Discovering the link between nutrition and skin aging

Silke K. Schagen,1† Vasiliki A. Zampeli,1,2† Evgenia Makrantonaki1,2 and Christos C. Zouboulis1,*

1Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center; Dessau, Germany; 2Laboratory for Biogerontology, Dermato-Pharmacology and Dermato-Endocrinology; Institute of Clinical Pharmacology and Toxicology; Charité Universitätsmedizin Berlin; Berlin, Germany

†These authors contributed equally to this work.

Keywords: nutrition, diet, ultraviolet protection, skin aging, antioxidants, fatty acids, flavonoids, vitamins

Abbreviations: 1,25(OH)2D3, 1,25-dihydroxy vitamin D3; CoQ10, coenzyme Q10; CR, caloric restriction; EFAs, essential fatty acids; EGCG, (-)-epigallocatechin-3-gallate; FoxO transcription factors, forkhead box class O transcription factor; GH, growth hormone; GTPs, green tea polyphenols; DHEAS, dehydroepiandrosterone sulphate; HRT, hormone replacement therapy; IGF-I, Insulin-like growth factor-I; IU, international unit; JNK, jun N-terminus kinase; mTORC1, mammalian target of rapamycin complex 1; MMP, matrix metalloproteinase; MST1, STE-like 20 protein kinase 1; ROS, reactive oxygen species; UL, upper intake levels; UV, ultraviolet

Introduction

Beauty comes from the inside. The connection between nutrition and skin condition or rather the effect of nutrition on skin aging has been an interesting topic for scientists and physicians throughout the centuries worldwide. Vitamins, carotenoids, tocopherols, flavonoids and a variety of plant extracts have been reported to possess potent anti-oxidant properties and have been widely used in the skin care industry either as topically applied agents or oral supplements in an attempt to prolong youthful skin appearance. This review will provide an overview of the current literature “linking” nutrition with skin aging.

Skin has been reported to reflect the general inner-health status and aging. Nutrition and its reflection on skin has always been an interesting topic for scientists and physicians throughout the centuries worldwide. Vitamins, carotenoids, tocopherols, flavonoids and a variety of plant extracts have been reported to possess potent anti-oxidant properties and have been widely used in the skin care industry either as topically applied agents or oral supplements in an attempt to prolong youthful skin appearance. This review will provide an overview of the current literature “linking” nutrition with skin aging.

Vitamins

L-ascorbic acid (vitamin C). Vitamin C, also named L-ascorbic acid, is water soluble, photosensitive and is the most important antioxidant in the hydrophilic phase. Vitamin C is not naturally synthesized by the human body and therefore adequate dietary intake of vitamin C is required and essential for a healthy human diet.

*Correspondence to: Christos C. Zouboulis; Email: christos.zouboulis@klinikum-dessau.de
Submitted: 02/16/12; Revised: 10/28/12; Accepted: 11/13/12
http://dx.doi.org/10.4161/derm.22876
The richest natural sources are fresh fruits and vegetables such as citrus fruits, blackcurrant, rose hip, guava, chili pepper or parsley. Stability of the vitamin C molecule depends on aggregate condition and formulation.

L-ascorbic acid can be used orally and topically for skin benefits. Vitamin C is a cofactor for lysyl and prolyl hydroxylase, which stabilize the triple helical structure of collagen. It also plays a role in cholesterol synthesis, iron absorption and increases the bioavailability of selenium. The most commonly described cutaneous manifestations accompanying vitamin C deficiency are attributed to the impaired collagen synthesis. Enlargement and keratosis of hair follicles mainly of the upper arms and curled hairs, the so-called ‘corkscrew hairs’, are usually described. The follicles become hemorrhagic with time and they sometimes mimic the palpable purpura of leucocytoclastic vasculitis.

Additionally, vitamin C deficiency is known for causing scurvy, a disease with some manifestations such as fragility, skin lesions in form of petechiae, gum bleeding, ease of developing bruises or slow wound healing.

Topically ascorbic acid is used in various cosmetic products, for example in lightening of skin dyspigmentation, anti-aging and sun protection formulations. The idea of sun protecting products is to have a combination product between a “passive” protection with a UV filter and an “active” protection with the antioxidant. UVB protection by vitamin C is frequently mentioned in the literature. However, the study by Wang et al. indicates that more work in formulation of cremes is needed, since there seem to be many products in which the desired effects are not measurable. The use of vitamin C in cosmetic products is difficult as its reducing capacity occurs very fast and its degradation may occur under the presence of oxygen even before the topical application to the skin.

