

LE Magazine June 2006

REPORT

The Sunscreen Paradox Popular Misconceptions About Skin Cancer Prevention

By Steven V. Joyal, MD



People apply sunscreen to protect against sunburn, skin aging, and skin cancer. Because of the way sunscreen products are labeled by FDA mandate, consumers are often confused about which ingredients they need to achieve optimal protection against the sun's damaging and deadly rays.

Fortunately, scientific data have emerged indicating that health-conscious individuals can achieve broad-spectrum protection against the increasing onslaught of ultraviolet light penetrating our atmosphere.

Like clockwork, the sound bites occur on television news programs at the start of the summer season:

“To prevent skin cancer and premature aging of the skin, apply sunscreen before going out in the sun.”

Well known to scientists, physicians, and the average person alike, sun exposure is the main environmental risk factor for skin cancer,¹ and sunburn is a well-established risk factor for skin cancer.²

Sun exposure in the form of ultraviolet light not only accelerates skin aging, but can also result in debilitating disfigurement from skin cancer. Some types of skin cancer can even lead to premature death. Furthermore, we are in the midst of a veritable epidemic of skin cancer. The incidence of basal and squamous cell carcinoma is increasing, as is the occurrence of deadly malignant melanoma, a dangerous form of skin cancer that develops in the pigment-producing cells of the skin, known as melanocytes.

Conventional wisdom indicates that, in addition to avoiding sun exposure, sunscreen is your best bet for preventing skin cancer. However, the sun protection factor (SPF) rating system used by the FDA to regulate sunscreen products has an inherent flaw that renders its ratings dangerously inaccurate. This may create a false and potentially disastrous sense of security in sunscreen users.

FLAWS IN THE SPF RATING SYSTEM

Basal cell and squamous cell skin cancers are caused primarily by a particular spectrum of sunlight called ultraviolet B, or UV-B. It is UV-B radiation that also causes sunburn. The FDA's SPF rating system rates sunscreen for protection against UV-B light, but not against ultraviolet A (UV-A) light.

UV-A, the longer-wavelength ultraviolet light, penetrates deeper than UV-B through the outer portion of the skin. This is very important, because UV-A damage is largely responsible for premature aging of the skin. Moreover, UV-A light exposes the melanocytes, which are the pigment-producing cells in the skin, to damage that can potentially result in malignant melanoma, the deadliest form of skin cancer.

Thus, despite slathering on sunscreen and not developing a sunburn (because of protection against burning UV-B rays), we can still develop a light tan because the UV-A rays are penetrating the skin.

To protect your skin, you need broad-spectrum protection against both UV-A and UV-B rays. You cannot rely solely on the SPF rating system, because it provides information only on UV-B protection.

Melanoma Mortality

The American Cancer Society estimates that the mortality rate from melanoma has increased 50% since 1973. Nearly 8,000 Americans die of the disease every year.³

The only way to be sure that your sunscreen provides UV-A protection is to read the label and make sure it contains effective UV-A blocking agents, which include avobenzone, oxybenzone, zinc oxide, and/or titanium oxide.

Lawsuit Accuses Sunscreen Makers of False Claims

A lawsuit filed in Los Angeles Superior Court in March accuses the nation's leading sunscreen

makers of making false and misleading claims about the effectiveness of their products. Given that the sunscreen products are manufactured and marketed in compliance with FDA regulations, the lawsuit underscores the problematic SPF rating system, and the dangers of relying on the FDA's flawed SPF (sun protection factor) rating system to protect against cancer and other sun-induced health dangers.

The lawsuit charges sunscreen makers such as Coppertone, Banana Boat, Hawaiian Tropic, and Neutrogena with making inflated claims about the safety and effectiveness of their products, and thus giving consumers a false sense of security about the health consequences of prolonged sun exposure.

The lawsuit targets product labels claiming that the sunscreens protect equally against harmful UV-A and UV-B rays, as well as claims concerning how long so-called waterproof sunscreens actually remain effective in water. While sunscreens are graded for protection against UV-B rays, research indicates that the FDA's SPF rating system does not assess for protection against longer-wavelength UV-A rays, which can contribute to skin cancer, aging, and wrinkling.

The suit also takes aim at claims made in labels for sunscreen products developed specifically for children, such as Schering-Plough's Coppertone Water Babies. The lawsuit alleges that, in fact, the Coppertone product provides protection only against UV-B rays.

