# ARE ALL VITAMIN C PRODUCTS THE SAME?

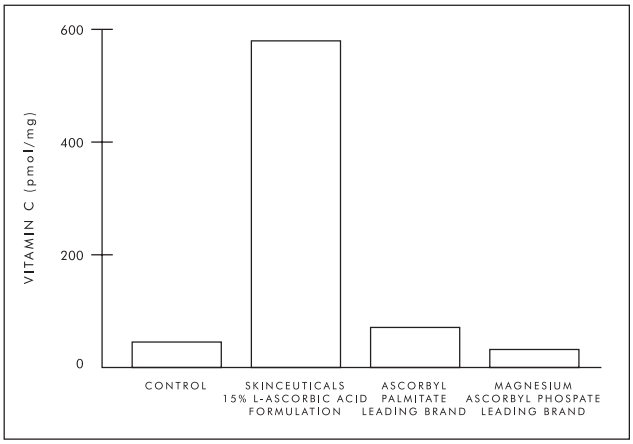
## ABSORPTION: THE KEY TO TRULY EFFECTIVE VITAMIN C

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.

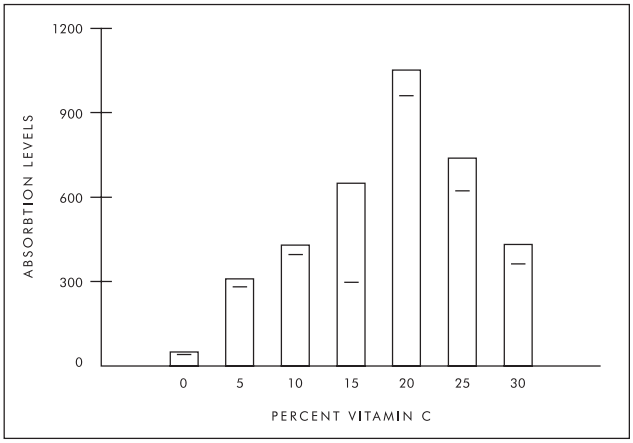
Not all products have pure vitamin C. SkinCeuticals does.




### 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.

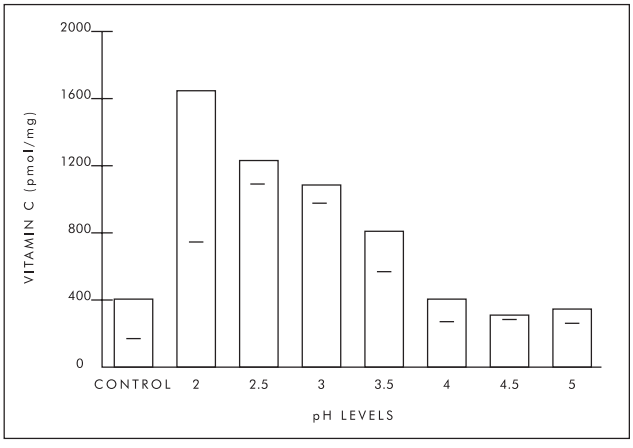
Not all products have enough vitamin C. SkinCeuticals does.




### 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.




SKINCEUTICALS

# 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 scientists and formulators have refined ways to stabilize and deliver additional amounts of key antioxidants into skin, thus adding to the body's natural reservoir of antioxidants. Continued research has demonstrated that properly formulated antioxidant combinations work synergistically to provide enhanced benefit. Recent studies show that topical application of optimized antioxidant combinations can provide up to eightfold antioxidant protection, 96 percent reduction of sunburn cells, and prevent the formation of thymine dimers in UV 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 between 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 (320-400 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

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

In addition to UV radiation, environmental elements including diet, stress, pollution, and cigarette smoking contribute to the generation of 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

Scientists have 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 struc-

ture 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.

Studies now reveal that even broad-spectrum sunscreens designed to block both UVB and UVA only protect against approximately 55 percent of UVA-induced free-radicals, continuing to leave skin vulnerable to the damaging effects of UVA (Haywood et al, *J Invest Dermatol,* 2003).

