

ANTIOXIDANTS AND SKIN AGING

“A paradigm for age related degenerative diseases”

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The average adult's skin weighs about 9-10 pounds and has a surface area of approximately twenty feet, although the epidemic increase in increased weight (BMI >25) and obesity (BMI >30) in the American populace probably under estimates both the weight and surface area of the skin. Whatever the weight and surface area, however, the skin is the body organ most exposed to toxic substances which include, but are not limited to, ultraviolet irradiation, including UVA (long range) and UVB (short range), aerosolized pollutants smoking including second hand smoke, excessive ethanol (>1 drink day for woman, 2 for men), heavy metal exposure and exposure to some clothing fabrics with or without additives. It is no wonder, therefore, that the skin is subject to the greatest probability of premature aging. What most consumers and physicians do not understand, however, is that unlike the portrait of Dorian Gray, where the skin remained youthful while the interior organs degenerated, our skin measures, albeit not directly, the aging occurring in many organs of our body and in a real, although not totally quantifiable way, reflects the potential acceleration of a many of degenerative diseases associated with aging. As a result, it is a fair, if not totally scientifically proven probability, that the youthful or aged appearance of our skin reflects many internal aspects of the maintenance of youth or the ravages of aging.

Of course, it would be naïve to claim that nutrition can eliminate skin aging which includes wrinkles, blotchiness, roughened texture a sallow coloration and sagging, but as will become clear in this chapter that the aging clock can not only be retarded but to a significant degree reversed. On the other hand, this antiaging effect will not be achieved by the 45 billion per year cosmetic industry which is more akin to placing a bandaid on a wound rather than ameliorating , if not curing, the wound from the inside. It is of note that most cosmetic formulations, although there are notable exceptions, do not penetrate the skin: they just sit there until the next time you perspire or bathe. Nonetheless many of these serve a useful function if used properly which include but again, are not limited to, humectants, moisturizers emollients and in some cases when they contain avobenzone and are applied sufficiently offer some protection for the skin's preeminent enemy, UV irradiation. Although, it has been reported that greater than fifty percent of our exposure to the sun occurs before we reach our eighteenth birthday, our daily exposure, albeit brief, creates a cumulative effect that results inevitably in signs of accelerated aging.

By the time we reach our forties or fifties, therefore, we have already experienced a significant decline if not the disappearance of two major skin protecting hormones melatonin (which typical stops being produced by the pineal gland in our brain by age 35) and a minimum decrease of at least 10% per decade of DHEA (dihydroepiandrosterone) assuming that we are not experiencing increased stress, decreased sleep, proper nutrition and appropriate physical activity as lack of any or all of these markedly accelerates the age related decline of DHEA which is integral, among other functions to maintaining the integrity of the delicate blood vessel system required to

deliver the appropriate nutrients and antioxidants to retard skin aging. Were this not enough of a problem, a further and important impediment to maintaining the healthy, youthful appearance and vitality of the skin involves the age related decline in the stomach's ability to produce hydrochloric acid which is required for proper absorption of either food or supplement derived nutrients and antioxidants and this age related decrease is enhanced significantly by the epidemic use of antacids and proton pump inhibitors (used to treat reflux (GERD) which further mitigates the stomachs ability to produce hydrochloric acid and your ability to absorb nutrients from either foods or supplements.

As a result of many of the issues discussed above, there is a theory, first promulgated by D. Harman, MD in the 1950's and now generally accepted that free radicals, a natural biologic process that results from the process using oxygen to create fuel for our body functions but which obligately creates unstable oxygen molecules (ROS- Reactive Oxygen Species), which are increased by environmental factors including UV irradiation, cigarette smoke (either primary or secondary) and our polluted environment. The cumulative effect of free radicals on the skin over time, and the decreased absorption of nutrients and antioxidants due to decreased production of hydrochloric acid due to age relate loss of one type of cell found in the stomach (Parietal Cells) which are charged with producing hydrochloric acid, the use (overuse) of antacids and the action, proton pump inhibitors (e.g., Nexium) and the increasing consumption of processed foods in our fast paced, overstressed and overworked society, result in a significantly reduced absorption of nutrients and antioxidants which are critical for protection of the skin as well as diminishing the significant increases in many degenerative diseases of aging. To put it simply, the eye may be the window of the soul but the skin is a real depiction of the aging occurring within the many organs of our bodies.

