifer Tetraclinis articulata. Anticancer Res., 19(6B): 5435-43.

[20] Barrero, A. F, Herrador, M. M., Arteaga, P., Quílez, J., Et al. (2005). Chemical Composition of the Essential Oils of Leaves and Wood of Tetraclinis articulata (Vahl) Masters. Journal of Essential Oil Research. Retrieved on December 3, 2008 from http://findarticles.com/p/articles/mi_qa4091/is_/ai_n13505314?tag=artBody;col1

[21] Tékaya-karou, A., Ben Jannet, H., Mighri Z.: (2007). Essential oil composition of terminal branches, cones and roots of tetraclinis articulata from Tunisia. Pakistan Journal of Biological Sciences, 10 (15): 2495-2499

[22] Cheung, S. & Tai, J. (2007). Anti-proliferative and antioxidant properties of rosemary Rosmarinus officinalis. Oncology reports, 17(6):1525-1531

Frankincense

Antitumor and chemopreventive effects were shown in a study using an isolated isometric compound containing alpha- and beta-boswellic acid acetate isolated from the plant *Boswellia carteri*.[23] The authors concluded that the compound would be useful in prevention of primary tumor invasion and metastasis. Several studies have documented the chemopreventive effects of boswellic acid on a variety of cancer cells.[24] [25] [26] In treatment study using the whole essential oil extract of frankincense, defined only as "medicinal grade, sterile frankincense," the oil was used on a horse with multi-centric malignant melanoma.[27] [28] The oil was injected directly into the tumors and also applied topically. In biopsies following the treatment small tumor cells were destroyed from the injected treatments while the tumors treated topically were reduced in size.

Copaiba Oil

The oil obtained from the resin of *Copaifera multijuga* was studied to evaluate cytotoxity

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[23] Zhao, W., Entschladen, F., Liu, H., Niggemann, B., Fang, Q., Zaenker, K. S., & Han, R. (2003). Boswellic acid acetate induces differentiation and apoptosis in highly metastatic melanoma and fibrosarcoma cells. Cancer Detect Prev., 27(1):67-75

[24] Xia, L., Chen, D. Han, R.,Fang, Q., Waxman, S., & Jing, Y. (2005). Boswellic acid acetate induces apoptosis through caspase-mediated pathways in myeloid leukemia cells. Mol Cancer Ther, 4:381-388

[25] Lu, M., XIA , L. Hua , H., & Jing, Y. (2008). Acetyl-Keto-β-Boswellic Acid Induces Apoptosis through a Death Receptor 5-Mediated Pathway in Prostate Cancer Cell. Cancer research. 68(4):1180-1186

[26] Meng, Y. O., Zhao, L. X., Wang, Z., Liu, D., & Jing, Y. K. (2005). Chinese Chemical Letters, 16(7):867-870

[27] Examining Malignant Melanoma In Horses And People. (2006). Medical News Today. Retrieved on 11/20/2008 from http://www.medicalnewstoday.com/articles/37299.php

[28] Virginia Tech researcher examining malignant melanoma in horses. (2006). Retrieved on December 3, 2008 from The American Association for the Advancement of Science (AAAS) http://www.eurekalert.org/pub_releases/2006-01/vt-vtr013106.php

on B16F10 melanoma cells in mice.[29] Experiments showed copaiba oil reduced melanoma cell line viability in a concentration and time-dependent manner. It was also determined that the diterpenic and sesquiterpenic fractions induced cytotoxicity. The in vitro and in vivo studies support tumoricidal activity in melanoma cells of copaiba oil. *Copaifera multijuga* also showed antineoplasic properties against Ehrlich ascitic tumor after oral administration.[30] The diterpene kaurenoic acid extracted from Copaifera langsdorffii was evaluated for its genotoxic effect against Chinese hamster lung fibroblast (V79) cells in vitro.[31] Results showed the higher concentrations of kaurenoic acid (30 and 60 microg/mL) caused significant increases in cell damage.
There are several species of Copaifera from the Amazonian forests used medicinally. The copaiba oils, though similar, have a varied composition and anti-inflammatory activity. The sesquiterpene β-caryophyllene is most abundant in examined species[32] followed by α-humulene, α-copaene, α-bergamotene, δ-cadinene. The diterpene, copalic acid was the main component from *Copaifera multijuga* Hayne (6.2%) and among varied species and commercial samples the major diterpenes found are: copalic acid, kaurenoic acid, agatic