## UVA RADIATION MAY PLAY A ROLE IN MELANOMA FORMULATION

Scientists have 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). 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/cm$^2$ to skin. Multiple studies have concluded that users apply only one-fourth (Wulf et al, *Phtodermatolo, Photoimmunol & Photomed,* 1997) to one-fifth (Autier et al, *J Nat Can Inst,* 1999) the amount necessary to achieve full protection as measured. Thus, a SPF 30 sunscreen only offers protection of SPF 3 - 4 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 supplemental 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 the plant-derived ferulic acid are all examples of antioxidants that act as free radical scavengers. When formulated properly, these antioxidants can be used in topical preparations to protect and correct skin damage.

Antioxidants protect skin by neutralizing oxygen species, the oxidative "bombs" generated when skin is exposed to environmental insults. If not counteracted, these "bombs" would destroy skin and its components (Shindo et al, *J Invest Derm,* 1994), provoking damage and degradation of both cellular components (lipids, proteins, and DNA) and noncellular elements (collagen and elastin fibers). We perceive the results of such damage as "aging."

## 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 is helpful in order for vitamin E to 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 Gilchrest, 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

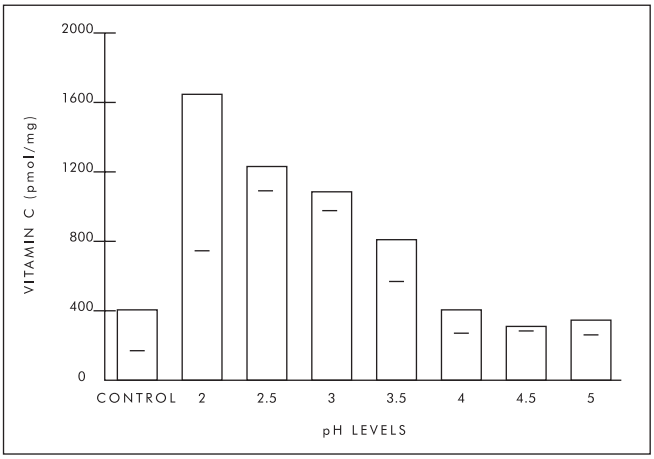
Skin inflammation — including that caused by inflammatory dermatoses, phototrauma, and carbon dioxide laser resurfacing — is mediated by reactive oxygen species. Vitamin C is depleted rapidly when skin is inflamed. Topical L-ascorbic acid has been reported to alleviate ultraviolet radiation-induced erythema 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).

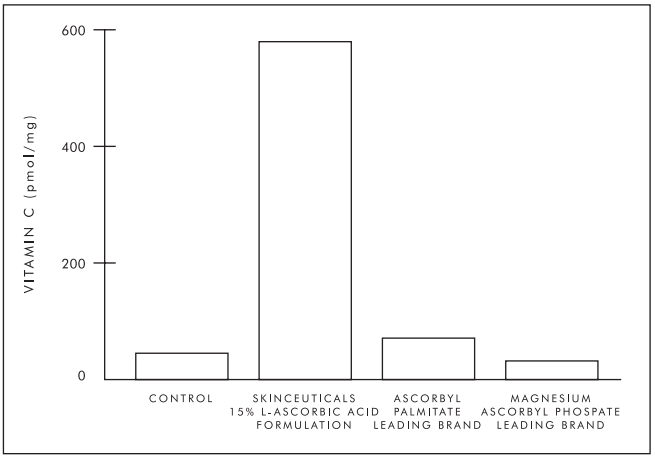
It is often recommended as a pre- and post-operative regimen for laser resurfacing patients. (Alster and West, *Dermatol Surg,* 1998) Dermatologic surgeons recommend using it as long as possible prior to laser resurfacing and beginning again as early as fourteen days following surgery. (Alster and West,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

