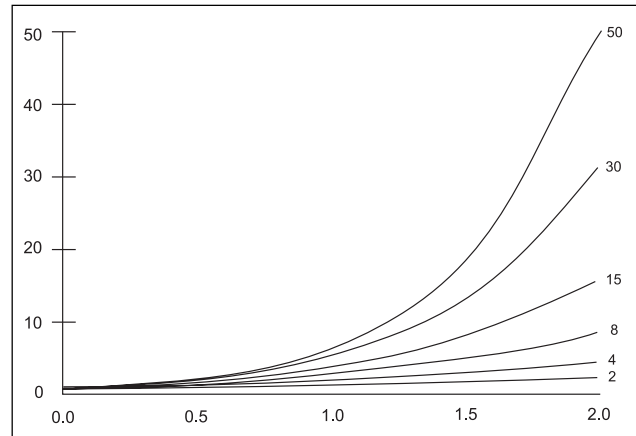


UV PHOTOPROTECTION BY TOPICAL VITAMINS C + E

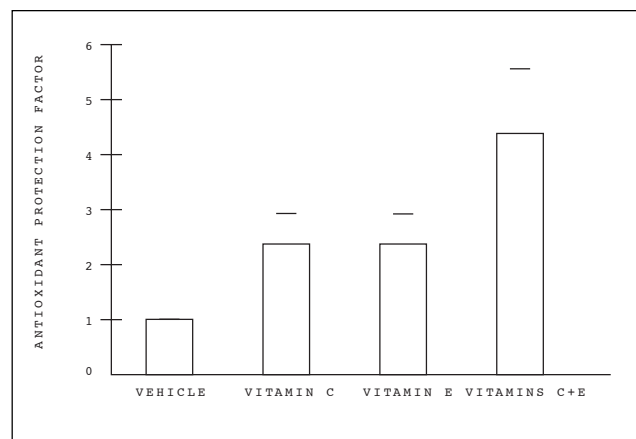
PROTECTING THE SKIN FROM UV LIGHT IS ESSENTIAL TO THE PREVENTION OF PHOTOAGING AND SKIN CANCERS. STUDIES SHOW THAT SUNBLOCK MAY NOT OFFER AS MUCH PROTECTION AS INDICATED. SKINCEUTICALS C + E OFFERS SIGNIFICANT ADDITIONAL PHOTOPROTECTION AND HELPS INHIBIT THE DEVELOPMENT OF THYMINE DIMERS. RECENT STUDIES SHOW THAT TOPICAL VITAMINS C AND E OFFER GREATER PROTECTION THAN PREVIOUSLY REALIZED.

The SPF Indication of sunblock may not be an accurate measurement of protection based on the amounts of sunblock the average person wears. Due to the small physical amounts of sunblock people wear regardless of the product's SPF, they may only be getting protection that ranges between 2 – 4.



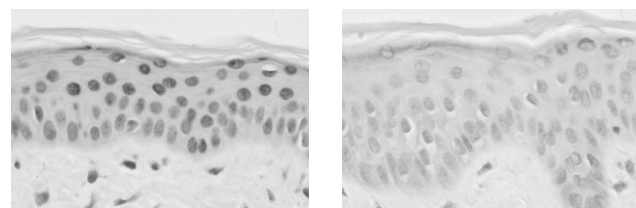
Wulf, H.C. et al., Photoderm Photoimmun Photomed, 13:129-32, 1997

Measuring the same criteria (erythema and sunburn cell formulation) used to determine protection from sunblock, we now know topical antioxidant C + E offers skin a protection of 4. Studies measuring UV induced erythema showed a reduction of redness in skin treated topically with pure vitamins C and E, as found in the formulation from SkinCeuticals.



Combination C + E provided fourfold protection compared to twofold protection provided by C or E alone.

Topical vitamins C and E together can also help protect against thymine dimer formation. The synergistic properties of pure vitamins C and E can help inhibit the development of thymine dimers. Unrepaired, thymine dimers are known to be associated with certain skin cancers.



Control

C + E

Marked reduction of thymine dimers in C + E-treated in comparison to control skin.

ARE ALL VITAMIN C PRODUCTS THE SAME?

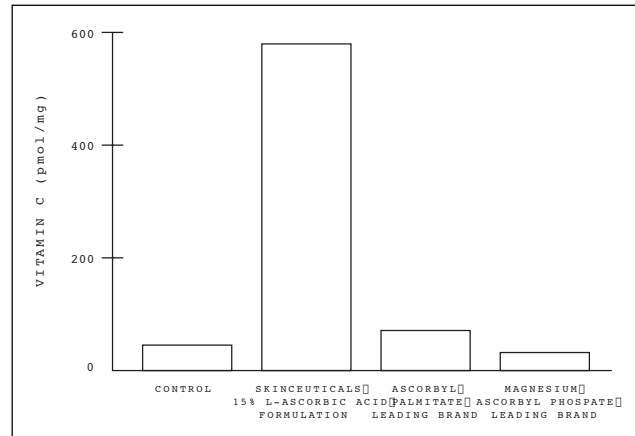
ABSORPTION: THE KEY TO TRULY EFFECTIVE VITAMIN C

PURITY, PERCENTAGE, AND PH LEVEL CAN AFFECT THE PERFORMANCE OF A VITAMIN C PRODUCT. BUT, MOST IMPORTANTLY, A VITAMIN C PRODUCT MUST BE ABSORBED BY THE SKIN TO BE TRULY EFFECTIVE. SKINCEUTICALS SERUMS ARE SPECIFICALLY FORMULATED TO EFFECTIVELY INCREASE LEVELS OF VITAMIN C IN THE SKIN. STUDIES SHOW THAT AN EFFECTIVE TOPICAL VITAMIN C PRODUCT MUST MEET THE FOLLOWING CRITERIA:

DOES THE PRODUCT CONTAIN PURE L-ASCORBIC ACID?

Vitamin C is L-ascorbic acid. Even though they can claim to be vitamin C, other ingredients like magnesium ascorbyl phosphate or ascorbyl palmitate are not vitamin C and are not recognized as vitamin C by the body. Studies show that these other ingredients do not significantly increase levels of vitamin C in skin.

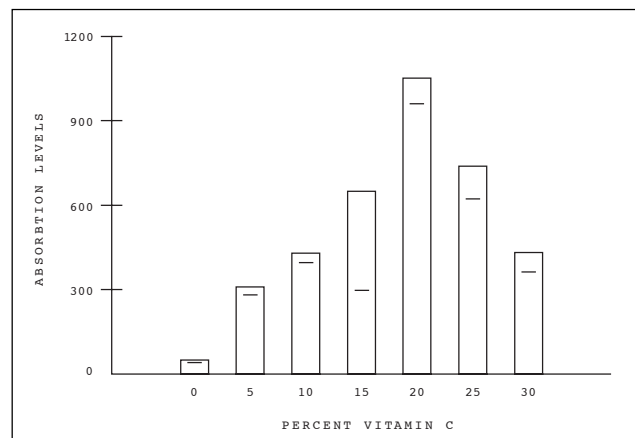
Not all products have pure vitamin C. SkinCeuticals does.



IS THERE ENOUGH VITAMIN C FOR THE PRODUCT TO WORK?

Studies show a topical vitamin C product must have a substantial amount of vitamin C to have an effect, and that 20% is optimal for absorption.

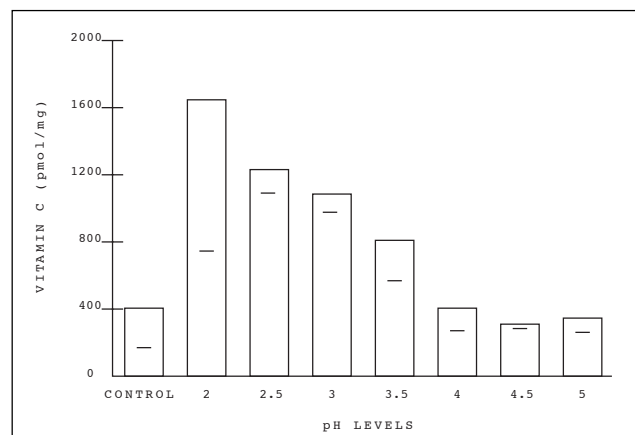
Not all products have enough vitamin C. SkinCeuticals does.



IS THE PH LOW ENOUGH TO ALLOW ABSORPTION?

To be absorbed by the skin, the pH of topical vitamin C must be very low. As the pH is increased, less vitamin C is absorbed.

Not all products have low pH. SkinCeuticals does.



THE SCIENCE SUPPORTING SKINCEUTICALS

TOPICAL ANTIOXIDANT SERUMS

ABSTRACT

The human body uses many internal antioxidant mechanisms to defend itself from oxidative damage, but excessive exposure to ultraviolet light as well as the natural aging process depletes the body of its internal supply of antioxidants. Antioxidants prevent oxidative damage by neutralizing oxygen-free radicals before they can attack the body. Some antioxidants are available to the body by oral ingestion, but many individuals do not achieve even the minimum daily requirement through diet or supplements. Furthermore, body control mechanisms tightly control the amounts available by oral ingestion to the cells. SkinCeuticals formulators have found a way to combine, stabilize and get additional amounts of key antioxidants into skin, thus adding to the body's natural reservoir of antioxidants. When applied topically, combination antioxidants can provide up to four-fold antioxidant protection, and prevent the formation of thymine dimers in irradiated skin.

UV RADIATION AND THE UV SPECTRUM

Exposure to ultraviolet radiation (UVR) is a well-documented health hazard. The ultraviolet spectrum is divided into the following key regions: UVC (270-290 nm), UVB (290-320 nm), UVAII (320-340 nm), and UVAI (340-400 nm).