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[29] Lima, S. R. M., Veiga, V. F., Christo, H. B., Pinto, A. C., Fernandes, P. D. (2003). In vivo and in vitro studies on the anticancer activity of Copaifera multijuga Hayne and its fractions. Phytotherapy research, 17(9):1048-1053

[30] Gomes, N. M., Rezende, C. M, Fontes, S. P., Hovell, A. M., Landgraf, R. G., Matheus, M. E., Pinto, A.C., & Fernandes, P. D. (2008) Antineoplasic activity of Copaifera multijuga oil and fractions against ascitic and solid Ehrlich tumor; 2008; J Ethnopharmacol. 2;119(1):179-84.

[31] Cavalcanti, B. C., Costa-Lotufo,, L. V. Moraes, M. O., Burbano, R. R., Silveira, E. R., Cunha, K. M. A., Rao, V. S. N., Moura, D, J., Rosa, R. M., Henriques, J. A. P., & Pessoa, C. (2006). Genotoxicity evaluation of kaurenoic acid, a bioactive diterpenoid present in Copaiba oil. Food and Chemical Toxicology, 44 (3) :388-92

[32] Veiga, V.F., Rosas, E. C., Carvalho, M.V., Henriques, M.G.M.O., Pinto, A. C. (2007). Chemical composition and anti-inflammatory activity of copaiba oils from *Copaifera cearensis* Huber ex Ducke, *Copaifera reticulata* Ducke and *Copaifera multijuga* Hayne —A comparative study. Journal of Ethnopharmacology, 112(2):248-254

acid, 3α-acethoxycopalic and hardiwickic acid.[33]

Thyme and Carvacrol

A patient with AJCC stage III melanoma, refusing the proposed treatment, used ground leaves and stems of thyme (*Thymus vulgaris*) in an herbal tea and for topical applications in compresses over the lesions. There was a progressive disappearance of all nodules over the period of a few weeks and a confirmed complete regression of cutaneous metastases.[34] A follow-up with the patient showed no evidence of disease after 5 years. As reported in the Journal of the American Academy of Dermatology, the authors were non-committal as to the regression being due to the use of thyme extract, though pointed out a chronological relationship between the use of thyme and regression.

Thyme extract, as used by the patient, was an infusion, making it difficult to assume that the essential oil alone would have a similar effect. There are other studies that support the anti-tumoral activity of thyme essential oil. The essential oil of *Thymus broussonettii,* determined by GC/MS to contain carvacrol (83.18%), along with P-cymene, g-terpinene, and transcaryophyllene, was shown to have anti-tumor effect.[35] There are many species of thyme and several chemotypes found within the varied species. The results of a study using eleven species and chemotypes of Moroccan thyme essential oils, it was determined that all had important cytotoxic effects, with carvacrol being the most

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[33] de Lima1, S. G., Pachecol, T., Duarte, M., Carvalho, J. E., Jara1, J. L. P., & Barata, L. Phytochemical study and standardization of Copaifera Oil; Retrieved on December 3, 2008 from Sociedade Brasileira de Química (SBQ), http://sec.sbq.org.br/cd29ra/resumos/T1102-1.pdf

[34] Carrera, C., Mariscal, A., Malvehy, J.,& Puig, S. (2005). Long-term complete remission of cutaneous melanoma metastases in association with a folk remedy. Journal of the American Academy of Dermatology, 52(4):713-715