Despite the caveats, there is a large and growing number of experimental and more importantly clinical studies which demonstrate unequivocally that certain nutrients and antioxidants can not only slow if not prevent, and/or repair skin aging and other age related degenerative diseases but may, in the proper construct, maintain the youthful appearance of the skin while simultaneously retarding the plethora of age related degenerative diseases. As the research continues to expand and be validated by corroborative studies, the list of these nutrients and antioxidants cannot but continue to grow. Nonetheless, as will be discussed below, the nutrients and antioxidants enumerated and explained should serve only as a harbinger of further discoveries and even more potent methodologies to combat the aging process.

It must be remembered, however, that antioxidants function interdependently as a single antioxidant, once utilized to clear an oxidant reaction resulting from the use of oxygen as fuel, itself becomes an oxidant. As a result a number of independent and interdependent antioxidants are required to prevent the ultimate tissue deterioration in the skin or other organs involved in the degenerative diseases of aging. A poignant example of this interdependency was the frequently touted study published in the New England Journal of Medicine that, Supprential B Carotene, a precursor of Vitamin A in smokers

actually increased the incidence of lung cancer in smokers. Although the data is undisputable, the lack of other antioxidants required by the body, suggests that isolated Vitamin A may be harmful in smokers but begs the more important question of the antioxidants working in tandem, or as a series, wherein each new oxidant, created by the action of an antioxidant, be it reactive oxygen species, hydroxyl radicals, peroxide or others is neutralized by the next antioxidant in the chain. Simply stated, the antioxidants perform their function interdependently and thus, must be administered together to mitigate if not prevent, the untoward effects of premature aging on the skin and, the development of many of the degenerative diseases associated with aging.

Given this background, albeit negative, there are a number of nutrients and antioxidants that can retard, if not prevent and/or redress the effects of aging in the skin and by analogy, many of the other degenerative diseases of aging. Although these should not individually or collectively be considered a panacea for antiaging, they certainly represent a definite beginning in retarding the ravages of the environment and lifestyle on the premature aging of the skin and, at least, by analogy, the deterioration of other organ systems associated with the plethora of degenerative diseases associated with aging.

Although arbitrary, we shall divide the skins antiaging agents into six separate groups with protective properties. These include vitamins which are discussed individually in alphabetical order although not necessarily in order of importance for skin protection, low molecular weight antioxidants which are of critical importance and not only function as protective agents but to a large extent recharge or recycle the other skin protective antioxidants, hormones, herbs, miscellaneous nutrients and trace elements. As stated above, however, each of these function both as independent and as interdependent series and although, they must, by logical necessity, be examined separately, we will attempt wherever possible to elucidate the interdependencies although our knowledge in this area remains imprecise and further work in this area is progressing. Nonetheless, we have provided an abbreviated list of suggesting reading for those interested in more information and if your question is still unanswered, please visit www.vitimmune.com and submit your question in the ask the doctor section and we will endeavor, answer your question.

Vitamin A

Beta Carotene, the precursor to Vitamin A and a safer supplement as a cumulative overdose of Vitamin A can result in liver and brain damage whereas, the body converts B Carotene into Vitamin A as needed and the excess B Carotene is available as an additional antioxidant.

In addition Vitamin A has been shown to increase the levels of Vitamin E, Superoxide Dismutase and Glutathione which are all critically important in protecting the skin against the ravages of the environment and which will be discussed below. In addition Vitamin A, markedly reduces the effects of a major detrimental UV induced skin free radical called lipid peroxide. This is of particular importance as lipid

peroxides breakdown the subcutaneous fat that exists as the third layer of skin which includes the outermost layer, the epidermis, the second layer, the dermis, and the subcutaneous fat which together with collagen and elastin, provides the youthful fullness in contradistinction to the aged associated sagging of the skin. In addition, Vitamin A as well as other substances are critical in producing epidermal cells (Keratinocytes) as well as loosening the intracellular connection of epidermal cells allowing those damaged by the environment to slough off more readily and promote the youthful smooth and uniform pigmented appearance of the skin. In this regard, it has been well documented that sufficient Vitamin A reduces the incidence of skin papillomas.