The ozone layer protects humans from damage against UVC rays, but not UVB and UVA rays. Reactive oxygen species (ROS), including oxygen-free radicals, are generated by exposure of the skin to UV radiation. UVB rays are known to cause burning. UVA rays are now known to cause photoaging (Lavker et al, *Photochem and Photobio*, 1995; Lowe et al, *J Invest Dermatol*, 1995).

UVB is heaviest during the hours of 10:00 a.m. and 3:00 p.m. and also during the summer. UVA is much more constant throughout the day and also throughout the year. UVA also can penetrate glass, including that of car, office and home windows; in contrast, UVB is blocked by glass. Approximately two-thirds of the UVA spectrum is UVAI, or long UVA. Compared to UVB, there is thirty times more UVA in the ultraviolet spectrum.

THE EFFECTS OF SUN ON SKIN

When sun shines on skin, the epidermis absorbs the short (290-320 nm) UVB rays. These generate oxygen-free radicals that can destroy and mutate cells and even cause skin cancer. The longer (320-420 nm) UVA (aging) rays go

deep into the skin's dermis, and even through skin. These rays penetrate thirty to forty times deeper than UVB rays, and also generate oxygen-free radicals which can mutate collagen, elastin, proteoglycan, cells, and even DNA. In time, it is believed that these changes may result in a breakdown in connective tissue. Visible signs of this destruction encompass intrinsic aging and photoaging changes — including wrinkles, solar lentigines (brown spots), actinic keratoses — and possibly even skin cancers.

UVA RADIATION MAY CAUSE PHOTOAGING AND SKIN CANCER

Just recently, a study co-authored by Duke University biophysicist John D. Simon, Ph.D. shows that UVA rays, a form of sunlight not blocked by most products, may cause photoaging and skin cancer (Hanson and Simon, *Proc Natl Acad Sci USA*, 1998).

Simon's study shows that UVA sunlight is absorbed by urocanic acid, a natural molecule made by the outermost skin cells. The sunlight chemically changes urocanic acid and causes it to create oxygen-free radicals within skin cells. These highly reactive molecules damage cells by degrading collagen and elastin; it is this degradation process that accelerates aging in skin (Hanson and Simon, *Natl Acad Sci USA*, 1998).

SMOKING CAUSES MORE WRINKLES THAN EXTENSIVE SUN EXPOSURE

Cigarette smoking also generates reactive oxygen species. Smoking has an even greater effect on premature wrinkling than extensive sun exposure. Smoking depletes L-ascorbic acid, resulting in lowered serum levels (Kadunce et al, *Ann of Int Med*, 1991).

UVAI (340-400 NM) LONG RAYS CAUSE PHOTOAGING DAMAGE

Just recently, scientists demonstrated that photoaging changes can be experimentally produced in normal human skin by UVAI (340-400 nm) or the long UVA rays. (Lavker, R.M. et al, *Photochemistry and Photobiology*, 1995). Given the structure of skin, dermatologists and photobiologists have long hypothesized that the long UVA rays that penetrate the skin deepest might be responsible for photoaging changes in skin, and now, it has been proven. Only eight relatively small dosages of UVA are necessary before

changes are evident, and these changes are not prevented by using a sunscreen with a sun protection factor (SPF) of 22 (Lavker et al, *J Am Acad Dermatol*, 1995; Lowe et al, *J Invest Dermatol*, 1995). Unfortunately, most currently-available sunscreens typically don't protect from UVAI insults.

UVA RADIATION MAY PLAY A ROLE IN MELANOMA FORMULATION

A recent study has detected a correlation between the use of sunlamps or sunbeds and the development of melanoma, especially in younger individuals (Autier et al, *Int. J. Cancer*, 1994). In addition, PUVA (ultraviolet A radiation plus oral methoxsalen) therapy is known to increase the incidence of melanoma (Stern et al, *N Eng J Med*, 1997). UVA radiation also is known to cause DNA mutations in cell culture (Nishigori et al, *J Invest Dermatol*, 1996) and melanoma in fish (Setlow et al *Proc Natl Acad Sci USA*, 1993).

Three international, well-controlled studies also have shown a higher incidence of melanoma skin cancers in individuals using UVB sunscreens (Wolf et al, *J Invest Dermatol*, 1996; Autier et al, *Int J Cancer*, 1995; Westerdahl et al, *Melanoma Research*, 1995). These studies show that using a UVB sunscreen may cause an increase in melanoma. Although several explanations are possible, it may be that individuals stay out in the sun longer than they would otherwise because they are not burning; without the signal to get out of the sun, UVA damage continues. Such findings lend impetus to the notion that excessive exposure to UVA through sunscreens and changing sunbathing habits may be contributing to the spiraling incidence of melanoma.

INADEQUATE SUNSCREEN APPLICATION FURTHER LESSENS PROTECTION

SPF is measured by applying 2 mg/cm² to skin. Recent studies have concluded that users apply only one-fourth (Wulf et al, *Photodermatolo, Photoimmunol & Photomed*, 1997) to one-fifth (Autier et al, *J Nat Can Inst*, 1999) the amount necessary to achieve full protection. Thus, the protection available in a SPF 30 sunscreen is only SPF 2.3 when applied at these levels. (Wulf et al, *Photodermatolo, Photoimmunol & Photomed*, 1997).

UV EXPOSURE DEPLETES OUR ANTIOXIDANTS

Antioxidants are inhibited following UV exposure. Ultraviolet radiation and smoking generate ROS that cause serious depletion of antioxidants. Alcohol, analgesics, antidepressants, anticoagulants, oral contraceptives, and steroids also may reduce the body's level of key antioxidants (Feinstein, et

al, *Healing with Vitamins*, 1996). Long-wave UVA rays alone can cause this damage. Since sunscreens do not fully protect against UV damage, topical antioxidants offer supplement protection from UV damage.

WHY ORAL INGESTION OF ANTIOXIDANTS ISN'T ENOUGH

Oral ingestion is one way to get antioxidant vitamins into skin, but body control mechanisms tightly regulate the levels of ingested vitamins. The skin only receives a tightly regulated amount of vitamins. Furthermore, most people don't get adequate supplies of antioxidant nutrients through diet. Applying antioxidants topically is a way to increase skin levels to help protect against ROS and combat cutaneous damage — provided the antioxidants first get into the skin, and then are in a form the body can use.

HOW ANTIOXIDANTS PROTECT SKIN

Vitamin C, vitamin E, and zinc are antioxidants that, when formulated properly, can be used in topical antioxidant preparations, to protect and correct skin damage. Vitamin C and vitamin E are both examples of antioxidants that act as free radical scavengers. Antioxidants protect skin by neutralizing reactive oxygen species, the oxidative "bombs" generated when skin is exposed to environmental insults — bombs that otherwise would destroy skin and its components (Shindo et al, *J Invest Derm*, 1994).

BENEFITS OF L-ASCORBIC ACID TO SKIN

By providing pharmacological levels of L-ascorbic acid that can be targeted directly to skin by topical applications, the goal is to interfere with environmental oxidative insults, including sunlight, smoking, and pollution. L-ascorbic acid provides the following key benefits to skin (Pinnell and Madey, *Aesth Surg J*, 1998):

- *Neutralizes Reactive Oxygen Species*
- *Protects against UVB and UVA Damage*
- *Regenerates Vitamin E and other antioxidants*
- *Stimulates Collagen Growth*
- *Prevents UV Immunosuppression*
- *Anti-inflammatory*

Neutralizes Reactive Oxygen Species

Vitamin C (L-ascorbic acid) is the major antioxidant in the water-soluble or aqueous phase of tissues, including both intracellular and extra-cellular fluids. It neutralizes reactive oxygen species destructive to the skin. Among the reactive oxygen species that L-ascorbic acid neutralizes are superoxide anion,

singlet oxygen, and hydroxyl radical (Halliwell and Gutteridge, *Arch of Biochem & Biophys*, 1990).

Protects against UVB and UVA Damage

Topical vitamin C both protects against and reduces harmful effects in skin caused by sunlight. It is equally effective in both the UVB (290-320 nm) and UVA bands (320-400 nm) (Darr et al, *Br J Derm*, 1992). Because topical vitamin C does not absorb light in the UVB/UVA range, it is not a sunscreen. Unlike sunscreens, it does not have to be between the sun and the skin to work. Topical vitamin C (L-ascorbic acid) exerts its effects by neutralizing oxygen-free radicals before they can damage skin.

Regenerates Vitamin E

Vitamin C is perhaps the body's most important antioxidant because it also helps vitamin E replenish itself. Whereas vitamin C protects the water parts of each cell, vitamin E protects the lipid parts of each cell, including cell membranes.

Stimulates Collagen Growth

Vitamin C stimulates collagen synthesis. It is the only antioxidant that has been proven to increase collagen synthesis. In human skin fibroblasts in culture, vitamin C (L-ascorbic acid) stimulates collagen synthesis without affecting other protein synthesis. L-ascorbic acid is known to be necessary for prolyl hydroxylase, an enzyme essential for producing a stable collagen molecule. In addition, ascorbic acid is necessary for lysyl hydroxylase, an enzyme necessary for cross-linking one collagen molecule to another collagen molecule. This reaction is required for tissue strength. Finally, L-ascorbic acid serves as a transcription signal that tells collagen genes to synthesize collagen.