SUNSCREENS, TOPICAL ANTIOXIDANTS, AND FREE RADICAL DAMAGE

No matter what the ads promise, sunscreens alone inadequately protect against sunlight's damaging, free radical-generating effects. In a study using special techniques to detect free radical damage to human skin after ultraviolet light exposure, application of conventional sunscreen with an SPF of 20+ resulted in a "free radical protection factor" of only 2!⁵

Ultraviolet light generates harmful free radicals such as the superoxide anion radical, hydrogen peroxide, the hydroxyl radical, and singlet oxygen, in addition to lipid peroxides.⁶

Studies demonstrate the critical importance of topical antioxidant protection to quench the free radicals generated by UV light that sunscreens miss. For example, adding simple antioxidants like vitamin E acetate and sodium ascorbyl phosphate (a stable form of vitamin C used topically) to a conventional sunscreen formula can decrease free radicals in the skin better than sunscreen alone.⁷ In addition, when antioxidants are combined with conventional sunscreen, greater-than-expected protection is achieved against sun damage.⁸

VITAMIN D AND CANCER PROTECTION

Epidemiological studies suggest that sunlight exposure is associated with a decreased risk of non-Hodgkin's lymphoma, a type of cancer of the lymph glands.^{14,15} Such studies also suggest that ultraviolet light exposure is associated with a lower risk of developing breast, colon, endometrial, esophageal, and ovarian cancer.¹⁶ Furthermore, death rates from cancers of the breast, prostate, and colon are higher in northern latitudes (which receive less sun exposure) than in southern latitudes (which enjoy relatively greater sun exposure).¹⁷

The question, then, is how could sunlight protect against cancer?

Vitamin D, synthesized in your skin after exposure to UV-B light, has a number of documented anti-cancer effects, including inhibiting cancer cell growth and promoting normal cell cycle activity.¹⁸⁻²⁰

Interestingly, the active form of vitamin D generated by sun exposure on the skin—1,25-dihydroxyvitamin D₃—is low in patients with malignant

FDA Fails to Warn Public of UV-A Dangers

It is bizarre but true—the FDA appears to recognize the limitations of its SPF rating system for sunscreen, yet has done nothing of substance to remedy the problem!

Back in 2000, the FDA discussed some of these issues in its consumer magazine, in which it described the inadequacy of UV-A rating as an "unresolved technical dilemma."⁴

Six years later and counting, the FDA's "unresolved technical dilemma" remains unresolved, while the population remains at risk. Is it any surprise that skin cancer has reached epidemic proportions?

melanoma, the deadliest of skin cancers.²¹ Melanoma cell lines express the vitamin D receptor, and 1,25-dihydroxyvitamin D₃ acts to decrease cancer cell growth as well as push the cell toward a more mature cell form. Medical scientists know that more immature cell types are seen with cancers that are more aggressive.

Although a very controversial idea, exposure to natural sunlight may be protective against melanoma. Recall that UV-B rays stimulate vitamin D in the skin, and vitamin D is likely protective against melanoma. Remember, too, that sunscreens that block UV-B but not UV-A rays will also block vitamin D production in the skin. This may be a deadly double whammy: no synthesis of protective vitamin D in the skin, yet exposure to the deeply penetrating UV-A rays.

A RISK/BENEFIT APPROACH TO SUN EXPOSURE

Given all the information available, what is the best sun exposure strategy—one that balances the risks and potential benefits?

As individuals, we each have a very different tolerance for sunlight exposure. For example, equatorial Africans have a much higher degree of natural protection from the sun than do people of northern European ancestry. In addition, there are many hypotheses in alternative medical circles regarding potential links between skin cancer and dietary overconsumption of omega-6 fatty acids, inadequate hormone status, and other factors. There may very well be some validity to such theories, but until more is known, the best strategy is to be prudent with regard to sun exposure.

This means that for many of us, brief exposure to sunlight (10-15 minutes, two to three times weekly) should allow adequate time for vitamin D synthesis by the skin, without greatly increasing the risk of skin cancer.²² Additional supplemental vitamin D (for example, 800 IU a day and higher) will be needed, however, because this short duration of UV-B exposure is unlikely to be sufficient for optimizing vitamin D status.

For people of northern European ancestry or those looking to minimize premature skin aging, sun exposure beyond 10-15 minutes should be accompanied by liberal application of a sunscreen with broad UV-spectrum protection and generous use of topical agents with demonstrated protective effects against free radical damage.