Vitamin C

No discussion of the skin health can avoid the critical importance of Vitamin C, which unfortunately has been shown to demonstrate decreased absorption during the aging process due to mechanisms discussed previously. In addition there is a plethora of data which demonstrate that smoking as well as secondary smoke markedly reduces the Vitamin C as well as the Glutathione levels not only in the skin but throughout the body. Vitamin C, also termed as ascorbic acid has been shown to protect against sunburn, particularly that related to the longer wave UVA irradiation, delay the onset of photocarcinogenesis (e.g., skin tumors) and reduce the wrinkling associated with the shorter wave UV B irradiation particularly in the epidermis.

Of course, a major deficiency in Vitamin C leads to a disease called scurvy which was particularly prevalent in sea farers in the eighteenth century until it was determined that fresh limes, high in Vitamin C content, could reverse the condition and is a major reason for seamen especially from Britain being given the nickname, limeys.

Milder deficiencies, although of equal importance to the health of the skin, often go undiagnosed. Nonetheless Vitamin C is critical for the removal of hydroxyl radicals, decreasing endothelial permeability and together with Glutathione, preventing the growth of new blood vessels and as a result, or coincident with this action together with amino acids which will be discussed below promotes the development of new collagen, the major protein for maintaining the youthful tautness of the skin and significantly reduces the incidence of oncogenes (C Jun & C fos) which promotes tumor production associated predominately with UVA irradiation.

Vitamins E

Vitamin E offers photo-protection thereby diminishing the effects of UV irradiation, which is associated with sunburn, variegated pigmentation, hyperplasia immunosuppression, DNA damage when taken orally – or topically. It counteracts immunosuppression induced by UV radiation. It also protects cells from oxidative stresses which inhibit biosynthesis of collagen, and elastin and provides protection against aging and the attendant risk of skin cancer.

There are several oral forms of Vitamin E; α -Tocopherol (D form) has the best absorption. The potency of Vitamin E as an antioxidant is enhanced by combination with other oral antioxidants including Co enzyme Q 10 which will be discussed below and the combination has been shown to reduce the premature death (apoptosis) of fibroblasts which provide the scaffolding for the collagen elastin and subcutaneous fat that maintains its useful appearance. High doses (greater than 800 IU day) should be avoided prior to surgery because Vitamin E has a blood thinning effect. In addition, although α tocopherol has the best absorption, there is increasing evidence that mixed vitamins including γ tocopherol and tocotrienols have additive protective effects on the damage to the skin from UV irradiation and our polluted environment. In contrast Vitamin C, Vitamin Es major effect is to protect against the oxidation caused by the shorter wavelength UVB.

Furthermore, Vitamin E has been shown to decrease the activity of cyclooxygenase which is responsible for the production of prostaglandin E2, a major inflammatory substance which activates a number of inflammatory molecules termed cytokines which further breakdown the protective barrier of the skin and contribute significantly to many of the degenerative diseases associated with accelerated or premature aging caused by UV irradiation.

Low Molecular Weight Antioxidants

Although the vitamins discussed above represent major protection against the damage and aging of the skin, perhaps the more important protectants reside in a group of elements collectively termed low molecular weight antioxidants. Among these substances, perhaps the most prominent in antioxidant protection is a tripeptide termed glutathione which functions predominantly in the organelle of skin and all other cells of the body termed mitochondria, and together with Co Enzyme Q10 Carnitine maximizes the energy production (ATP) and health of all cells in the human body.

Glutathione (GSH)

GSH is a tripeptide of three amino acids glutamate, cysteine and glycine and represents the most prevalent antioxidant in the human body. In skin, it has been shown to have a plethora of protective actions. These include but are not limited to protection against the production of the death pathway (apoptosis) by preventing the activation of caspases a series of enzymes which promote apoptosis and thus preventing the premature death of keratinocytes (skin cells) induced by short wavelength UVB irradiation in both the epidermis and the dermis. Secondly GSH has been demonstrated to prevent the activation of a series of enzymes termed metalloproteinases, which activate collagenase and thus protect the integrity of collagen and to a lesser extent, elastin, the two proteins most prominently involved in the elasticity, pliability and youthful appearance of the skin. This protection is augmented by both carnosine, and curcumin, an extract of curry, which will be discussed below and collectively prevent the cross linking of proteins to sugars, termed accelerated glycation end products (AGE) which inhibit further collagen

synthesis, creates rigidity in contradistinction to the pliability of youthful appearing skin and result in liver (age) spots, the brown spots which predominantly occur on sun exposed areas of the skin and result in the variegated pigmentation associated with the aged appearance of skin. Thirdly, it has been well documented that GSH in concert with Vitamin C protect the skin from the ultraviolet irradiation which up regulates the oncogenes C-Jun and C-Fos which promote the development of skin cancers, the most prevalent form of cancer suffered by humans. Furthermore, GSH protects the dermis of the skin from the damage to DNA which is a further promoter of carcinogenesis.