[35]Ait M'Barek, L., Ait Mouse, H., Jaâfari, A., Aboufatima, R., Benharref, A., Kamal, M., Bénard, J., El Abbadi, N., Bensalah, M., Gamouh, A., Chait, A., Dalal, A., & Zya, A. (2007). Cytotoxic effect of essential oil of thyme (*Thymus broussonettii*) on the IGR-OV1 tumor cells resistant to chemotherapy. Braz J Med Biol Res, 40(11) 1537-1544

cytotoxic compound.[36] Carvacrol, in an alternate study, was also shown be a very potent inhibitor of cell growth in human non-small cell lung cancer cell line (A549) cell line.[37] Thymol has demonstrated cytotoxicity on human leukemic K562 cells.[38] In all studies the compounds and oils showed no cytotoxicty to healthy cells

Chemopreventive action of polyphenolic compounds, flavonoids and carotenoids,

Dietary recommendations include high amounts of "colored" foods, all known to be rich in carotenoids and other flavonoids and polyphenolic compounds. These foods, and compounds, have been well researched for their antioxidant activity and potential to prevent and reverse cancers. They protect the skin from UV induced cancers and photoaging, making them invaluable in regards to sun protection.[39]

A general overview of flavonoids for UV related skin damage
Flavonoids are polyphenolic compounds whose major groupings; flavans, flavanones, flavones, flavanonols, flavonols, catechins, anthocyanidins and isoflavone; have common biological properties that include antioxidant, anti-inflamatory, antitumoral, antiviral and antibacterial, as well as a direct cytoprotective effect on coronary and vascular systems,

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[36] Jaafari, A., Ait Mouse, H.; Rakib, E. M., Ait Mbarek, L., Tilaoui, M., Benbakhta, C., Boulli, A., Abbad, A., & Zyad, A. (2007). Chemical composition and antitumor activity of different wild varieties of Moroccan thyme; Revista Brasileira de Farmacognosia, 17(4): 477-491

[37] Tansu, K. A., & Melih, Z. (2003). Effects of carvacrol on a human non-small cell lung cancer (NSCLC) cell line, A549; Cytotechnology; Japanese Association for Animal Cell Technology. Annual and International Meeting N°15, Tokyo , JAPON (11/11/2002) vol. 43, n° 1-3 (161 p.) [Document : 6 p.] (13 ref.), pp. 149-154

[38] Horvathova, E., Turcaniova, V., & Slamenova, D. (2007). Comparative study of DNA-damaging and DNA-protective effects of selected components of essential plant oils in human leukemic cells K562. Neoplasma, 54(6):478-83

[39] Svobodová, A., Psotová, J., & Walterová, D. (2003). Natural Phenolics in the Prevention of UV-Induced Skin Damage: A Review; Biomed. Papers 147(2), 137–145

the pancreas and the liver.[40] There are many studies that provide research to better understand the actions flavonoids have on melanoma cells. Luteolin, for example, has been shown to penetrate into human skin and displays specific anti-inflammatory and anti-carcinogenic effects, which can only partly be explained by its anti-oxidant and free radical scavenging capacities.[41] Flavonoids have been examined for their effect on cell proliferation and cell cycle distribution in human melanoma cells. Among the compounds studied, quercetin and luteolin, correlated to a Gl cell cycle arrest, kaempferol and apigenin correlated to a G2 block.[42]
Flavonoids have also been studied as potent tyrosinase inhibitors[43] and the ability to reduce hyperpigmentation[44] The flavones, such as hesperidin, eriodictyol, and naringenin, may have potential as skin lightening agents when used in cosmetics designed to treat

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[40] Cazarolli, L. H., Zanatta L., Alberton E. H., Figueiredo M. S., Folador P., Damazio R. G., Pizzolatti M. G., & Silva F. R. (2008). Flavonoids: prospective drug candidates. Mini Rev Med Chem., 8(13):1429-40.