Nutricosmetic products with L-ascorbic acid work as free radical scavengers and repair the membrane bound oxidized vitamin E. A long-term study observed the effects of a combination of ascorbic acid and D-α-tocopherol (vitamin E) administered orally to human volunteers on UVB-induced epidermal damage. The treatment was well-tolerated and could be used prophylactically against the hazardous effects of solar UV irradiation and skin cancer, according to the authors. Another paper describes an 8-week study, which compared topical and systemic antioxidant treatment. Topical and systemic treatment both seemed to be good photoprotectors.

There are many preparations of vitamin C based products available on the market, but these are predominantly based on more stable esters and other derivatives of vitamin C which more readily penetrate the skin but are not necessarily converted to the only active vitamin C, L-ascorbic acid. These topical or oral products do not have the effects provided by L-ascorbic acid.

**Vitamin C and vitamin E act synergistically.** When UV-activated molecules oxidize cellular components, a chain reaction of lipid peroxidation in membranes rich in polyunsaturated fatty acids is induced. The antioxidant D-α-tocopherol is oxidized to the tocopheroxyl radical in this process and it is regenerated by ascorbic acid to D-α-tocopherol. Beside ascorbic acid, glutathione and coenzyme Q10 can also recycle tocopherol.

Higher amounts of tocopherol are available in vegetables, vegetable oils like wheat germ oil, sunflower oil, safflower oil and seeds, corn, soy and some sorts of meat. The intake of natural vitamin E products helps against collagen cross linking and lipid peroxidation, which are both linked to aging of the skin.

With the process described above, D-α-tocopherol is involved in stabilizing the cell membrane by inhibiting oxidation of polyunsaturated fatty acids, such as arachidonic acid of membrane phospholipids. Topical applied vitamin E is described to reduce erythema, sunburned cells, chronic UVB-induced skin damage and photocarcinogenesis in the majority of the published studies. Vitamin E deficiency has been associated with a syndrome of edema with papular erythema or seborrhoiec changes, dryness and depigmentation in premature infants.

There are many clinical studies, which have tested the effects of tocopherol. The data seem to be controversial, but high doses of oral vitamin E may affect the response to UVB in humans. Data of Ekanayake-Mudiyanselage and Thiele suggest that vitamin E levels are dependent on the density of sebaceous glands in the skin. In a 3-week study with daily oral supplementation of moderate doses of α-tocopherol significantly increased vitamin E levels measured in skin sites rich in sebaceous glands, such as the face. This should be considered when designing clinical vitamin E studies.

Oral combination treatments of vitamins C and E, partly with other photoprotective compounds, did increase the photoprotective effects dramatically compared with monotherapies. Experts recommend that this synergetic interplay of several antioxidants should be taken into consideration in future research on cutaneous photoprotection.

**Carotenoids (vitamin A, β-carotene, astaxanthin, retinol).** Carotenoids are vitamin A derivatives like β-carotene, astaxanthin, lycopene and retinol, which are all highly effective antioxidants and have been documented to possess photoprotective properties. Findings of Scarmo et al. suggest that human skin, is relatively enriched in lycopene and β-carotene, compared with lutein and zeaxanthin, possibly reflecting a specific function of hydrocarbon carotenoids in human skin photoprotection.

β-carotene is the most prominent member of the group of carotenoids, natural colorants that can be found in the human diet. Compared with other carotenoids, the primary role of β-carotene is its provitamin-A activity. β-carotene can be cleaved by BCMO1 enzyme into 2 molecules of all-trans-retinal. There is no difference between naturally occurring and chemically synthesized β-carotene. Furthermore, β-carotene can also act as a lipid radical scavenger and as a singlet oxygen quencher, as demonstrated in vitro. Based on the distribution of BCMO1 in human tissues it seems that β-carotene metabolism takes place in a wide variety of organs, including the skin.
Carrots, pumpkin, sweet potatoes, mangos and papaya are some examples of β-carotene containing fruits and vegetables.