Protect Yourself Against UV-B and UV-A

The best skin-protection strategy combines a blend of sunscreens that provide broad-spectrum protection against both UV-A and UV-B light.⁹ Some ingredients, such as zinc oxide, physically block the penetration of UV-A and UV-B rays into the skin. Other sunscreen ingredients like octinoxate, also known as octyl methoxycinnamate, protect the skin not only against sunburn, but also against UV light-induced damage to cellular DNA.^{10,11}

Always make sure that your sunscreen contains a blend of ingredients to achieve broad-spectrum UV-A and UV-B protection.

Zinc oxide in particular has come a long way from the glop that many of us remember smearing on our noses when we were children. Applications of microfine zinc oxide preparations appear to be almost invisible and provide great wide-spectrum UV-A and UV-B blockage.¹² Zinc oxide has other important skin benefits besides physically blocking UV light. For example, topical zinc oxide helps skin wounds to heal faster.¹³

A critical point with regard to sunscreen is to use plenty of it—slather it on! Many people use far too little sunscreen to obtain its maximum benefits.

<u>Ingredient</u>	<u>UV-B protection</u>	<u>UV-A protection</u>
Avobenzene	No	Yes (but degrades rapidly after application and is a potential skin irritant)
Oxybenzone	No	Yes (more stable than avobenzene and less likely to be a skin irritant)
Zinc oxide	Yes	Yes
Octyl methoxycinnamate	Yes	No
Titanium dioxide	Yes	Yes

REPORT

The Sunscreen Paradox Popular Misconceptions About Skin Cancer Prevention

By Steven V. Joyal, MD

THE BEST SKIN-PROTECTING TOPICAL INGREDIENTS

Exciting recent research shows that, in addition to broad-spectrum UV-A and UV-B blocking ingredients, natural topical ingredients can help protect skin against free radical-generated damage induced by UV light. Such natural agents may offer protection against photoaging, hyperpigmentation, and skin cancers.

- **Green tea extract (epigallocatechin gallate, or EGCG).** Deriving the health benefits of green tea is not limited to drinking it or taking it in the form of a high-potency extract. Topical administration likewise provides great benefits, including protecting against damage that can contribute to skin cancer and skin aging.

EGCG, a prime component of green tea, provides broad-spectrum protection against UV light-induced DNA damage and immune system dysfunction of the skin.^{24,25} Topical green tea extract is exceptional in preventing the inflammation and oxidative stress associated with UV light-induced skin damage.²⁶⁻³¹ As a result, scientists believe green tea may help prevent skin cancers that commonly result from exposure to the sun's radiation.

Exciting data from validated models of skin cancer strongly suggest that topically applied green tea extract can reduce the incidence and size of skin tumors. Importantly, this protection occurred even when green tea was applied following (not just before) UV light-induced damage.³² Thus, green tea may not only help prevent damage from UV rays, but also may help repair damage that has already occurred.

EGCG's benefits also include anti-aging effects. In aging human skin, topically applied green tea extract stimulates structural support cells in the skin called keratinocytes, leading to an increase in skin thickness. Furthermore, subsequent UV exposure fails to destroy these cells, suggesting that topical green tea provides a protective effect against UV light.³³ Thus, green tea helps reverse two of the hallmarks of aging skin: reduced skin thickness and keratinocyte destruction. This suggests a central role for green tea in preventing skin aging and promoting youthful skin.



Rosemary (*Rosmarinus officinalis*)

- **Rosemary extract (ursolic and carnosic acids).** The aromatic herb rosemary, used for thousands of years as both a spice and medicinal agent, is particularly rich in carnosic and ursolic acids, two potent antioxidant and anti-inflammatory agents. More than a decade ago, scientists found that carnosic and ursolic acids effectively prevent skin cancer in a validated model of human skin cancer carcinogenesis.³⁴

Ursolic acid acts powerfully to inhibit the growth of cancerous melanoma cells.³⁵ It also inhibits reactive oxygen species in skin cells and prevents damage from the skin-aging effects of UV-A light.³⁶

In addition, research has demonstrated that when specially formulated with lipids, ursolic acid enhances the dermal collagen and ceramide content of normal human skin cells, which are called epidermal keratinocytes.^{37,38} Collagen provides the "skeleton" that gives shape and structure to the skin, while ceramide is a lipid that helps maintain proper immune function, as well as youthful moisture content, in the skin. Keratinocytes make up as much as 95% of epidermal tissues and are responsible for producing keratin, the tough protein that contributes to healthy hair, nails, and skin.