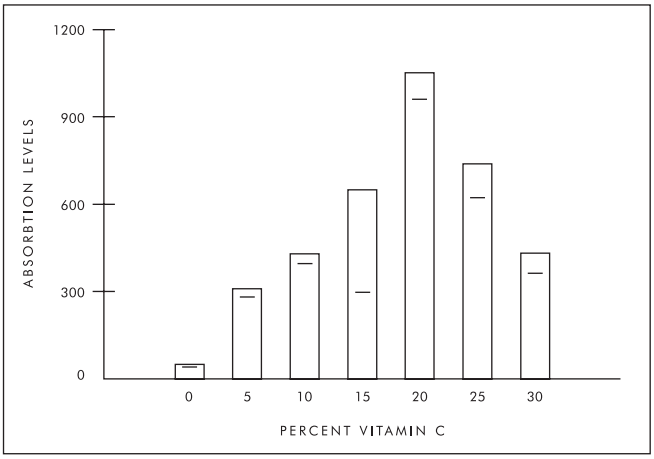
## DERIVATIVES OF VITAMIN C

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 PH AND CONCENTRATION

Studies show that vitamin C must be formulated at acid pH below 3.5 to effectively be absorbed by the skin. Studies also 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 (alpha 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 alpha tocopherol; it comprises about 90 percent of the tocopherols in animal tissues and displays the greatest biological activity in most bioassay systems. The empirical formula for vitamin E or alpha tocopherol is $C_{29}H_{50}O_2$. 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, alpha tocopherol is not an unstable molecule, but vitamin E requires vitamin C in order to replenish itself.

Vitamin E (alpha 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 alpha 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: alpha 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.

## FERULIC ACID

Ferulic acid is a plant phenolic acid found in the seeds and leaves of most plants, especially in the brans of grasses such as wheat, rice and oat. It belongs to the family of plant hydroxycinnamic acids with the chemical name 4-Hydroxy-3-methoxycinnamic acid and the formula $C_{10}H_{10}O_4$. Ferulic acid has a phenolic nucleus and extended side chain conjugation and, because of this, readily forms a resonance stabilized phenoxy radical, which accounts for its potent antioxidant potential. UV absorption by ferulic acid catalyzes stable phenoxy radical formation and thereby potentiates its ability to terminate free radical chain reactions (Graf E. *Free Radic Biol Med*, 1992). Ferulic acid has been shown to scavenge superoxide and hydroxyl radical as well as nitric oxide (Ogiwara T et al, *Anticancer Res*, 2002) and has proven to afford protection against UVB-induced erythema (Saija A et al, *Int J of Pharmaceutics*, 2000)

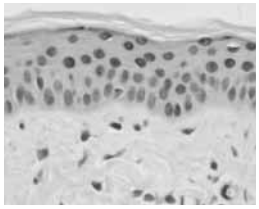
Ferulic acid is a safe compound, as manifested by its presence in many common foods, that is low in toxicity. With both hydrophilic and lipophilic properties, it can be absorbed and metabolized easily. Ferulic acid provides the following key benefits to skin:

- *Protects from aging effects of UV light*
- *Neutralizes free radicals*
- *Acts as a sunscreen by absorbing UV*
- *Has anti-inflammatory properties*

## VITAMIN C, VITAMIN E, AND FERULIC ACID HAVE SYNERGISTIC EFFECT

Vitamin C and vitamin E are known to have synergistic effects in that vitamin C can effectively regenerate vitamin E. Due to their structure, the two were long thought to be impossible to combine. Vitamin C is aqueous and vitamin E is lipid-soluble; in essence, it's like mixing oil and water. An extraordinary technology was developed that allowed for both of these antioxidants to be combined.

When combined and applied topically, a formulation of 15 percent L-ascorbic acid and 1 percent dl-alpha tocopherol provided synergistic photoprotection not achieved by either antioxidant alone. The combination of vitamins C and E delivered fourfold antoxidant protection, compared to twofold protection for vitamin C or E alone. (Pinnell et. al., *JAAD*, 2003). The combination of vitamins C and E applied topically also prevent the formation of thymine dimers in UV irradiated skin. (Pinnell et. al., *JAAD*, 2003).



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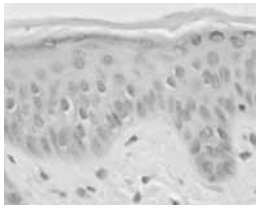
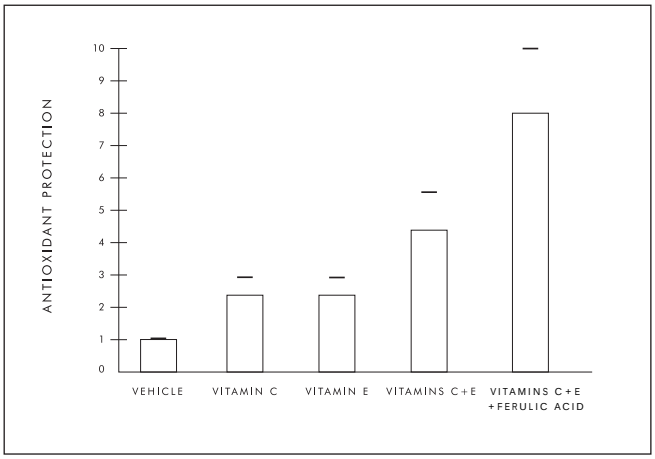


C + E

Continuing to advance the study of effective antioxidant combinations, 0.5 percent ferulic acid was added to the mixture of 15 percent L-ascorbic acid and 1 percent dl-alpha tocopherol. This new combination was shown to double the previous antioxidant protection provided by the combination of vitamins C and E, now delivering eightfold photoprotection.