Prevents UV Immunosuppression

Topical vitamin C prevents UV immunosuppression. (Nakamura, T., et al, *J Invest Dermatol*, 1997). This phenomenon, in which the activity of the immune system is stifled following exposure to sunlight, occurs in approximately one-third of humans. However, it is found in over 90 percent of individuals who get skin cancer, both melanoma and non-melanoma skin cancers (Granstein, R., *Arch Dermatol*, 1995; Streilein, W., in Gilchrist, B., *Photoprotection*, 1995).

When skin is immunosuppressed, it is paralyzed in its ability to respond to sensitizers, such as poison ivy. For reasons that are not clear, sunscreens only partially aid in the prevention of UV immunosuppression. Studies show that topical L-ascorbic acid prevents the loss of contact hypersensitivity in animals exposed to UV radiation and also prevents UVB-induced tolerance (Nakamura, T., et al, *J Invest Dermatol*, 1997). However,

one should not infer a protective effect against skin cancer, because such studies have not been done.

Alleviates Inflammation

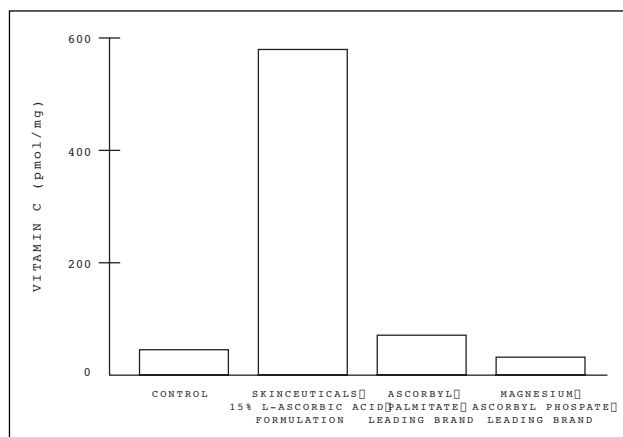
Skin inflammation — including that caused by inflammatory dermatoses, phototrauma, and carbon dioxide laser resurfacing — is mediated by reactive oxygen species. Vitamin C is depleted rapidly when skin is inflamed. Topical L-ascorbic acid has been reported to alleviate ultraviolet radiation-induced erythema on porcine and human skin (Darr et al, *Br J Derm* 1992). It is protective even when it is applied after sun exposure and is helpful in speeding the healing process and is capable of controlling the inflammatory response associated with ultraviolet light (sunburn).

It is often recommended as a pre- and post-operative regimen for laser resurfacing patients. (Alster and West, *Dermatol Surg*, 1998) Dermatologic surgeons recommend using it as long as possible prior to laser resurfacing and beginning again as early as fourteen days following surgery. (Alster and West, *Dermatol Surg*, 1997).

DERIVATIVES OF VITAMIN C

L-ascorbic acid is an inherently unstable molecule, which is what makes it such a good antioxidant (Darr et al, 1996). To overcome the instability problem, many formulators use derivatives of vitamin C to provide stable cosmetic formulations.

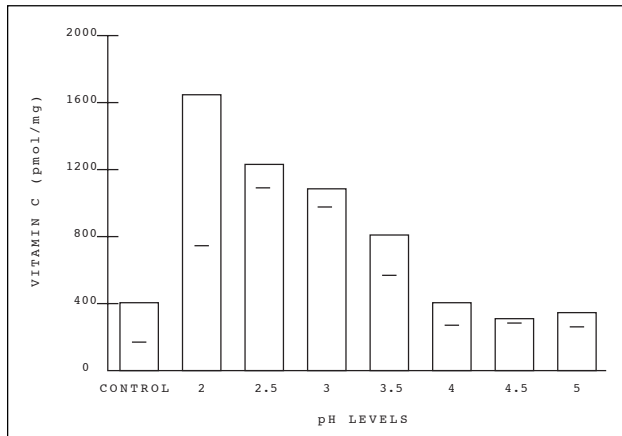
New scientific evidence shows decisively that derivatives don't increase skin levels of vitamin C. They may get in, but they are not converted. In contrast, L-ascorbic acid gets into skin. The key is to get a high enough concentration of L-ascorbic acid into skin so that it can have an effect, and still preserve its stability.



EFFECTIVE VITAMIN C FORMULATIONS

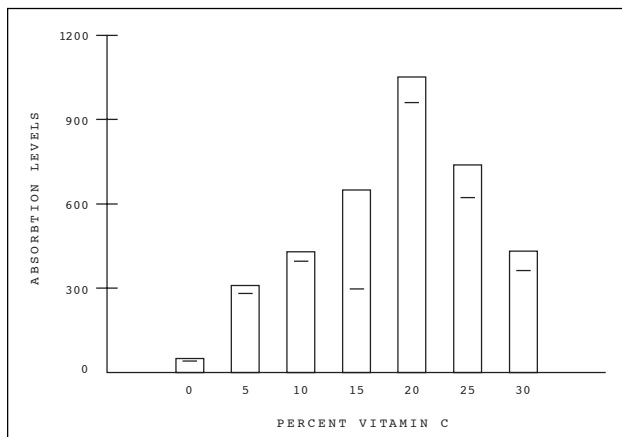
In order to achieve these benefits, a vitamin C formulation must have the following characteristics:

- *It must contain L-ascorbic acid, the only form of vitamin C the body can use*
- *The vitamin C must be present at high concentrations;*
- *It must be at acid pH; only unionized vitamin C is able to be absorbed by the skin*
- *It must be stable*



OPTIMAL CONCENTRATION

New studies show that a 20% concentration of L-ascorbic acid gets the maximum amount of vitamin C into skin. These levels cannot be achieved by diet and are pharmacological levels.



VITAMIN E

Vitamin E (a-tocopherol) is the body's most important lipid or fat-soluble antioxidant. It has significant antioxidant functions, especially in cell membranes and lipoproteins. It is important to keep the cell membrane intact, or the cell and its components are destroyed by reactive oxygen species. As an antioxidant, it protects other fat-soluble vitamins from oxidative damage. It is necessary for tissue repair; it is a natural anticoagulant and promotes healing.

The predominant form of vitamin E in human and animal tissues is a-tocopherol; it comprises about 90% of the tocopherols in animal tissues and displays the greatest biological activity in most bioassay systems. The empirical formula for vitamin E or a-tocopherol is C₂₉H₅₀O₂. Other names used for vitamin E are mixed tocopherols, d-alpha tocopherol, and DL-alpha tocopherol. Tocopherol is the form the body uses. Unlike L-ascorbic acid, a-tocopherol is not an unstable molecule, but vitamin E requires vitamin C in order to replenish itself, and zinc in order to maintain proper levels in the blood.

Vitamin E (a-tocopherol) provides the following key benefits to skin:

- *Neutralizes ROS damage*
- *Protects against UV Damage*
- *Promotes Healing*
- *Prevents UV Immunosuppression*

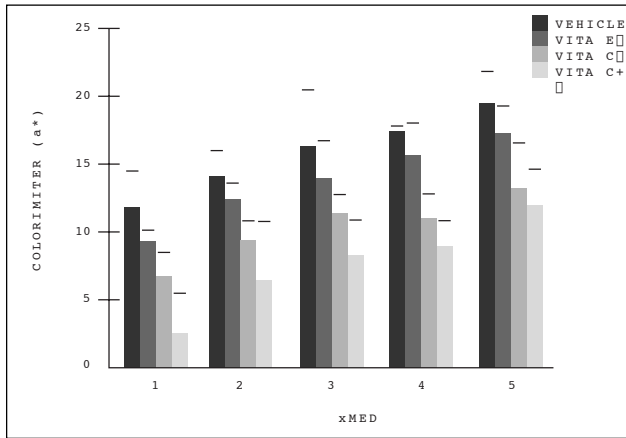
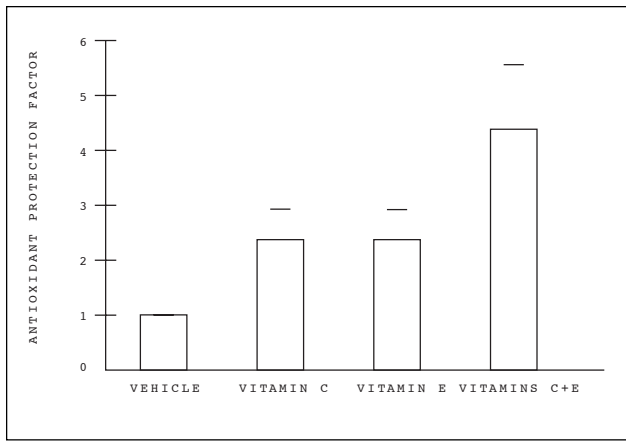
DERIVATIVES OF VITAMIN E

Vitamin E derivatives do not have the antioxidant effects of pure vitamin E or a-tocopherol, because they are not antioxidants. Cosmetic companies often misuse the term vitamin E, using it to refer to a derivative, thus confusing consumers. The best suggestion is to read the ingredient list and to know what vitamin E really is: a-tocopherol. While this is the only form of vitamin E the body can use, there are many derivatives that are used in cosmetic foundations. This is not to say that the vitamin E derivatives aren't useful in skin care formulations. Vitamin E derivatives are excellent emollients.

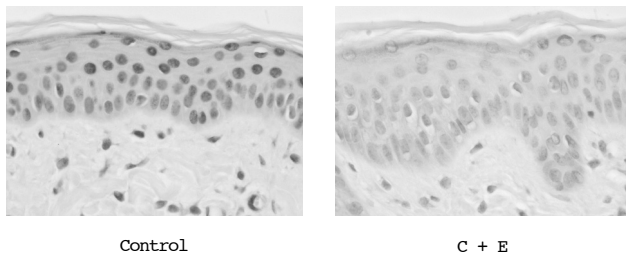
VITAMIN C AND VITAMIN E HAVE SYNERGISTIC EFFECT

Previously, vitamin C and vitamin E were thought to be impossible to combine due to their structure. Vitamin C is aqueous and vitamin E is lipid-soluble; in essence, it's like mixing oil and water. Now, an extraordinary new technology allows for both of these antioxidants to be combined.