Retin-A® and Other Cancer-Preventive Strategies

Retin-A® (tretinoin), or trans-retinoic acid, was introduced more than 30 years ago as a highly successful acne treatment. It is currently available by prescription.

Topical tretinoin use may be very useful for people who are predisposed to developing skin cancer—such as those with a light complexion, a history of heavy sun exposure, or past basal or squamous cell skin cancer—since retinoids prevent tumor progression, a process known as chemoprevention.

In addition, in people with severe photodamage from the sun, the combination of nightly tretinoin and twice-daily topical application of the chemotherapeutic agent 5-fluorouracil (Efudex® or Fluoroplex®) is an effective anti-cancer regimen.²³

Retin-A® can be quite irritating to the skin, particularly early in a treatment regimen. A 0.05% emollient cream formulation (Renova®) is currently available and is less irritating than 0.05% Retin-A® cream. Another new form is Retin-A Micro®, with "microsponges" that allow slow, metered release to reduce irritation.

• **Turmeric extract (tetrahydrocurcumin).** Curcumin is fast becoming known as a cure-all nutrient, and for good reason. Derived from the pungent spice turmeric, curcumin has excellent anti-inflammatory and antioxidant properties. Curcumin inhibits cancer initiation and promotion in validated cancer models.^{39,40}



Turmeric (*Curcuma longa*)

Curcumin induces the powerful tumor suppressor gene p53 and promotes the death of basal cell skin cancer cells.⁴¹ Furthermore, research shows that curcumin can make mutant, treatment-resistant malignant melanoma cell lines more responsive to chemotherapy.⁴²

While these and other studies suggest that topical curcumin may benefit the skin, the staining properties of its bright yellow native pigment have prevented its widespread use in topical products. Fortunately, a major metabolite of curcumin called tetrahydrocurcumin does not possess the staining characteristics of native curcumin, yet it demonstrates anti-cancer effects that are similar to those of native curcumin. In fact, validated skin cancer models have shown that tetrahydrocurcumin inhibits skin cancer promotion.⁴³

Laboratory studies indicate that topical tetrahydrocurcumin is a safe and effective skin-lightening agent.^{44,45} Skin-lightening agents help fade sun-induced areas of hyperpigmentation, or skin darkening. Many such agents work by inhibiting tyrosinase, a key enzyme involved in melanin synthesis. Thus, the colorless turmeric root derivative tetra-hydrocurcumin may help protect the skin against the detrimental effects of UV light and may help prevent (or fade) hyperpigmented areas of skin. While hyperpigmentation is not a medically harmful condition, it is always advisable to have a physician examine new brown spots to rule out skin cancers.

• **Milk thistle extract (silibinin).** The milk thistle plant contains silibinin and silymarin, two compounds that are well known for their anti-oxidant, anti-inflammatory, and immune-enhancing properties in the context of liver disease. Less well known—but equally important—are the documented benefits of milk thistle extract against skin cancer.

Topical application of silymarin significantly decreased skin cancer number and size in a validated model of tumor promotion.⁴⁶ These findings are supported by other studies that show similar effects for silibinin. For example, silibinin protects against UV light-induced DNA damage and cancer cell growth.⁴⁷

Additionally, research shows that silibinin enhances the powerful tumor suppressor gene p53, a genetic factor that protects against cancer. Silibinin acts by other mechanisms to prevent UV light-induced skin cancer. In fact, some findings suggest that silibinin can help to repair DNA damage caused by previous exposure to UV light.⁴⁸

Since milk thistle extract is well tolerated and acts in several ways to fight the cancer-causing effects of solar radiation, leading researchers believe it may be an ideal addition to sunscreen formulations.⁴⁹

• **Licorice root.** The medicinal properties of licorice root have been known since ancient Greece and Rome.⁵⁰ A powerful skin protectant, licorice has anti-inflammatory, immune-boosting, and anti-cancer effects, including protecting against DNA damage.⁵¹ Licorice extract also has demonstrated efficacy in treating atopic dermatitis, an allergy-related, intensely itchy swelling of the skin.⁵²



Licorice (*Glycyrrhiza glabra*)

Glycyrrhizin, the main component of licorice root, protects against UV-B light-induced damage in the context of human melanoma cells.⁵³ Glycyrrhetic acid, another constituent of licorice, protects against skin tumor initiation and promotion in a validated model of skin cancer.⁵⁴