Upon dietary supplementation, β-carotene can be further enriched in skin, in which it is already a major carotenoid. β-carotene is an endogenous photoprotector, and its efficacy to prevent UV-induced erythema formation has been demonstrated in various studies. In healthy volunteers, a 12-week oral administration of β-carotene may result in a reduction of UV-induced erythema. Similar effects have been described in volunteers receiving a lycopene-rich diet.

The systemic photoprotecting effect of β-carotene depends both on dose and duration of treatment. In studies documenting protection against UV-induced erythema, supplementation with carotenoids lasted for at least 7 weeks, with doses > 12 mg/d of carotenoids. With treatment periods of only 3–4 weeks, studies reported no protective effects. Furthermore, β-carotene supplementation can significantly reduce the rate of mitochondrial mutation in human dermal fibroblasts after UV irradiation.

Astaxanthin is found in microalgae, yeast, salmon, trout, krill, shrimp, crayfish and crustacea. Astaxanthin is biosynthesized by microalgae or phytoplankton, which are consumed by zooplankton or crustacea. They accumulate astaxanthin and, in turn are ingested by fish which then accrue astaxanthin in the food chain. Therefore, astaxanthin has considerable potential and promising applications in human health and nutrition and has been attributed an extraordinary potential for protecting the organism against a wide range of diseases (reviewed in refs. 40 and 41).

The UV protective effects of algal extract containing 14% of astaxanthin compared to synthetic astaxanthin have also been tested. The authors of this study reported that preincubation with synthetic astaxanthin or an algal extract could prevent UV-induced alterations in cellular superoxide dismutase activity and decrease in cellular glutathione content.

In a study of Camera et al. the modulation of UVA-related injury by astaxanthin, canthaxanthin, and β-carotene for systemic photoprotection in human dermal fibroblasts has been compared. Astaxanthin showed a significant photoprotective effect and counteracted UVA-induced alterations to a great extent. The uptake of astaxanthin by fibroblasts was higher than that of canthaxanthin and β-carotene, which lead to the assumption that the effect of astaxanthin toward photooxidative changes was stronger than that of the other substances. A recent study of Suganuma et al. showed that astaxanthin could interfere with UV-A-induced matrix-metalloproteinase-1 and skin fibroblast elastase/neutral endopeptidase expression. Both studies suggest that effects of UVA radiation, such as skin sagging or wrinkling can be prevented or at least minimized by topical or oral administration of astaxanthin.

Lycopene is a bright red carotene and carotenoid pigment and phytochemical found in tomatoes and other red fruits and vegetables, such as red carrots, watermelons and papayas (but not strawberries or cherries). Although lycopene is chemically a carotene, it has no vitamin A activity.

β-carotene and lycopene are usually the dominating carotenoids in human blood and tissues and are known to modulate skin properties when ingested as supplements or as dietary products. While they cannot be compared with sunscreen, there is evidence that they protect the skin against sunburn (solar erythema) by increasing the basal defense against UV light-mediated damage.

A study confirmed that the amounts of lycopene in plasma and skin are comparable to or even greater than those of β-carotene. When skin is exposed to UV light stress, more skin lycopene is destroyed compared with β-carotene, suggesting a role of lycopene in mitigating oxidative damage in tissues. Lycopene and tomato products are also mentioned for preventing cancer.

Retinol is important for the human body; however the body itself cannot synthesize it. Retinol, a fat-soluble unsaturated isoprenoid like its two important metabolites retinaldehyde and retinoic acid, is essential for growth, differentiation and maintenance of epithelial tissues and influences reproduction. In human skin two retinoid receptors are expressed, which can be activated by retinol and its metabolites.

Retinaldehyde, additionally being important for vision, is created by in vivo oxidation of retinol in a reversible process. The normal plasma concentration of vitamin A in humans is 0.35–0.75 μg/ml. Retinol must derive from diet. Natural retinol and retinol ester are contained in liver, milk, egg yolk, cheese and fatty fish etc. Naturally occurring and synthetic vitamin A (retinol) show similar biological activities. Different retinol products, both for cosmetic (topical) and pharmaceutical (topical, systemic) use can be found on the market.

In a review of topical methods to counteract skin wrinkling and irregular pigmentation of aging skin, Bayerl evaluates the effects of vitamin A acid derivatives, chemical peeling and bleaching agents. Also, the effects of UV protection by using sunscreens and topical antioxidants are reviewed. The topical retinoid treatments inhibit the UV-induced, MMP-mediated breakdown of collagen and protect against UV-induced decreases in procollagen expression.