Although the above would appear to be sufficient for a single antioxidant, it must be reiterated that GSH works both independently and interdependently with other small molecular weight antioxidants including superoxide dismutase (SOB), catalase, and alpha lipoic acid. In fact the combination of GSH, SOB and catalase are critical for normal wound healing and the reduction in these associated with UVR, lifestyle, smoking excess ethanol, decreased sleep and a poor diet as well as stress significantly retard normal wound healing. In addition, UVR decreases GSH in both the skin and red blood cells thus reducing the blood flow and oxygen delivery to the skin and in concert with the decreased DHEA associated with aging increases the cumulative photo damage with all its negative ramifications for the maintenance of the youthful appearance of the skin. In addition, it has been demonstrated that GSH protects the skin from the skin damage associated with heavy metal and pesticide exposure. Due to its interdependent actions with other antioxidants as well as hormones (thyroid) in the skin and all other organs of the body, it is logical, teleologically to understand why it is the most prevalent antioxidant throughout the human body.

In addition, GSH is also involved in regulating the melatonin production in the pigment producing cells of the skin as well as protecting the levels of BCL2, the cellular factor that prevents premature cell death. It is of note that Vitamin A increases the levels of glutathione in skin and other body organs and is regenerated by Vitamin C and alpha lipoic acid which will be discussed below. Although the mechanisms of these actions remain obscure they are currently under intensive study.

Alpha Lipoic Acid (ALA)

Another, multifunctional skin antioxidant is termed alpha lipoic acid. In fact, it has been shown to quench hydroxyl, nitrogen and many other free radicals. In addition as it is both water and lipid soluble it can perform its antioxidants functions in all three layers of the skin and in all components including the cell membrane, cytoplasm, nucleus and all the associated organelles of the cells including the mitochondria.

Furthermore, it can activate a collagen related protein termed AP which when activated by ALA, digests cross linked glycated collagen (AGE) which are a hallmark of aged skin and significantly retard the production of new pliable collagen. It also has been shown to retard, if not prevent, the activation of a cellular factor NFkB induced by UVR and which, when activated up regulates the production of inflammatory molecules, termed cytokines, which were discussed previously and which exacerbate the photo

damage and aging induced by the sun, the environment, smoking and other unhealthy factors discussed previously. Finally, ALA represents a prototypic example of the interdependency of antioxidants as it regenerates the antioxidant activity of Vitamin C, and glutathione and to an extent Vitamin E, and in reciprocation, ALA's antioxidant activity is regenerated by both Vitamin E and Vitamin C which also regenerates the antioxidant activity of GSH.

In addition to the low molecular antioxidants, there are two hormones DHEA and melatonin which were discussed briefly before but their importance in maintaining the youthful appearance of the skin and, at the very least retarding many of the degenerative diseases of aging, deserve further elucidation. In fact, there are numerous studies that suggest that DHEA produces many of the same effects on the body as caloric restriction, which has been shown in animal studies to markedly prolong the life span of the animals.

DHEA

As previously stated DHEA declines approximately 10% per decade under ideal circumstances. It is of note that in addition to protecting the vascular integrity of the skin, it, together with omega three fatty acids which will be discussed below are integral to develop protective antibodies after vaccination to influenza and pneumonia, in part, as it is a critical element in activating the body's defenses (the immune) system. In addition it along with the other antioxidants previously discussed has been shown to retard the development of a variety of cancers including those which occur in the skin.

DHEA, however, also serves other protective antiaging functions in the skin. These include stimulating the sebaceous glands, which act as part of the skin barrier and maintain the youthful moisture retaining properties of the skin as well as stimulating the maturation of keratinocytes, the major type of cell in the dermis and epidermis. Together with Vitamin A, therefore, they produce both the stimulation of keratinocyte production, the orderly maturation of keratinocytes from dermis of epidermis and the sloughing off of damaged keratinocytes, all of which foster the maintenance of youthful, healthy skin.