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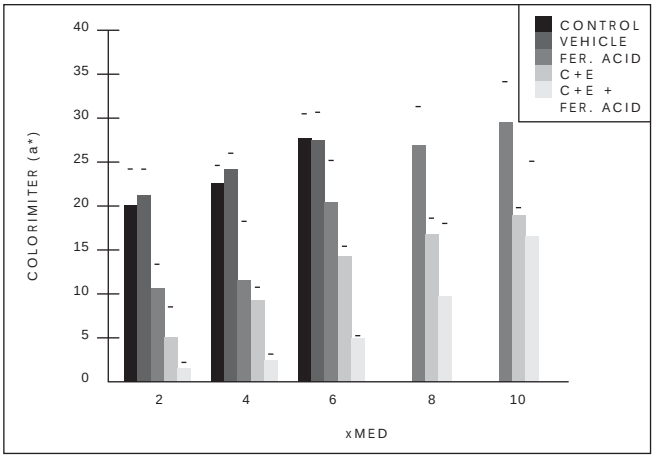
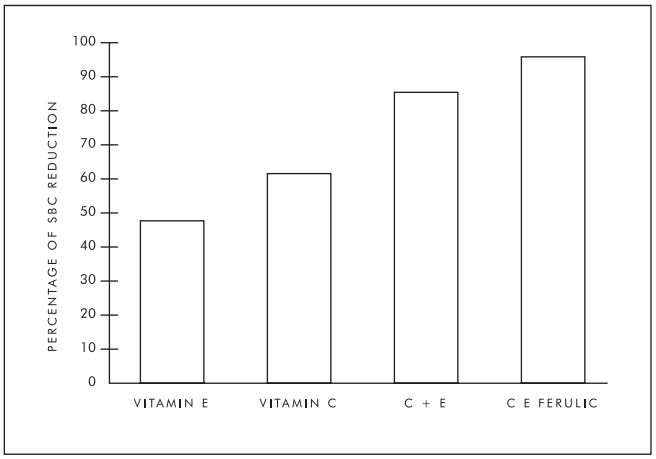
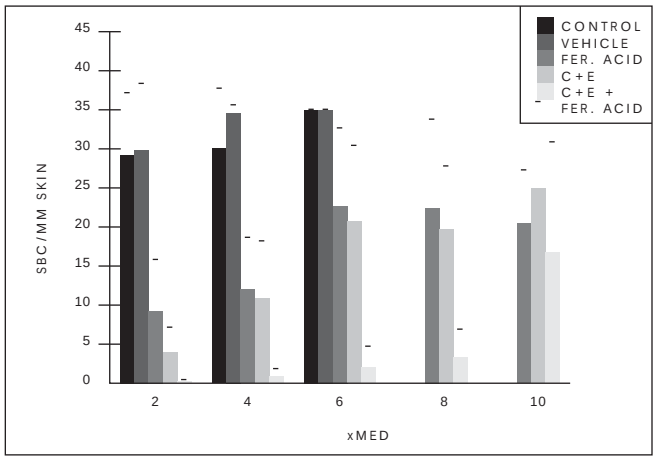



Both erythema and sunburn cell formation are reduced, providing up to 96 percent reduction of sunburn cells in UV irradiated skin. Studies also demonstrated that this powerful new combination provided virtually complete protection against solar-induced caspase-3, which occurs in both epidermis and dermis and leads to cell apoptosis. Ferulic acid alone and vitamins C and E provided only partial protection. (Pinnell et. al., *JEADV*, 2004).




The combination of 15 percent L-ascorbic acid, 1 percent dl-alpha tocopherol, and 0.5 percent ferulic acid provides the highest levels of photoprotection currently available from topical antioxidant formulations.

## SKINCEUTICALS ANTIOXIDANT PRODUCTS

SkinCeuticals team of scientists 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.*