An extract of licorice called glabridin reduces inflammation resulting from UV light exposure. In fact, when a licorice extract rich in glabridin was applied to the skin before exposure to UV light, it helped prevent the redness and pigmentation that would normally have occurred. Licorice extract also reduces melanin synthesis, suggesting that it may have applications in preventing and fading unsightly “age spots,” or areas of hyper-pigmented skin.⁵⁵

Furthermore, licorice extract’s antioxidant activity has been shown to enhance the stability of other compounds when added to a topical dermatological cream.⁵⁶

SUMMARY

The FDA’s sun protection factor (SPF) rating system is inherently flawed in that it measures the effectiveness of sunscreen products against UV-B light, but not against deeper-penetrating UV-A light. Unfortunately, despite the FDA’s public acknowledgment of this shortcoming back in 2000, the rating system has still not been changed.

Natural sunlight activates vitamin D in the skin, and vitamin D has extraordinary anti-cancer benefits. For those at greatest risk of skin cancer, consuming additional vitamin D may be a more appropriate strategy than additional sun exposure. Although there are many unusual theories about skin cancer in the medical literature, until these theories have more definitive proof, a cautious approach to sun exposure is indicated. For most of us, a prudent strategy suggests 10-15 minutes of exposure to natural sunlight two to three times weekly, with additional vitamin D supplementation as a reasonable option.

Natural topical products such as green tea extract, turmeric, and licorice root extract offer remarkable protection against premature skin aging and skin cancer that all too often result from excessive sun exposure and sunburn.

Your skin is designed to last a lifetime—treat it well, and it will!

References

1. Solar and ultraviolet radiation (IARC). Monographs on the evaluation of the carcinogenic risk of chemicals to humans. IARC. 1992;55.
2. Naylor MF, Farmer KC. The case for sunscreens. A review of their use in preventing actinic damage and neoplasia. *Arch Dermatol.* 1997 Sep;133(9):1146-54.
3. Available at: www.cancer.org/docroot/CRI/content?CRI_2_4_1X-What_are_the_key_statistics_for_melanoma_50.asp?sitearea. Accessed March 27, 2006.
4. Available at: www.fda.gov/FDAC/features/2000/400_sun.html. Accessed March 27, 2006.
5. Haywood R, Wardman P, Sanders R, Linge C. Sunscreens inadequately protect against ultraviolet-A-induced free radicals in skin: implications for skin aging and melanoma? *J Invest Dermatol.* 2003 Oct;121(4):862-8.
6. Sakurai H, Yasui H, Yamada Y, Nishimura H, Shigemoto M. Detection of reactive oxygen species in the skin of live mice and rats exposed to UVA light: a research review on chemiluminescence and trials for UVA protection. *Photochem Photobiol Sci.* 2005 Sep;4(9):715-20.
7. Hanson KM, Clegg RM. Bioconvertible vitamin antioxidants improve sunscreen photoprotection against UV-induced reactive oxygen species. *J Cosmet Sci.* 2003 Nov;54(6):589-98.
8. Darr D, Dunston S, Faust H, Pinnell S. Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants. *Acta Derm Venereol.* 1996 Jul;76(4):264-8.
9. Available at: http://www.uspdqi.org/pubs/monographs/sunscreen_agents.pdf#search='sunscreens%20and%20titanium%20dioxide%20and%20cinnamates%20and%20PABA'. Accessed March 27, 2006.
10. Krekels G, Voorter C, Kuik F, et al. DNA protection by sunscreens: p53 immunostaining. *Eur J Dermatol.* 1997;7(4):259-62.
11. Farmer KC, Naylor MF. Sun exposure, sunscreens, and skin cancer prevention: a year-round concern. *Ann Pharmacother.* 1996 Jun;30(6):662-73.
12. Mitchnick MA, Fairhurst D, Pinnell SR. Microfine zinc oxide (Z-cote) as a photostable UVA/UVB sunblock agent. *J Am Acad Dermatol.* 1999 Jan;40(1):85-90.
13. Tarnow P, Agren M, Steenfoss H, Jansson JO. Topical zinc oxide treatment increases endogenous gene expression of insulin-like growth factor-1 in granulation tissue from porcine wounds. *Scand J Plast Reconstr Surg Hand Surg.* 1994 Dec;28(4):255-9.
14. Smedby KE, Hjalgrim H, Melbye M, et al. Ultraviolet radiation exposure and risk of malignant lymphomas. *J Natl Cancer Inst.* 2005 Feb 2;97(3):199-209.
15. Berwick M, Armstrong BK, Ben-Porat L, et al. Sun exposure and mortality from melanoma. *J Natl Cancer Inst.* 2005 Feb 2;97(3):195-9.
16. Grant, WB. A multifactor ecologic analysis of the geographic variation in cancer mortality rates in the USA. *Cancer Causes & Control* (submitted).