[41] Seelinger G., Merfort I., Wölfle U., Schempp C. M. (2008). Anti-carcinogenic effects of the flavonoid luteolin. Molecules, 13(10):2628-51.

[42] Casagrande, F., & Darbon, J. (2001). Effects of structurally related flavonoids on cell cycle progression of human melanoma cells: regulation
of cyclin-dependent kinases CDK2 and CDK1. Biochemical, 61(10):1205-1215

[43] Badria, F. A., el Gayyar, M. A. (2001). A new type of tyrosinase inhibitors from natural products as potential treatments for hyperpigmentation. Boll Chim Farm., 140(4): 267-71.

[44] Yates, Paula R., Charles nee Newsham, R. L. (2008). Skin lightening compositions comprising vitamines and flavonoids; USPTO Application #: 20080058281; Retrieved on December 8, 2008 from http://www.freshpatents.com

hyperpigmentation.[45]

Carotenoids

One of the more popular categories of compounds in nutritional sciences, and well known antioxidants, are the carotenoids. These are well researched and studied botanical compounds in the successful treatment and prevention of skin cancer and UV related skin damage. The carotenoids beta-carotene and astaxanthin have also been shown to protect against sunburn through internal supplementation.[46] [47]

Carotenoids act as direct and indirect antioxidants and as anti-inflammatory and immunomodulatory agents and through this, affect multiple signaling pathways to protect against UVR photooxidative damage.[48] Protection from UV light-induced erythema can be achieved through the daily consumption of tomato paste, providing about 16mg of lycopene.[49] Possible suppression of melanoma by carotenoids was demonstrated in a study showing beta–carotene's ability to significantly reduce the number of tumor-directed capillaries and how it could inhibit the activation and nuclear translocation of transcription factors in melanoma cells.[50] Tumor growth and metastasis are dependent on the formation of new blood vessels.

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[45] Zhu, W. & Gao, J. (2008). The Use of Botanical Extracts as Topical Skin-Lightening Agents for the Improvement of Skin Pigmentation Disorders. Journal of Investigative Dermatology Symposium Proceedings, 13, 20–24

[46] Köpcke, W., Krutmann, J. (2008). Protection from sunburn with beta-Carotene--a meta-analysis. Photochem Photobiol, 84(2):284-8

[47] Internal Beauty Pill? Sunscreen in a Pill? Retrieved December 15, 2008 from http://uvexmed.com/articles/articlesforphysicians/sunburn/sunscreeninapill.pdf

[48] Dinkova-Kostova, A. T. (2008). Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Planta Med., 74(13):1548-59

[49] Stahl, W., Heinrich, U., Wiseman, S., Eichler, O., Sies, H., & Tronnier, H. (2001). Dietary tomato paste protects against ultraviolet light-induced erythema in humans. J Nutr., 131(5):1449-51

[50] Guruvayoorappan, C. & Kuttan, G. (2007). Beta-carotene inhibits tumor-specific angiogenesis by altering the cytokine profile and inhibits the nuclear translocation of transcription factors in B16F-10 melanoma cells. Integr Cancer Ther., 6(3):258-70.

Resveratrol

Resveratrol is a polyphenol from the class of compounds called stilbenes found in grape skin, red wine, peanuts and berries. Interest in resveratrol was heightened by the "French Paradox," the surprisingly low incidence of heart disease in populations who consume diets high in saturated fats and red wine.[51] In studies, resveratrol was found to produce anti-aging effects in some animals and extend cell life by 70%.[52] Studies have shown that resveratrol may be an attractive candidate for the treatment of uveal melanoma,[53] and has shown to inhibit cell growth in a dose- and time-dependent manner and upregulated the expression of cyclins A, E, and B1 with subsequent irreversible arrest of melanoma cells.[54]

Green tea polyphenols (-)-epigallocatechin-3-gallate

Green tea (*Camellia sinensis*) contains potent antioxidants and is known to protect genes and cells from oxidative damage.[55] Epidemiological observations have shown that people