Finally DHEA, when present in sufficient quantities increase collagen production and decreases collagenase, the enzyme responsible for degrading collagen and producing the sagging appearance of aged skin. Maintenance of youthful levels of DHEA, therefore, promotes the youthful appearance of the skin as well as maintaining the strength of the bodily defenses, the immune system, and retarding many other degenerative diseases of aging. It is important to remember, however, that DHEA can be converted into other hormones including testosterone and dihydrotestosterone as well as estradiol and thus is contraindicated in patients with elevated Prostate Specific Antigen (PSA) levels, as well as men with prostate cancer and women with breast cancer. As a result, appropriate testing should be performed in conjunction with your physician before beginning supplementation of reestablish youthful levels. It is, also critical that you purchase micronized DHEA such as that produced by Vitimmune and a few other companies as failure to micronize the DHEA engenders changes in the molecule DHEA to DHEAs as

non micronized DHEA is metabolized by the liver.

Melatonin

A second hormone with major implications for the maintenance of youthful skin is melatonin. This hormone is produced by the pineal gland in the brain and unfortunately due to stress from any cause whether it be work, relationship of financially generated results in the pineal glands production of melatonin, which is only produced in the dark, completely, stopping by age thirty five although it has been shown in animals reared in a non stressed environment that normal melatonin productions continues to the human equivalent of age sixty. Melatonin in a manner similar to glutathione protects the skin against oxidative damage from the sun and other environmental pollutants by scavenging free radicals including the hydrophxl, perhaps the most damaging singlet oxygen and nitric oxide. It also is involved in healing burned skin and in small amounts (the maximum production of melatonin from pineal gland is between 0.25 and 0.5 mg per night) causes keratinocytes to proliferate and has been shown to increase glutathione levels after UV irradiation. As such it has a sparing effect on glutathione, the importance of which has been discussed previously. In fact, in unpigmented (melanin depleted) derived from melatonin keratinocytes, glutathione depletion induced significant lipid damage and premature death to both keratinocytes and fibroblasts while in pigmented kerationcytes depletion of glutathione did not alter either kerationcytes or fibroblasts subject to UVA irradiation. In this regard, it also reduces the erythema associated with UV (sun) irradiation and has been shown to be protective against the damage induced by either/or UVA or UVB irradiation. Experiments clearly demonstrate that melatonin reverses the UVB induced premature death of skin fibroblasts induced by UVB irradiation.

Finally, the age related lack of melatonin, in addition to the loss of an important skin antioxidant, antiaging substance is even more harmful as melatonin has been reported to promote delta, or deep wave sleep and it is during this period of sleep that growth hormone, another critical skin antiaging hormone is produced. As such, the loss of melatonin production by age 35 results in a variety of changes, which cumulatively result in accelerated skin aging. Fortunately, it can be replaced with supplements but as a caveat our experiments with melatonin demonstrate that only pharmaceutical grade melatonin can both promote deep wave sleep at dose (.25 - .5mg) can promote the growth of new keratinocytes, which as previously stated, is crucial to the maintenance of youthful appearing skin.

Herbs

There are a number of herbs, which in experimental studies has demonstrated skin protective properties. These include quercitin, perhaps although not completely proven by regenerating glutathione especially when skin is subjected to UVA irradiation. In a similar vein, pycnogenol, and green tea extracts particular those containing and silymarin which is better known by its alternate name, milk thistle, and reservatol, found in red

wine all demonstrate UV and environmental pollutant induced skin damage in both the epidermis as well as the dermis. If ingested orally, however, rather than applied topically it is of critical importance to only use brands that are standardized extracts and which are not contaminated with pesticides, heavy metals or other pollutants which may be present in the soil in which they are grown. In this regard caveat emptor applies and although it is beyond the scope of this chapter to list safe brands, any questions regarding safety of various brands can be addressed to www.vitimmune.com using the ask the doctor section.