17. Devesa SS, Grauman MA, Blot, WJ, Pennello GA. Hoover RN, Fraumeni JF. Atlas of cancer mortality in the United States: 1950 to 1994. NIH. 1999;99:4564.
18. Kawa S, Nikaido T, Aoki Y, et al. Vitamin D analogues up-regulate p21 and p27 during growth inhibition of pancreatic cancer cell lines. *Br J Cancer*. 1997;76(7):884-9.
19. Verlinden L, Verstuyf A, Convents R, et al. Action of 1,25(OH)2D3 on the cell cycle genes, cyclin D1, p21 and p27 in MCF-7 cells. *Mol Cell Endocrinol*. 1998 Jul 25;142(1-2):57-65.
20. Liu M, Lee MH, Cohen M, Bommakanti M, Freedman LP. Transcriptional activation of the Cdk inhibitor p21 by vitamin D3 leads to the induced differentiation of the myelomonocytic cell line U937. *Genes Dev*. 1996 Jan 15;10(2):142-53.
21. Hutchinson PE, Osborne JE, Lear JT, et al. Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. *Clin Cancer Res*. 2000 Feb;6(2):498-504.
22. Holick MF. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. *Curr Opin Endocrinol Diabetes*. 2002;9:87-98.
23. Robinson TA, Kligman AM. Treatment of solar keratoses of the extremities with retinoic acid and 5-fluorouracil. *Br J Dermatol*. 1975 Jun;92(6):703-6.
24. Katiyar SK, Elmets CA. Green tea polyphenolic antioxidants and skin photoprotection (Review). *Int J Oncol*. 2001 Jun;18(6):1307-13.
25. Morley N, Clifford T, Salter L, et al. The green tea polyphenol (-)-epigallocatechin gallate and green tea can protect human cellular DNA from ultraviolet and visible radiation-induced damage. *Photodermatol Photoimmunol Photomed*. 2005 Feb;21(1):15-22.
26. Katiyar SK. Skin photoprotection by green tea: antioxidant and immunomodulatory effects. *Curr Drug Targets Immune Endocr Metabol Disord*. 2003 Sep;3(3):234-42.
27. Vayalil PK, Mittal A, Hara Y, Elmets CA, Katiyar SK. Green tea polyphenols prevent ultraviolet light-induced oxidative damage and matrix metalloproteinases expression in mouse skin. *J Invest Dermatol*. 2004 Jun;122(6):1480-7.
28. Katiyar SK, Mukhtar H. Green tea polyphenol (-)-epigallocatechin-3-gallate treatment to mouse skin prevents UVB-induced infiltration of leukocytes, depletion of antigen-presenting cells, and oxidative stress. *J Leukoc Biol*. 2001 May;69(5):719-26.
29. Vayalil PK, Elmets CA, Katiyar SK. 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*. 2003 May;24(5):927-36.
30. Mittal A, Piyathilake C, Hara Y, Katiyar SK. Exceptionally high protection of photocarcinogenesis by topical application of (-)-epigallocatechin-3-gallate in hydrophilic cream in SKH-1 hairless mouse model: relationship to inhibition of UVB-induced global DNA hypomethylation. *Neoplasia*. 2003 Nov;5(6):555-65.
31. Elmets CA, Singh D, Tubesing K, et al. Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. *J Am Acad Dermatol*. 2001 Mar;44(3):425-32.
32. Lu YP, Lou YR, Xie JG, et al. Topical applications of caffeine or (-)-epigallocatechin gallate (EGCG) inhibit carcinogenesis and selectively increase apoptosis in UVB-induced skin tumors in mice. *Proc Natl Acad Sci USA*. 2002 Sep 17;99(19):12455-60.
33. Chung JH, Han JH, Hwang EJ, et al. Dual mechanisms of green tea extract (EGCG)-induced cell survival in human epidermal keratinocytes. *FASEB J*. 2003 Oct;17(13):1913-5.
34. Huang MT, Ho CT, Wang ZY, et al. Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. *Cancer Res*. 1994 Feb 1;54(3):701-8.
35. Harmand PO, Duval R, Delage C, Simon A. Ursolic acid induces apoptosis through mitochondrial intrinsic pathway and caspase-3 activation in M4Beu melanoma cells. *Int J Cancer*. 2005 Mar 10;114(1):1-11.