When combined and applied topically, a formulation of 15% L-ascorbic acid and 1% a-tocopherol provide synergistic photoprotection not achieved by either antioxidant alone. A combination of vitamins C and E delivered fourfold antioxidant protection, compared to twofold protection for vitamin C or E alone. Both erythema and sunburn cell formation are reduced. (Pinnell et al., *JAAD*, 2003).



The combination of vitamins C and E applied topically also prevent the formation of thymine dimers in irradiated skin. (Pinnell et. al., *JAAD*, 2003).



ALPHA HYDROXY ACIDS (GLYCOLIC ACID/LACTIC ACID)

Glycolic acid has been shown to increase the production of collagen and fibroblast proliferation, both in vivo and in vitro (Moy et al, *Dermatol Surg*, 1996; Kim, S. et al, *Dermatol Surg*, 1996). In vitro, glycolic acid has proliferative effects on cells. In vivo, glycolic acid increases collagen production without inflammatory action (Kim, S. and Won, Y., *J of Dermatol*, 1998).

Topical 8% glycolic acid and 8% lactic acid, were both modestly useful in ameliorating signs of chronic cutaneous photodamage. In this single-center, 22-week double-blind vehicle-controlled randomized clinical trial that started with 74 female patients aged 40 to 70 years and ended with 68 patients, results were more noticeable on the forearms than the face. On the face, the percentage of patients using 8%

glycolic or 8% lactic acid achieved at least one grade of improvement in severity of photodamage was significantly greater than the vehicle cream (76% glycolic, 71% lactic acid, and 40% vehicle; $p < .05$). On the forearms, glycolic acid reduced the overall severity of photodamage and sallowness ($p < .05$). Lactic acid reduced the overall severity of photodamage ($p < .05$), mottled hyperpigmentation ($p < .05$), sallowness ($p < .05$) and roughness ($p < .05$) (*Arch Dermatol* 1996; 132:631-636).

Alpha hydroxy acids provide the following key benefits to skin:

- *Exfoliate Skin's Outer Surface*
- *Accelerate Cell Renewal*

ZINC

The trace mineral, zinc, plays a significant role as an antioxidant. Like vitamin C, zinc provides antioxidant protection from UVB and UVA damage. Zinc also must be present for other antioxidants to work properly. It alleviates inflammation, promotes wound healing, and improves immunity. The body does not synthesize zinc. The body's supply of zinc also is depleted by increased calcium intake and by intense perspiration.

Dermatologic features of severe zinc deficiency include erythema and scaling in the nasolabial and retro-auricular folds. Later, the neck, inguinal, axillary, and perineal skin become involved. At the same time, angular cheilitis, stomatitis, and glossitis may be present. Areas such as the knees, elbows, heels, and occipital scalp, which are prone to friction and trauma, are frequently involved (Aggett, P.J., *Zinc in Human Biology*). Characteristically, the rash is symmetric and consists of orange-brown, erosive, and crusted, well-demarcated patches or plaques. With time, these plaques may be hyperkeratotic and resemble psoriasis (Aggett, P.J., *Zinc in Human Biology*) Vesicular or bullous lesions may occur on the fingertips and palms. Nail changes may be observed with brown discoloration and paronychia commonly reported.

Mild zinc deficiency has also been reported in various disease states, including those that involve (1) absorption abnormalities (e.g., cystic fibrosis and inflammatory bowel disease); (2) conditions of excessive loss via urine and hemolysis (e.g., insulin-dependent diabetes and sickle cell anemia); and (3) increased zinc requirements (e.g., growth hormone replacement therapy). Xerotic or roughened skin and impaired wound healing has been reported in mild zinc deficiency. (Hambridge, K.M., *Zinc in Human Biology*)

The recommended daily value for oral intake of zinc is 15 milligrams. Achieving this amount by diet alone is difficult because you have to ingest about 2,400 calories a day to get

the recommended dietary allowance (RDA) for zinc. Most Americans probably don't get enough zinc. In fact, one study found that 30 percent of healthy elderly people are zinc-deficient (Feinstein, 1996).

Zinc can be applied topically to skin. Zinc salts, such as zinc sulphate, have been shown to penetrate skin.

Zinc provides the following key benefits to skin:

- *Neutralizes ROS Damage*
- *Protects Against UVB and UVA Damage*
- *Helps Other Antioxidants Work Properly*
- *Alleviates Inflammation*
- *Promotes Healing*
- *Improves Immunity*

SKINCEUTICALS ANTIOXIDANT PRODUCTS

SkinCeuticals formulators have developed a complete line of antioxidant treatments containing these key ingredients.

For more information, or for a complete bibliography of scientific research supporting SkinCeuticals products, please visit the SkinCeuticals, Inc. website at www.skinceuticals.com, or call toll free 800-811-1660.

THE SCIENCE SUPPORTING SKINCEUTICALS SUNBLOCK PRODUCTS

ABSTRACT

Until the advent of recently-patented technologies, not one sunscreen or sunblock existed that provided both substantial UVA and UVB protection without turning skin white. Recent scientific findings reveal that it is the long UVAI (340-400 nm) rays that cause photoaging. Only two sunscreen ingredients (zinc oxide and Parsol 1789) protect in this range, with zinc oxide being the preferred ingredient. By incorporating two patented technologies (Z-Cote® transparent zinc oxide and SunCaps®) in one sunblock product line, SkinCeuticals provides superior sun care products for daily use.

UV RADIATION AND THE UV SPECTRUM

Exposure to ultraviolet radiation (UVR) is a well-documented health hazard. The ultraviolet spectrum is divided into the following key regions: UVC (270-290 nm), UVB (290-320 nm), UVAIL (320-340 nm), and UVAI (340-400 nm). The ozone layer protects humans from damage against UVC rays, but not UVB and UVA rays. UVB rays are known to cause burning. UVA rays are now known to cause photoaging.

THE EFFECTS OF SUN ON SKIN

When sun shines on skin, the short (290-320 nm) UVB (burning) rays are absorbed by the epidermis. These generate oxygen-free radicals which can destroy and mutate cells and even cause skin cancer. The longer (320-420 nm) UVA (aging) go deep into the skin's dermis, and even through skin. These rays go thirty to forty times deeper than UVB rays, and also generate oxygen-free radicals. Oxygen-free radicals are like indiscriminate bombs, destroying and/or mutating anything in their way, including collagen, elastin, proteoglycan, and cells.

REPEATED UVA (320-400 NM) EXPOSURE CAUSES PHOTOAGING IN HUMAN SKIN

Photoaging is damage to the skin caused by the sun. Photoaging damage includes, but is not limited to: wrinkles, dark blotches, freckles, leathery texture, and loss of elasticity. UVA rays penetrate the skin's surface, invading the layers below and eventually destroying the collagen and elastin that give skin its firm, plump texture and elasticity. Recent studies show that it takes relatively small amounts of repeated UVA exposure to cause photoaging in human skin. Only eight moderate dosages of UVA are necessary before changes are evident (Lavker et al, *J Am Acad Dermatol*, 1995; Lowe et al, *J Invest Dermatol*, 1995).

THE UVAI (340-400 NM) LONG RAYS CAN CAUSE PHOTOAGING DAMAGE

Just recently, scientists proved that specifically it is the long UVA rays (UVAI, 340-400 nm) that are responsible for photoaging damage in skin (Lavker, R.M. et al, *Photochemistry and Photobiology*, 1995). Given the structure of skin, dermatologists and photobiologists have long hypothesized that the UVA rays which penetrate the skin deepest, might be responsible for photoaging changes in skin; finally, it has been proven. Unfortunately, most currently available sunscreens typically don't protect from UVAI insults.

UVA RADIATION MAY PLAY A ROLE IN MELANOMA FORMULATION

A recent study has detected a correlation between the use of sunlamps or sunbeds and the development of melanoma, especially in younger individuals (Autier et al, *Int J Cancer*, 1994). In addition, PUVA (ultraviolet A radiation plus oral methoxsalen) therapy is known to increase the incidence of melanoma (Stern et al, *N Engl J Med*, 1997). UVA also is known to cause DNA mutations in cell culture (Nishigori et al, *J Invest Dermatol*, 1996).

UVA RADIATION MAY PLAY A ROLE IN MELANOMA FORMULATION

Three international, well-controlled studies also have shown a higher incidence of melanoma skin cancers in individuals using UVB sunscreens (Wolf et al, *J Invest Dermatol*, 1996; Autier et al, *Int J Cancer*, 1995; Westerdahl et al, Melanoma Research, 1995). These findings lend impetus to the notion that excessive exposure to UVA through sunscreens and changing sunbathing habits may be contributing to the spiraling incidence of melanoma.

The most important preventable cause of melanoma is excessive exposure to UV radiation from the sun. Malignant melanoma also has been linked to past sunburns and sun exposure at younger ages. (Other possible causes of melanoma include genetic factors and immune system deficiencies). With the introduction of true broad spectrum sunblocks containing transparent zinc oxide, excessive sun exposure to UVA radiation can be controlled.

COMMON SUNSCREEN INGREDIENTS PROTECT SKIN MAINLY AGAINST UVB RAYS

Recent studies show that the most common sunscreen ingredients protect mainly against UVB rays (290-320 nm), the rays

responsible for most sun burning, but not UVA rays (320-400nm), the rays that cause photoaging. Only zinc oxide blocks UVB, UVBII and UVBIII rays.