Miscellaneous Nutrients

These miscellaneous substances fall into two basic categories, amino acids required for production of new collagen and omega 3 fatty acids, which are critical for the maintenance of the subcutaneous fat which promotes the smoothness of youthful skin. With regard to the proteins, the amino acids glutathione, proline, histadine argenine and ornithine as well as glutathione are all required for collagen synthesis and as previously discussed may decrease as we age since the hydrochloric acid in the stomach, responsible and for breaking down proteins into their constituent amino acids decreases. To guarantee sufficient quantities and absorption of these as well as other amino acids necessary for collagen synthesis as well as the amino acids including the branched chain amino acids, those interested in maintaining youthful skin as well as retarding other degenerative diseases of aging. The first of these is a daily Whey shake which if extracted at low temperatures to prevent the cross linking of proteins and ion exchanged to remove milk components especially if you are one of the millions of people who are lactose intolerant. Taking a Whey shake before bed maximizes the repair of the skin, which occurs during sleep when melatonin and growth hormone are synthesized and/or released. The second, and by no means mutually exclusive mechanism to ensure sufficient hydrochloric acid to breakdown proteins assuming the consumption of a good balanced diet, is to add betaine which acts like hydrochloric acid to ensure to adequate breakdown of protein to the constituent amino acids. Finally to ensure the adequate growth of new collagen, it is critical to prevent the accelerated glycation end products (AGEs) previously discussed which cross links sugars with proteins and prevents or at least inhibits new collagen synthesis. curcumin which was discussed previously functions to prevent the production of AGEs and carnosine which not only prevents but to an extent can reverse AGEs and thus reestablish the production of new collagen as well as preventing / treating the age spots (liver spots) associated with aged skin.

Another element with UV protective properties as well as being demonstrated to be of significant benefit in reducing the incidences of many of the degenerative diseases of aging are the omega –3 fatty acids. As previously discussed, these substances as well as DHEA to a large degree determine the skin's response to vaccination, which generate inadequate if any responses in many elderly patients. Omega 3 fatty acids have also been demonstrated to reduce the erythema associated with UV irradiation by reducing inflammatory cytokine production although they require Vitamin E to prevent epidermal lipid peroxidation as well as participating in the maintenance of the subcutaneous layer of skin which provides the plumpness associated with youthful skin. It is of paramount

importance, however, that these be used at a dose of 1000 mg/day only with the other antioxidants including Vitamin E, Vitamin K as well as glutathione and melatonin as omega 3 fatty acids can actually increase the sun damage as well as retarding melanoma production.

Finally, both selenium, which among other functions is required to regenerate glutathione and copper which is critical to the production of superoxide dismutase as well as other trace elements such as magnesium which is critical to the effective function of the bodily defenses (the immune system) which in effect raises the level of damage induced by the synthesis of prostaglandin E2 to activate inflammatory cytokines which exacerbated UV induced skin damage.

The above represents but an overview of a field with expanding importance and discoveries in the field of aging in the skin. Of course, since many of the antioxidants mentioned have ramifications in retarding many of the other degenerative diseases of aging, we recommend strongly oral supplementation even given the caveats discussed above as topical application, which is applicable for many of the substances discussed may well protect the skin from aging due to the ravages of the environment, the sun and our lifestyles but cannot be absorbed systemically and penetrate the other organs of the body and thus are essentially useless in protecting the cells and organelles especially the mitochondria which are so intricately linked to other internal degenerative disease of aging.

Suggested Reading

1. Yu BP.
Approaches to anti-aging intervention: the promise and the uncertainties.
Mech Ageing Dev. 1999 Nov; 111(2-3): 73-87
2. Bell E, et al
Recipes for reconstituting skin.
J. Biomech Eng. 1991 May; 113(2): 113-9
3. Irshad M, et al
Oxidant-antioxidant system: role and significance in human body.
Indian J Exp Biol. 2002 Nov; 40(11): 1233-9.
4. Varani J, et al
Molecular mechanisms of intrinsic skin aging and retinoid-induced repair and reversal.
J. Investig Dermatol Symp Proc. 1998 Aug; 3(1): 57-60
5. Rhie G, et al
Aging –and photoaging-dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo.
Invest Dermatol. 2001 Nov; 117(5): 121-7

6. Zimmerman JA, et al
Nutritional control of aging.
Exp Gerontol. 2003 Jan-Feb; 38(1-2): 47-52
7. MacKay D, et al
Nutritional support for wound healing.
Altern Med Rev. 2003 Nov; 8(4): 359-77
8. Hu HL, et al
Antioxidants may contribute in the fight against aging; an in vitro model.
Mech Aging Dev. 2000 Dec 20; 121(1-3):217-30

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