36. Soo LY, Jin DQ, Beak SM, Lee ES, Kim JA. Inhibition of ultraviolet-A-modulated signaling pathways by asiatic acid and ursolic acid in HaCaT human keratinocytes. *Eur J Pharmacol.* 2003 Aug 29;476(3):173-8.
37. Both DM, Goodtzova K, Yarosh DB, Brown DA. Liposome-encapsulated ursolic acid increases ceramides and collagen in human skin cells. *Arch Dermatol Res.* 2002 Jan;293(11):569-75.
38. Yarosh DB, Both D, Brown D. Liposomal ursolic acid (merotaine) increases ceramides and collagen in human skin. *Horm Res.* 2000;54(5-6):318-21.
39. Phan TT, See P, Lee ST, Chan SY. Protective effects of curcumin against oxidative damage on skin cells in vitro: its implication for wound healing. *J Trauma.* 2001 Nov;51(5):927-31.
40. Huang MT, Newmark HL, Frenkel K. Inhibitory effects of curcumin on tumorigenesis in mice. *J Cell Biochem Suppl.* 1997;27:26-34.
41. Jee SH, Shen SC, Tseng CR, Chiu HC, Kuo ML. Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells. *J Invest Dermatol.* 1998 Oct; 111(4):656-61.
42. Bush JA, Cheung KJ, Jr., Li G. Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53. *Exp Cell Res.* 2001 Dec 10;271(2):305-14.
43. Huang MT, Ma W, Lu YP, et al. Effects of curcumin, demethoxycurcumin, bisdemethoxycurcumin and tetrahydrocurcumin on 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion. *Carcinogenesis.* 1995 Oct;16(10):2493-7.
44. Research Report, Sami Labs Ltd, 2002.
45. Research Report, Sabinsa Corporation, 2003.
46. Lahiri-Chatterjee M, Katiyar SK, Mohan RR, Agarwal R. A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model. *Cancer Res.* 1999 Feb 1;59(3):622-32.
47. Mallikarjuna G, Dhanalakshmi S, Singh RP, Agarwal C, Agarwal R. Silibinin protects against photocarcinogenesis via modulation of cell cycle regulators, mitogen-activated protein kinases, and Akt signaling. *Cancer Res.* 2004 Sep 1;64(17):6349-56.
48. Singh RP, Agarwal R. Mechanisms and preclinical efficacy of silibinin in preventing skin cancer. *Eur J Cancer.* 2005 Sep;41(13):1969-79.
49. Katiyar SK. Silymarin and skin cancer prevention: anti-inflammatory, antioxidant and immunomodulatory effects (review). *Int J Oncol.* 2005 Jan;26(1):169-76.
50. Fiore C, Eisenhut M, Ragazzi E, Zanchin G, Armanini D. A history of the therapeutic use of liquorice in Europe. *J Ethnopharmacol.* 2005 Jul 14;99(3):317-24.
51. Wang ZY, Nixon DW. Licorice and cancer. *Nutr Cancer.* 2001;39(1):1-11.
52. Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. *J Dermatolog Treat.* 2003 Sep;14(3):153-7.
53. Rossi T, Benassi L, Magnoni C, et al. Effects of glycyrrhizin on UVB-irradiated melanoma cells. *In Vivo.* 2005 Jan;19(1):319-22.
54. Wang ZY, Agarwal R, Zhou ZC, Bickers DR, Mukhtar H. Inhibition of mutagenicity in *Salmonella typhimurium* and skin tumor initiating and tumor promoting activities in SENCAR mice by glycyrrhetic acid: comparison of 18 alpha- and 18 beta-stereoisomers. *Carcinogenesis.* 1991 Feb;12(2):187-92.
55. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. *Pigment Cell Res.* 1998 Dec;11(6):355-61.
56. Morteza-Semnani K, Saeedi M, Shahnava B. Comparison of antioxidant activity of extract from roots of licorice (*Glycyrrhiza*

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.