Common UVB (290-320 nm) sunscreen ingredients are octinoxate, octisalate (OCS), para-aminobenzoic acid (PABA), and octocrylene. Zinc oxide also protects in this range, uniformly covering from 290-380 nm.

Common UVBII (320-340 nm) sunscreen ingredients are oxybenzone (benzophenone-3) and titanium dioxide. Of these two UVBII blocks, only titanium dioxide also protects against UVB rays, which is why most commercially-available sunblocks combine two or more sunscreen ingredients. In contrast, zinc oxide protects not only in this range, but also in the UVB and UVBIII range, uniformly covering from 290-380 nm.

UVBIII (340-400 nm) sunscreen ingredients are limited to only two: avobenzone (Parsol 1789) and zinc oxide. Parsol 1789 is not an adequate UVBII block, which is why it often is combined with a common UVBII block, oxybenzone. The effective range of Parsol 1789 is approximately only 340-375 nm. Zinc oxide, in contrast, protects uniformly from 290-380 nm.

ONLY ZINC OXIDE BLOCKS UVB, UVBII AND UVBIII RAYS

To protect against photodamage, including sun burning and photoaging, one needs a sun protection product that blocks UVB, UVBII and UVBIII rays. Only one sunscreen ingredient protects against all three types of ultraviolet radiation: zinc oxide.

GENERAL INFORMATION ABOUT SUNSCREENS AND SUNBLOCKS

Any sun protection product with an SPF of 2 or higher is considered a sunscreen. Any sun product that contains a physical sunscreen ingredient and an SPF of 12 or higher is considered a sunblock.

TWO TYPES OF SUNSCREEN INGREDIENTS

In reality, all sunscreen ingredients are chemicals. However, the sunscreen industry labels sunscreen ingredients as either chemical (organic chemical) or physical (inorganic chemical). The differentiation is based on how the ingredients behave on skin. Chemical sunscreen ingredients typically are absorbed into the epidermis, are thought to be metabolized by the body, and sometimes cause allergic reactions. Physical sunscreen ingredients lie on top of the skin's surface and are not absorbed into the epidermis or metabolized by the body. Many companies combine both chemical and physical sunscreens to enhance a product's SPF abilities.

CHEMICAL SUNSCREEN INGREDIENTS

Chemical sunscreen ingredients, when used on their own, provide

only partial UV protection. Octinoxate, Octocrylene, Octisalate, PABA (Para-aminobenzoic acid), Octyl Dimethyl Paba (Padimate-O), Oxybenzone (Benzo-phenone-3), and Avobenzone (Parsol 1789), all are chemical sunscreens. Many of these chemicals are not preferred sunscreen ingredients because of their tendency to cause allergic reactions.

PHYSICAL SUNSCREEN INGREDIENTS

Titanium dioxide and zinc oxide are physical sunscreen ingredients, which form a protective barrier over the skin, stopping UV rays from penetrating the skin's surface. Both titanium dioxide and zinc oxide offer total UVB protection; however, zinc oxide offers far more UVA protection than titanium dioxide. Typically, physical sunscreen ingredients are white, pasty, and turn blue on contact with water.

Titanium dioxide is a common physical sunblock; it protects in the UV range from 290-340 nm. It protects against UVB radiation fully, but only protects against short UVA radiation (320-340 nm). Titanium dioxide offers no protection from the long UVA rays (340-400 nm) recently proven to cause photoaging changes in human skin. Using titanium dioxide alone, skin turns white or bluish at SPF7.

Zinc oxide uniformly covers from 290-380 nm, thus protecting against UVB (290-320 nm) and most of the UVA (320-400 nm). No other sunscreen ingredient provides broader protection.

Zinc oxide is so safe and gentle that it is one of only two sunscreen particulate ingredients that also is recognized by the FDA as a Category 1 skin protectant, meaning that the FDA acknowledges it as safe for use on compromised or environmentally-challenged skin. Zinc oxide is so safe that it often is the leading ingredient in baby care products.

Unfortunately, traditional zinc oxide is white and pasty. Often used by lifeguards for sun protection, traditional zinc oxide is not cosmetically elegant, and hence, not widely used for total body sun protection. However, the newly available transparent zinc oxide, Z-Cote®, overcomes these disadvantages.

TRANSPARENT MICRO-FINE ZINC OXIDE (Z-COTE HP1®)

Z-Cote HP1® is a particle of micro-fine zinc oxide, coated with a patented form of dimethicone. This coating process turns the traditionally granular and pasty particles of zinc oxide into a smooth, elegant formulation which is completely transparent, and hence, perfect to wear alone or under make-up or cosmetics. This transparent zinc oxide provides true broad-spectrum UVA/UVB protection, uniformly protecting from 290-380 nanometers (nm).

ENCAPSULATED OCTINOXATE

Octinoxate is the leading UVB sunscreen ingredient, known for being non-irritating. By encapsulating octinoxate, it is possible to use less chemical sunscreen ingredients and improve SPF. The result is increased protection, using less potentially irritating ingredients.

SKINCEUTICALS SUNBLOCK PRODUCTS

SkinCeuticals manufactures sunblock products which incorporate both Z-Cote HP1® and encapsulated octinoxate for true broad spectrum protection. SkinCeuticals sunblocks are cosmetically elegant, unlike the pasty white zinc oxide sunscreens in the past, providing protection from UVA/UVB damage, using less potentially irritating sunscreen ingredients.

For more information, or for a complete bibliography of scientific research supporting SkinCeuticals sunblocks, please visit the SkinCeuticals, Inc. website at www.skinceuticals.com, or call toll free 800-811-1660.

Z-Cote HP1® is a registered mark of BASF Corp.

THE SCIENCE SUPPORTING SOY ISOFLAVONES

ABSTRACT

Research suggests that estrogen deficiencies following menopause may contribute to signs of aging in skin. Systemic and topical estrogens have been shown to counter these effects and to have antioxidant properties. Although much weaker, soy isoflavones (phytoestrogens) have been shown to mimic estrogen and to have antioxidant effects, making them ideal for use on maturing skin.

AGING SKIN AND HORMONAL FLUCTUATIONS

As humans age, the skin becomes dry, loses its elasticity, and begins to wrinkle — these are the primary visible effects of chronological aging. Following menopause¹⁻³ it has been shown that skin thickness decreases and collagen levels in the skin diminish, which may further contribute to these negative age-related changes in the skin. Scientific studies strongly suggest that these changes may be attributed to menopausal and/or age-related hormonal fluctuations. More specifically, research suggests that estrogen deficiency may primarily be responsible.

ESTROGEN: A CRUCIAL PART OF THE AGING EQUATION

Estrogen works by joining with estrogen receptors in the body and signaling genes in cells to be switched on or off. Flipping these switches can cause the body to generate new cells or to produce special substances. For example, raised estrogen levels can cause breast growth during pregnancy, as well as the production of milk following pregnancy. Following menopause, the body stops producing much estrogen. Although the exact mechanisms are unknown, this reduction in estrogen is believed to contribute to decreases in skin thickness, dryness, and loss of elasticity.

Estrogen receptors have been detected in the skin, and systemic^{2,4} and topical^{5,6} estrogen have now been shown to increase skin thickness, increase collagen levels, and improve wrinkling and dryness.^{7,8} While estrogen is important, researchers also believe that decreased estrogen levels are only part of the aging equation; free radical attack caused by exposure to environmental elements like sunlight, smoke, and pollution also contributes to premature aging in skin. Antioxidants can help counter these effects by neutralizing free radicals, and estrogens are strong antioxidants with even stronger activity than vitamin E and vitamin C.⁹⁻¹¹

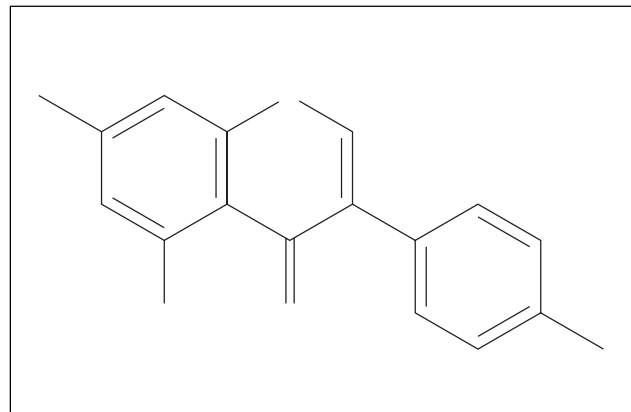
SOY ISOFLAVONES: AN ALTERNATIVE TO ESTROGEN

Soy isoflavones are phytoestrogens, substances that mimic the activity of estrogen. The estrogenic effect of phytoestrogens is considerably weaker than estrogens, but is appreciable¹² and both oral and topical application of phytoestrogens have been shown to have many beneficial effects for the skin. In addition to estrogenic activity, soy isoflavones have antioxidant properties,^{13,14} and like other antioxidants, help to prevent free-radical damage to DNA.

Soy-containing foods may contain as much as 1/1000 of their content as phytoestrogens and are credited with the low incidence of cardiovascular disease¹⁵⁻¹⁷ and breast cancer¹⁸ in Asian populations that consume large amounts of these substances.^{19,20} Phytoestrogens have also been effective for preventing skin cancer in mice, both orally²¹ and topically.²²

GENISTEIN: BENEFITING SKIN

Figure 1. Chemical Structure of Genistein



Two key isoflavones found in soy are genistein and diadzein. Genistein is the most abundant isoflavone in soy, and there is a strong body of research supporting the benefits genistein provides the skin. Genistein is a strong antioxidant^{23,24} and may be effective in preventing cancer. Although its exact anti-cancer mechanism is unknown, genistein has been proven to protect against sunburn in humans²⁵ and to block the formation of reactive oxygen species. The antioxidant effect of phytoestrogens is also synergistically enhanced in the presence of vitamin C.²⁶ This makes soy isoflavones an ideal alternative to estrogen therapies, and perfect for use on maturing skin.