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[51] Nayor, D. & Kiefer, D. (2008). Living Longer, Healthier Lives with Resveratrol. LE Magazine Febuary 2008. Retrieved on December 8, 2008 from http://www.lef.org/magazine/mag2008/feb2008_Living-Longer-Healthier-Lives-With-Resveratrol_01.htm

[52] Barclay, L. (2007). Growing Evidence Links Resveratrol to Extended Life Span; LE Magazine March 2007, Retrieved on December 8, 2008 from http://www.lef.org/magazine/mag2007/mar2007_report_resveratrol_01.htm

[53] van Ginkel, Paul R., Darjatmoko, S. R., Sareen, D. Subramanian, L., Bhattacharya, S., Lindstrom, M. J., Albert, D. M., & Polan, A. S. (2008). Resveratrol Inhibits Uveal Melanoma Tumor Growth via Early Mitochondrial Dysfunction. Invest Ophthalmol Vis Sci., April; 49(4): 1299–1306

[54] Larrosa, M., Tomas-Barberan, F. A., & Espin, J. C. (2003). Grape polyphenol resveratrol and the related molecule 4-hydroxystilbene induce growth inhibition, apoptosis, S-phase arrest, and upregulation of cyclins A, E, and B1 in human SK-Mel-28 melanoma cells. Journal of Agricultural and Food Chemistry, 51(16):4576-4584

[55] O'Sullivan, J., Sheridan, J., Mulcahy, H., Tenniswood, M., Morrissey, C. (2008). The effect of green tea on oxidative damage and tumour formation in Lobund-Wistar rats. Eur J Cancer Prev, 17(6):489-501

in green-tea consuming countries have very low rates of cancer.[56] A study was performed to see if the results demonstrating that green tea polyphenols (GTP) reduced the risk for skin cancer in a murine photocarcinogenesis model could also be observed in human cells. It was confirmed that in "human living skin equivalent" models the reported UV-protective effects of GTP appear to be mediated in human cells via IL-12, most likely through induction of DNA repair.[57] An in vivo study provided evidence that GTP and specifically the component (-)-epigallocatechin-3-gallate (EGCG) has the potential to attenuate UVB-induced oxidative stress and oxidative stress-mediated cellular signaling of mitogen-activated protein kinases (MAPK), which are associated with the high risk of skin carcinogenesis.[58] The authors found it “tempting to suggest” that green tea polyphenols be used in sun protective skin care products to prevent UV induced skin damage.

Ginger and [6]-Gingerol

The naturally occurring polyphenol, [6]-Gingerol of fresh ginger (*Zingiber officinale*) with anti-oxidant, anti-apoptotic, and anti-inflammatory activities, was also found to provide protection against UVB-induced skin disorders.[59] A correlation between

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malignant melanomas and COX-2 expression has been established.[60] [6]-gingerol suppressed NF-kappaB DNA binding activity, an essential transcription factor responsible for COX-2.[61] Other components found in ginger; vallinoids, [6]-paradol shogaols, and zingerone; have also been studied and related to the chemopreventive effects from laboratory studies in a wide range of experimental models.[62]

Tumeric and curcumin

The polyphenol, curcumin, is an extract of tumeric (*Curcuma longa*) and known as the Indian spice curry powder. Curcumin has been used in treatment of squamous cell carcinoma and melanoma, as well as many other forms of cancer, with actions that may be explained by its ability to interfere with multiple cell signaling pathways.[63] [64] Curcumin was investigated at the Xi'an Jiaotong University in China and shown to effect apoptosis in human melanoma A375 cell line[65] and also demonstrated to block a key biological pathway needed for development of melanoma and other cancers at The

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University of Texas M. D. Anderson Cancer Center.[66]

Pomegranate seed oil

In an experiment to determine chemopreventive efficacy in mice of pomegranate (*Punica granatum*) seed oil, it was determined to be an agent against skin cancer.[67] The major components found in pomegranate seed oil; anthocyanins, ellagitannins and hydrolyzable tannins; are phenolic antioxidants that exhibit very strong radical scavenging effects.[68] Another study performed on mice skin found that topical application of pomegranate seed oil showed significant antitumor inhibiting effects by modulating MAPK and NF-B pathways.[69]

Oils and fatty acids

Olive oil

Topical treatment with extra-virgin olive oil (*Olea europa*) reduced UVB-induced skin

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tumors in mice that received the treatment following exposure.[70] It has been reported that an abnormally augmented expression of connexin 26 (Cx26) is responsible for the enhanced spontaneous metastasis of mouse BL6 melanoma cells[71] and, from a study conducted at Osaka University, Japan, that "oleamide derivatives, called MI-18 and MI-22, that specifically inhibit Cx26-mediated gap junction-mediated intercellular communications, prevent the spontaneous metastasis of BL6 cells."[72] Olive oil was also found to be as effective as the oleamides.[73]

Polyunsaturated and other fatty acids

In several studies, vegetable and fruit extracted fatty acids were used to decrease the number of melanoma cells in experiment. In one study the saturated and unsaturated fatty acids were shown to affect cell death and/or decrease numbers of melanoma cells.[74] Results showed arachidonic[75] and linoleic acids most effective in decreasing S91 murine melanoma cells, palmitic acid was most toxic toward B16F10 murine melanoma cells. The study points out that "human melanoma cell lines were more resistant to the toxic

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effect of fatty acids."
Omega-3 fatty acids are, overall, shown most successful in their toxic effects on melanoma. Docosahexaenoic acid (DHA), an omega -3 polyunsaturated fatty acid (PUFA), inhibits the proliferation of human metastatic melanoma cells.[76] Studies using fish oils, rich in omega-3 PUFA, demonstrate the protective benefits against UVR damage with dietary supplementation.[77] [78]

Sesame and sunflower: Sesamol
Sesame (*Sesamum indicum*) seed has been recognized as a potent contributor to health and healing, especially within the Ayurvedic practice. There are fatty acids within sesame, including linoleic acid and oleic acid, acknowledged as having anticarcengenic

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effects[79] [80] and cytotoxic to melanoma cells.[81] An evaluation of the effects of the phenolic compound sesamol, found in both sesame seed and sunflower seed oils, has shown it to have “remarkable” chemopreventitive effects as well as “profound” free radical scavenging activity.[82] The study showed sesamol to reduce mouse skin papillomas by 50%.

Diet and Supplementation with UVR Protective Nutrients

It’s well documented that a diet of vegetables, fruit and herbs rich in flavonoids and

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carotenoids will help to protect the body and skin from damage by UVR exposure[83] [84], including skin cancers, melanoma, photoaging and hyperpigmentation. The amount of the compounds found within the beneficial foods and necessary for complete protection may exceed that which would be consumed in even the healthiest diet. With this in mind, it appears that supplementation would be a sensible approach to enhance the benefits available from these nutrients.

There are many supplements available in the marketplace with the available dietary and supplemental choices being diverse to the extreme. Choosing the right supplements may require experimental and experiential tactics as there are similar known benefits to the selections available, whether it be a carotenoid complex, green tea or grape skin extract, or isolated compounds that may include resveratrol, quercitin or a vitamin (A, C or E). Supercritical extracts are a relatively new addition to supplementation and offer a therapeutic dosage of essential oil compounds and triterpenoids, such as carotenoids, that have been studied for their UVR protection.[85] [86] Dosage amounts may vary according to needs, for example whether the need is for prevention or "cure." It is advisable, in fact necessary, to give proper respect and attention to the quality of the supplements and foods purchased.

Formulation suggestions for topical application

The current topical sunscreens available in the marketplace contain organic compounds, most commonly oxybenzone and octyl methoxycinnamate, or the inorganic nanoparticles,

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[84] Sies, H & Stahl, W. (2004). Nutritional protection against skin damage from sunlight. Annu Rev Nutr., 24:173-200.