SUMMARY

Soy isoflavones or phytoestrogens mimic estrogen behavior and may have beneficial effects in maturing skin. Estrogen deficiencies in post-menopausal women may contribute to decrease of skin thickness, dryness, and loss of elasticity and it is believed that topical application of soy isoflavones may help counter some of these negative age-related changes.

For more information, or for a complete bibliography of scientific research supporting SkinCeuticals products, please visit the SkinCeuticals, Inc. website at www.skinceuticals.com, or call toll free 800-811-1660.

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THE SCIENCE SUPPORTING SILYMARIN

ABSTRACT

Exposure to ultraviolet (UV) radiation generates oxygen-free radicals and has been proven to cause photoaging and certain forms of cancer in skin. The body uses antioxidants to protect itself from free radical attack and antioxidants are depleted by sun exposure. Silymarin is an extract of the milk thistle plant that has been shown to have strong antioxidant and anti-tumor effects. This makes silymarin an excellent addition to protective skin care formulations.

UV EXPOSURE AND ANTIOXIDANTS

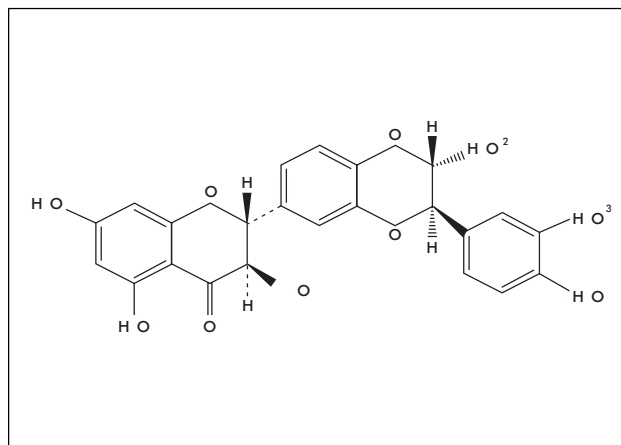
Exposure to UV radiation, smoke, and air pollution generates oxygen-free radicals that can destroy the structural components of the skin. This assault can cause visible changes in skin, including wrinkles (photoaging), solar lentigines (brown spots), actinic keratoses — and possibly even the development of skin cancer.

The body uses antioxidants to protect itself from free-radical attack, and antioxidant levels in the body are depleted significantly by sunlight and smoking. Alcohol, analgesics, antidepressants, anticoagulants, oral contraceptives, and steroids also may reduce the body's levels of key antioxidants. Oral ingestion is one way to replenish depleted antioxidant levels, but body control mechanisms tightly regulate the levels of ingested vitamins that actually get to the skin. For that reason, it is important to supplement the skin's reservoir of antioxidants with topical applications.

SILYMARIN: A STRONG ANTIOXIDANT

Silymarin is an extract of the milk thistle plant: *Silybum marianum*. Milk thistle belongs to the aster family (Asteraceae or Compositae) that includes daisies, thistles, and artichokes.^{1,2} Silymarin consists of a mixture of three bioflavonoids found in the fruit, seeds, and leaves of the milk thistle plant: silybin, silydianin, and silychristine.¹ Silybin is the main component (60-70%) and is thought to have the most biologic activity.

Figure 1. Chemical Structure of Silybin



Silymarin is extremely safe; no lethal dose exists. Oral doses of 1000 mg can be administered daily to humans without toxicity¹ and no known lethal dose exists for animals.⁷ Historically, since the 4th century BC, milk thistle extract has been used to treat disorders of the spleen, liver and gall bladder.¹

Silymarin has been shown to have utility in many liver disorders including toxin-induced liver toxicity, hepatitis, and alcoholic liver disease.^{4,5} In the animal model of cirrhosis produced by bile duct obliteration, silymarin has an anti-fibrotic effect.⁶

The mechanism of action for the beneficial effects of silymarin for liver disease is unknown. However, antioxidant activity is a leading theory. Silymarin can prevent lipid peroxidation,⁹⁻¹² inhibit LDL oxidation,¹³ and scavenge reactive oxygen species.¹⁴⁻¹⁶ Silymarin inhibited DNA synthesis,¹⁷ and fibroblast¹⁸ and epidermal cell proliferation.¹² It modulated the activation of NFκB to stimulate transcription.^{19,20}

SILYMARIN: ANTI-CARCINOGENIC EFFECTS

Because silymarin is known to have antioxidant effects, it was tested for its anti-carcinogenic effects in cancer-prone Sencar mice. First, it was tested to see if it had an effect on a group of cancer-promoting chemicals. It could be demonstrated that low doses of silymarin could essentially almost completely inhibit the effect of TPA, a tumor promoter from inducing ornithine decarboxylase activity.⁸ This suggested that silymarin might have useful tumor prevention effects.

Subsequently, topical silymarin has been shown to have a remarkable anti-tumor effect. The number of tumors induced in the skin of hairless mice by UVB light was reduced by 92%.² Silymarin reduced UV-induced sunburn cell formation and apoptosis. The result was not related to a sunscreen

effect and an antioxidant mechanism may be responsible. Figures 2 and 3 show the percentage and number of tumors in mice, treated with UVB alone compared to mice treated with UVB and silymarin.²

Figure 2. Silymarin Protects Against UVB Induced Skin Tumors (Percentage of Mice with Tumors)

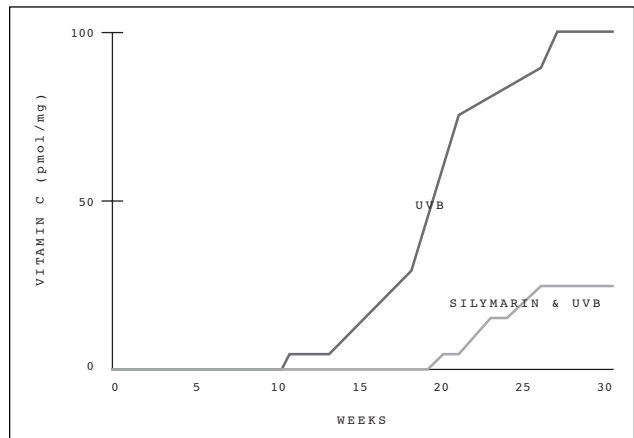
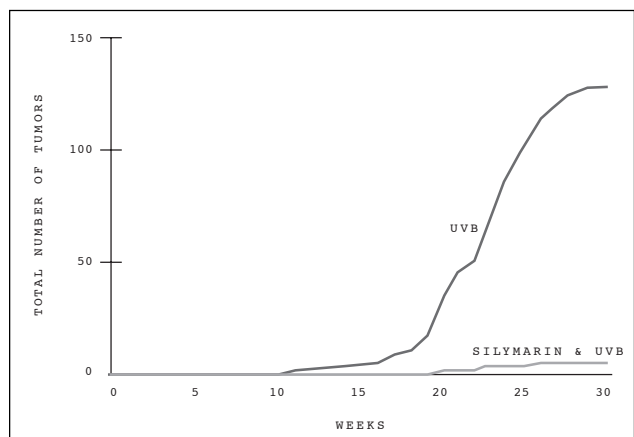


Figure 3. Silymarin Protects Against UVB Induced Skin Tumors (Total Number of Tumors per Mouse)



The mechanism of the anti-tumor effect for silymarin is unknown, although its antioxidant activity may be important.

Silymarin also prevented the formation of pyrimidine dimers following UVB exposure to hairless mouse skin.¹¹ It protected against DNA changes produced by peroxide²¹ and gamma radiation.²² Silymarin demonstrated both a potent anti-inflammatory effect²³ and anti-angiogenic action.²⁴

Silymarin has an equally protective effect against skin tumors caused by chemical carcinogenesis (i.e., no UV light).⁹ In these studies, tumors were initiated by a chemical carcinogen, DMBA and promoted by a chemical promoter, TPA.

SUMMARY

Silymarin is a strong antioxidant and has successfully been used to treat liver disorders. Silymarin scavenges reactive oxygen

species, and inhibits sunburn cells, apoptosis, and lipid peroxidation. Topical silymarin has been shown to have an anti-tumor effect although its mechanism of anti-carcinogenesis is unknown. For these reasons, it is believed that silymarin has powerful protective benefits when used in topical skin care formulations.

For more information, or for a complete bibliography of scientific research supporting SkinCeuticals products, please visit the SkinCeuticals, Inc. website at www.skinceuticals.com, or call toll free 800-811-1660.

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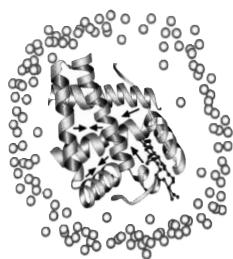
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THE SCIENCE SUPPORTING ECTOIN

Ectoin is an innovative, multi-functional natural active substance that has been shown to have an effect in protecting the skin against external aggressors by protecting Langerhans cells, protecting DNA and cells from UV-induced damage, significantly reducing formation of sunburn cells, and retaining moisture in the skin.

Ectoins belong to the family of compatible solutes, also referred to as stress protection substances, and were discovered in extreme halophilic bacteria such as *Halomonas elongata*. The natural environment of these organisms is characterized by high UV-radiation, dryness, extreme temperature, and high salinity. The bacteria protect themselves against damages from these hostile conditions by synthesizing ectoins.^{1,2} These, in turn, stabilize the bacteria's biopolymers such as proteins, nucleic acids, and membranes,^{3,4,5,6} allowing them to function optimally and to thus help the bacteria survive in their inhospitable environments.