[85] Camera, E., Matrofrancesco, A., Fabbri, C., Daubrawa, F., Picardo, M., Sies, H., Stahl, W. (2008). Astaxanthin, canthaxanthin and beta-carotene differently affect UVA- induced oxidative damage and expression of oxidative stress-responsive enzymes. Exp Dermatol., [Epub ahead of print]. Retrieved on December 13, 2008 from http://www.ncbi.nlm.nih.gov/pubmed/18803658

[86] Choo, Y. M., Ng, M. H., Ma, A. N., Chuah, C. H., & Hashim, M. A. (2005). Application of supercritical fluid chromatography in the quantitative analysis of minor components (carotenes, vitamin E, sterols, and squalene) from palm oil. Lipids, 40(4): 429-32.

titanium dioxide and zinc oxide, all of which come with safety concerns.[87] [88] [89] [90] [91] The generally accepted approach is to "block" or absorb sun induced UVR to protect the skin using the SPF (sun protection factor) as a guide. Formulation of safe and effective UVR protection can be accomplished with botanical extracts and nutrients for topical application. Following are examples. Concentration of each ingredient will be written as an approximate, suggested percentage range.

The easiest formula to concoct would be a simple fixed oil and essential oil blend.

olive oil	30 – 70%
sunflower seed oil	30- 70%
cranberry seed oil	3 – 10%
essential oil complex	2 – 5%

(in order of suggested higher to lower concentration: Palmarosa,[92] lavender, copaiba, clove, frankincense)

rose hip seed CO2	0.5% - 2%
d-alpha-tocopherol	1 – 2%

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[90] Collins, P. & Ferguson, J. (1994). Photoallergic contact dermatitis to oxybenzone. Br J Dermatol.131(1):124-9.

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Oil and nutrient blend:
olive oil 35 – 70%
sesame seed oil 25 – 40%
raspberry seed oil 3 – 10%
essential oil complex 2 – 5%
(in order of suggested higher to lower concentration: lavender, rosemary verbenone, tea tree,[93] cedarwood,[94] sandalwood)
rosehip seed CO2 0.5 – 2%
d-alpha-tocopherol 1 – 2%
Ester-C®[95] 0.5 – 1%

Oil/nutrient/tincture formula:
olive oil 1
5 – 40%
sesame oil 10 – 30%
sunflower seed oil 15 – 40%
rosehip seed oil 2 – 10%
cranberry seed oil 2 – 10%
shea butter 5 – 20%
cocoa butter 5 – 15%
essential oil complex 2 – 5%
(in order of suggested higher to lower concentration: rosemary verbenone, copaiba,

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[93] Calcabrini, A,. Stringaro, A., Toccacieli, L., Meschini, S., Marra, M., Colone, M., Salvatore, G., Mondello, F., Arancia ,G., & Molinari, A. (2004). Terpinen-4-ol, the main component of Melaleuca alternifolia (tea tree) oil inhibits the in vitro growth of human melanoma cells.; J Invest Dermatol, 122(2):349-60

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frankincense, helichrysum italicum, angelica, Artemisia douglasiana[96], clove, myrrh[97])
arnica tincture[98] 2 – 5%
green tea extract[99] 2 – 5%
sea buckthorn CO2[100] 0.5 – 1%
rosehip seed CO2 0.5 – 1%
tocotrienol mix (Tocotrol®)[101] 1 – 2%
d-alpha-tocopherol 1%
alpha lipoic acid[102] 0.25%
MSM 1 – 2%

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[101] Goh, S. H., Hew, N. F., Norhanom, A. W., Yadav, M. (1994). Inhibition of tumour promotion by various palm-oil tocotrienols; Int J Cancer. 57(4):529-31.

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ascorbyl palmitate,[103] [104] 1%

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