Ectoins are amphoteric, organic molecules that are able to bind water and form a large hydrate sheath, i.e., they are excellent water structure formers.² This allows them to protect the biomolecules in their cells against a variety of aggressors such as UV, osmotic stress, heat, dryness, or frost^{4,7}



Protein, active center, compatible solute

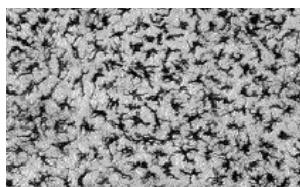
Ectoins are non-toxic, are highly compatible with cell metabolism and are extremely active even at low concentrations. They are readily accepted by cells and are chemically, physically, and biologically stable.

Human skin, when exposed to a variety of environmental hazards, also has to cope with a number of specific stress factors.⁸ UV-radiation, e.g., can result in cell damage (protein, lipid, DNA, membrane) and immunosuppression, and cell membranes can be damaged by pollutants, allergens, or surfactants.

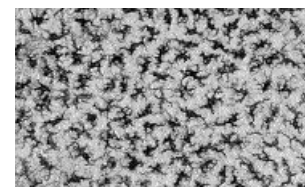
The ingredient ectoin, produced in a patented process in the biotech industry (often referred to as “bacteria milking”), showed great efficacy in improving the biological processes available to counteract environmental aggressors:

IMMUNE SYSTEM PROTECTION

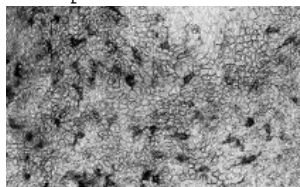
Human skin has its own specific immunological defense system, the skin immune system (SIS). Within the epidermis, it is primarily Langerhans cells that are the key elements of the SIS and are able to correct damages done by damaging environmental influences, pathogens, and transformed skin cells. UV radiation causes Langerhans cell death, thereby diminishing the function of the SIS. Tests have demonstrated the protective effect of ectoin with respect to the number of Langerhans cells; this effect can be seen under the microscope



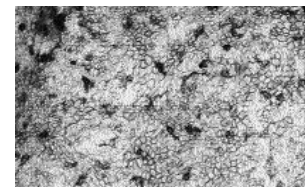
A) Untreated, non-irradiated area of epidermis



B) Untreated, irradiated area of epidermis



C) Placebo-treated, irradiated area of epidermis



D) Ectoin-treated irradiated area of epidermis

Human epidermis. The Langerhans cells have been visualized using ATPase staining. The photographs were taken 48 hours after irradiation of the skin with 1.5 MED (Sun-Simulator Sol 500).

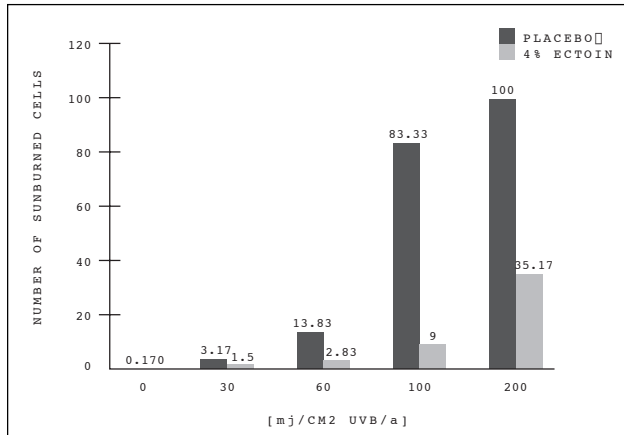
CELL PROTECTION

Tests have shown that ectoin also supports the repair and protective mechanisms of the cells. In cases of external stress such as UV-irradiation, heat, and other physical and chemical stress factors, human skin cells are able to produce so-called stress proteins or Heat Shock Proteins (HSP). These have the particular tasks of recognizing, stabilizing, and helping to metabolize damaged proteins. The more quickly this function is activated, the better the cells can cope with these stress factors and protect themselves early against cell damage. In tests (using proteins of the HSP 70 family) it was shown that cells pre-treated with ectoin were able to synthesize HSP two to three times faster than non-treated cells.

PROTECTION AGAINST UV-INDUCED DAMAGE

When cells are damaged to such an extent that repair is no longer possible, apoptosis (controlled cell death) is initiated. Sun Burn Cells (SBC) are apoptotic keratinocytes, formed in the epidermis as a result of excess UV irradiation. Their existence in human skin indicates severe UV-induced cell damage.

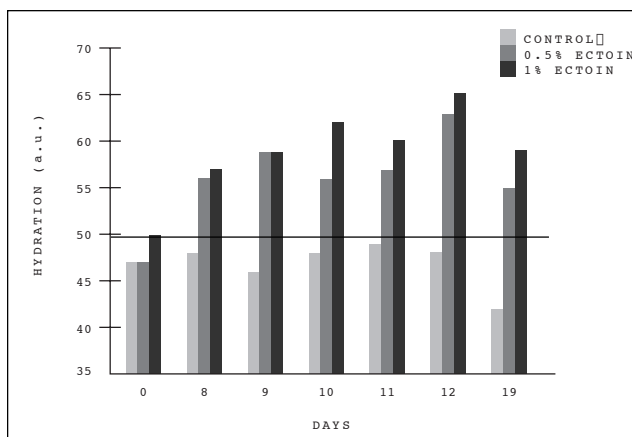
An in vitro study using a skin model, Skinthetic, showed that ectoin significantly reduces the formation of



SBCs under irradiation.

MOISTURE RETENTION

Human skin is equipped with a Skin Lipid System that, together with excretions from the sebaceous glands, serves as a shield against moisture loss and as a barrier against unfavorable outside factors. The very sensitive equilibrium of the substances comprised in the Skin Lipid System can easily be disturbed by external or internal factors and conditions. These can include dryness due to high temperatures or very low temperatures at low humidity, high salt concentrations in the skin due to, e.g., perspiration, surfactants contained in soap, etc. The result can be transepidermal water loss (TEWL) and dry, flaky skin. In tests exposing skin to these conditions, which we encounter on a daily basis, much improved hydration levels were evident when skin had been treated with an



ectoin-enriched formulation.

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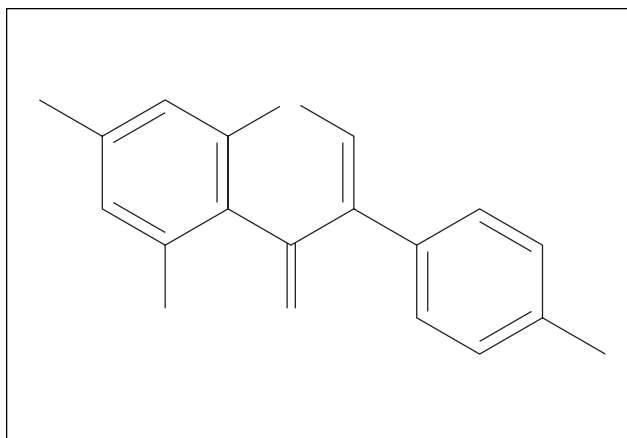
THE SCIENCE SUPPORTING TITRATED EXTRACT OF CENTELLA ASIATICA

Titrated Extract of Centella Asiatica (TECA) is a reconstituted mixture of three triterpenes extracted from the plant and is being used in Europe in wound healing drugs. TECA has been shown to stimulate collagen synthesis in fibroblast cultures and to increase the tensile strength of tissues.

Centella asiatica (also known as gotu kola, tiger grass and indian pennywort) is a perennial creeping plant which grows spontaneously around the Indian Ocean. The use of centella asiatica in the management of dermatological conditions has a long tradition in its native areas where it is used to support faster healing of small wounds, chaps and scratches, superficial burns and, as an oral preparation, for atonic wounds and hypertrophic healing. Centella also has been used traditionally as an anti-inflammatory, particularly for eczema, and also for minor itching and insect bites. Paradoxically, centella asiatica appeared relatively late in modern Western medicine, making its entrance in the Codex only in 1884. The first dry extract was not produced until 1941, three years before the triterpenoids were isolated by P. Boiteau in 1944.

The active constituents of centella asiatica are pentacyclic triterpenoids which are found as genins (asiatic and madecassic acid) and heterosides (asiaticoside and madecassoside). The triterpenoidic molecules are particularly interesting due to their regulating and activating functions, which act on the collagen present in numerous organs.

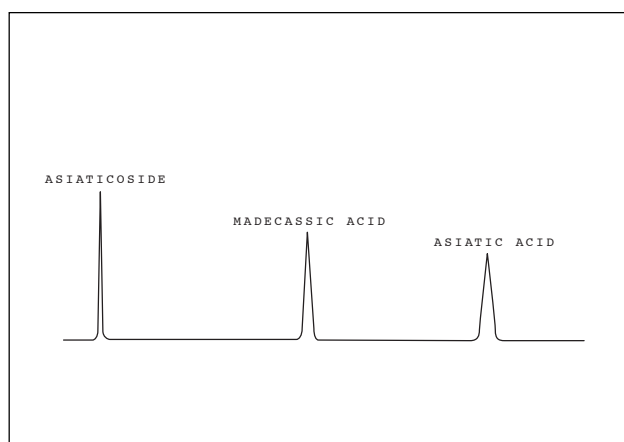
TECA



The TECA is a perfectly standardized extract of centella asiatica of pharmaceutical quality. Isolated in purified fractions, free genins (asiatic and madecassic acids) and asiaticoside, these active ingredients are combined in constant proportions to guarantee optimal activity.

The TECA was traditionally used in pharmaceutical

applications. Administered in ointments, powders, or in tablet form, TECA proved very successful in the treatment of burns, scars and wound healing defects. Studies showed that wound chambers to which TECA had been applied were characterized by increased dry weight, DNA, total protein, collagen, and uronic acid contents. Peptidic hydroproline was also increased, showing an increased remodeling of the collagen matrix in the wound. Asiaticoside exerted a preferential stimulation of collagen synthesis and was active at low doses only. In addition to collagen, the three components were also able to stimulate glycosaminoglycan synthesis¹ (glycosaminoglycan synthesis was also shown in a study by DelVecchio et al, 1984).

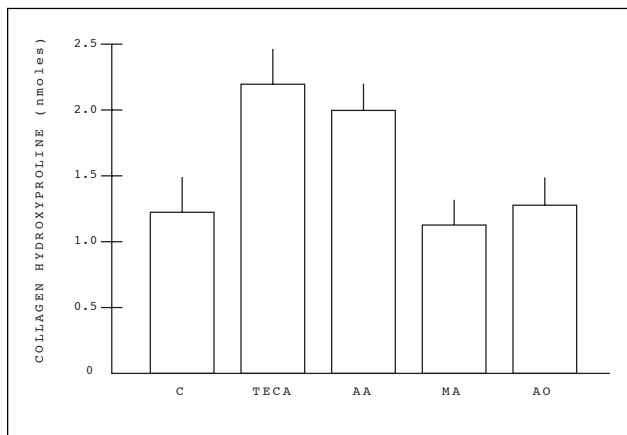


In skin, the major components are collagens type I and III. Skin aging is related mainly to a decrease in type I collagen levels,² which also plays a major role in wound healing. Since the late 1980s, numerous studies have been conducted regarding the stimulation of collagen synthesis in human skin fibroblasts by either asiatic acid, madecassic acid, asiaticoside, or a combination of all three.^{2,3,4,5} The results produced in these studies vary to the effect that the collagen synthesis effect was associated with asiatic acid only in one study, but was shown to be stimulated by all components in others. The reason for these variations is not known and could be associated with the test methods and analyses; however, it is clearly undisputed that the main constituents of centella asiatica increase collagen synthesis. It is interesting to note that in one study, the level of collagen I secretion was higher for each individual component as well as for the mixture in the presence of ascorbic acid.

Some of the test results are depicted below.

Collagen I Ng/10,000 fibroblasts per 48 hrs	Medium +DMSO	Madecass. Acid 4.5mg/ml	Asiatic Acid 4.5mg/ml	Asiaticoside 6mg/ml	Mix. (1) + (2) +
Secreted	470 +/- 97	1362 +/- 82 (+189%)	1597 +/- 199 (+239%)	1597 +/- 245 (+231%)	1769 +/- 45 (+276%)
Cell-associated	183 +/- 43	158 +/- 29	150 +/- 19	140 +/- 37	133 +/- 30

Table 1: Collagen I synthesis (source: LVMH Recherche, Colombes,



France) ²

Table 2: Stimulation of collagen I synthesis (source: Laboratory of Biochemistry, Reims, France) ⁴

In addition to stimulating the synthesis of collagen, the latter is also improved qualitatively, i.e., there is an increase in tensile strength as measured by the resistance to traction.⁶

In summary, centella asiatica — and specifically the Titrated Extract of centella asiatica — has revealed astonishing curative properties for the treatment of venous insufficiency, wound healing disturbances and, based on test results outlined above, clearly is of great value with regards to supporting skin health.

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THE SCIENCE SUPPORTING SKINCEUTICALS LIGHTENING PRODUCTS

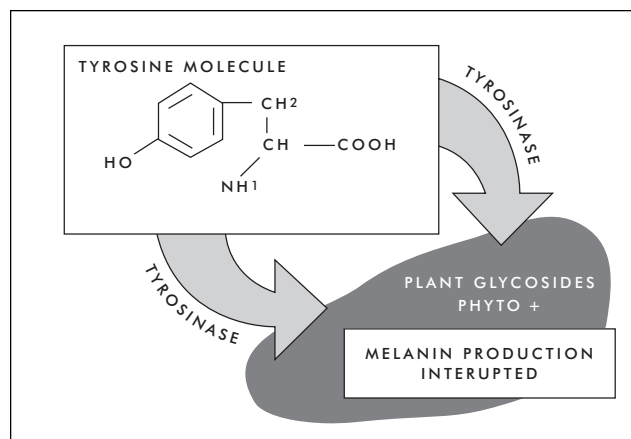
ABSTRACT

The enzyme tyrosinase converts the amino acid tyrosine into melanin in the skin. Hyperpigmentation can result when too much melanin is produced. Ingredients such as arbutin, kojic acid, and thymol inhibit or suppress tyrosinase, preventing the appearance of additional pigmentation.

HOW SKIN COLOR IS FORMED

Normal skin color is formed by melanin, a natural pigment that also determines hair and eye color. In the skin, the enzyme tyrosinase biochemically converts the amino acid tyrosine into melanin. Hyperpigmentation occurs when too much melanin is produced and forms deposits in the skin.

The cells that make pigment are called melanocytes. They are located at the bottom of the epidermis. Melanocytes produce melanosomes, which are passed onto other cells of the epidermis and make their way up to the top layer of skin. Synthesis of melanin occurs exclusively in melanosomes.



When too much melanin is produced, deposits are formed and hyperpigmentation appears in the skin. Phyto + contains natural plant glycosides – extracts shown to interfere in the process that causes melanin to appear in the skin, preventing further accumulation of excess melanin and discoloration.

Hyperpigmentation is not a medically harmful condition. However, it always is advisable to have new brown spots checked by a dermatologist to make sure they are not skin cancers.

Hyperpigmentation is a common clinical condition for which many people seek remedies because they view it as being cosmetically displeasing. It can affect people of all skin colors and races, and tends to increase as we age. For example, almost all African-American infants become darker shortly after birth. Freckles — small, flat tan-to-black spots that can be anywhere on the body — also become more permanent during the first or second decade of life. Often hereditary,

freckles also can darken with sun exposure and fade with less sun exposure.

Age spots or liver spots are small, mottled or darkened patches of skin which appear in older adults — especially on the face, the backs of hands, and arms in individuals who have been exposed to the sun. The medical name for this condition is solar lentigines.

Hyperpigmentation also results from inflammation or other skin insults. For example, skin diseases such as acne or shingles may leave darkened spots. Scars from skin injury or surgery also may become hyperpigmented. Cosmetic procedures — including laser resurfacing, laser hair removal, chemical peels and dermabrasion — also may leave the affected area darker than the normal skin color. All these conditions may be categorized as post-inflammatory hyperpigmentation.

In addition to hyperpigmentation, many women suffer from melasma, a hormonal mask-like skin condition that often results from birth control pills and/or pregnancy. Melasma appears as blotchy brown spots — most often on the cheeks, forehead and temples of the face, but also on the abdomen and other areas. Chloasma is another name for melasma.

SKIN LIGHTENERS

Hydroquinone

Hydroquinone is a common ingredient in skin lightening products. It is available over the counter in concentrations up to 2 percent, and can be prescribed in concentrations up to 4 percent. However, hydroquinone can be very irritating at high concentration, can cause ochronosis with prolonged use, and is tumorigenic in rats. (Maeda and Fukada, *J Pharmacol Exp Ther*, 1996.)

Uva-Ursi Extract/Arbutin

Arbutin is a plant glycoside and skin lightener found in a natural plant, Uva-Ursi (which also has antioxidant properties). Arbutin is a natural hydroquinone molecule attached to a sugar molecule (C₆H₆O₆) which makes it water soluble. Arbutin helps prevent additional brown spots from occurring by stopping the production of melanin. Specifically, arbutin works by suppressing tyrosinase, the enzyme that biochemically converts tyrosine into melanin in skin.

Uva-Ursi also contains three strong antioxidants: ferulic acid, caffeic acid, and chlorogenic acid. These antioxidants neutralize oxygen free radicals that can damage skin. The three acids also act as intermediary acids which produce three

flavonoids —myricetin, quercetin and rutin — which help protect skin.

Kojic acid

Kojic acid is a skin lightener produced from fungus. Discovered in Japan in 1989, it has been used with excellent results to lighten skin and reduce brown spots. Like arbutin, it blocks the formation of melanin pigment in skin cells.

Thyme Extract/Thymol

Thyme, an herb plant indigenous to the Mediterranean, is known for its antiseptic and soothing properties. Thyme extract contains thymol, which has strong antiseptic and antioxidant properties, and helps to prevent future oxidative breakdown of cells. Thymol stops the production of melanin by inhibiting tyrosine conversion from tyrosine to 3, 4-Dihydroxyphenylalanine (Dopa), which is the first step in the biochemical path to melanin. Importantly, thymol does not damage the melanocytes, the factories that make melanosomes where melanin synthesis occurs.

Cucumber Extract

The bitter part of the cucumber plant which contains cucurbitacin (forms A, B, C and D) — known for its emollient and soothing properties. Traditionally, cucumber slices have been used to remove dark circles from the area underneath the eyes.

SKINCEUTICALS SKIN LIGHTENING PRODUCTS

SkinCeuticals formulators have developed several skin lightening products containing these key ingredients.

For more information, or for a complete bibliography of scientific research supporting SkinCeuticals Skin Lightening Products, please visit the SkinCeuticals, Inc. website at www.skinceuticals.com, or call toll free 800-811-1660.