Endogenous retinoids cannot be linked to the pathogenesis of common skin diseases like acne and psoriasis. Oral treatment with retinol or retinoid derivatives has not been proposed as a possible anti-aging treatment. Humans require 0.8–1 mg or 2400–3000 IU vitamin A per day (1 IU = 0.3 μg).

Unfortunately the large CARET trial mentioned lung cancer-promoting effects of 25,000 IU retinyl palmitate combined with 30 mg β-carotene intake in smokers. Thus, the belief that chemical quenching of free radicals by natural compounds like retinyl palmitate and β-carotene exerts always beneficial effects has been challenged. Omenns data showed that an artificial systemic increase of antioxidants by dietary supplementation intended to modify UV erythema thresholds may have severe internal adverse effects which even may not only increase risk of cell aging but of tumor promotion. However experts still recommend dietary intake of fruits and vegetable.

Vitamin D. In humans vitamin D serves two functions, it acts as a prohormone and the human body can synthesize it itself through sun exposure. Skin is the major site for UV-B mediated vitamin D3, and 1,25-dihydroxy vitamin D3 synthesis. Smaller
amounts of vitamin D2 and D3 come from the dietary intake of animal-based foods such as fatty fish or egg yolk. Some products like milk, cereals and margarine can be enriched with vitamin D.

Excess of vitamin D is stored in fat of the body and can result in toxic effects. This toxicity presents with nausea, vomiting, poor appetite, weakness, weight loss and constipation. Food-intake of vitamin D high enough to cause toxicity is very unlikely.

The skin is one of the key tissues of the human body vitamin D endocrine system. It is important for a broad variety of independent physiological functions, which are reviewed in Reichrath et al.51 Besides its role in calcium homeostasis and bone integrity, 1,25-dihydroxy vitamin D3 [1,25(OH)2D3] is also essential for numerous physiologic functions including immune response, release of inflammatory cytokines and regulation of growth and differentiation in normal and malignant tissues such as breast, lung and colon.31 1,25(OH)2D3 protects human skin cells from UV-induced cell death and apoptosis,57 inhibits the activation of stress-activated protein kinases,58 such as the c-Jun NH2-terminal kinase and p38, and suppresses IL-6 production. Several in vitro and in vivo studies have documented the protective effect of 1,25(OH)2D3 against UVB-induced skin damage and carcinogenesis.58,59 Furthermore, 1,25(OH)2D3 induces the expression of antimicrobial peptide genes in human skin60 and plays a significant role in preventing opportunistic infections. With increasing age the capacity of the skin to produce vitamin D3 declines and consequently the protective effects of the vitamin. There are several factors contributing to this deficiency state among them behavioral factors, for example limited sun exposure or malnutrition, which can be partially altered by behavior modification and various intrinsic factors like reduced synthetic capacity. In skin, the concentration of 7-dehydrocholesterol—a vitamin D3 precursor—showed an approximately 50% decline from age 20 y to age 80 y61 and the total amount of pre-vitamin D3 in the skin of young subjects was at least two times greater than when compared with that of the elderly subjects. Vitamin D and calcium supplementation is therefore of great importance in the elderly population.15

Chang et al. also suggest an association between skin aging and levels of 25(OH)D3, another precursor of vitamin D. It may be possible that low 25(OH)D3 levels in women, who show less skin aging may reflect underlying genetic differences in vitamin D synthesis.62

Many other studies that tested oral vitamin D treatment showed skin cancer prevention, which is linked to anti-aging effects.63,64

In 2009, the American Academy of Dermatology and the Canadian Cancer Society recommended a 200 IU/day dosis for children (0–14 y), 200 IU for the age population between 14–50 y, 400 IU for the 50–70 y and 600 IU for people over their 71st year of age.65

A higher dose of vitamin D 1000 IU/day (adults) and 400 IU/day (children 0–14 y) intake has been recommended for individuals with known risk factors for vitamin D insufficiency like dark skin individuals, elderly persons, photosensitive individuals, people with limited sun exposure, obese individuals or those with fat malabsorption.66

The Food and Nutrition Board published a new recommendation for dietary allowance levels and tolerable upper intake levels (ULs) for vitamin D intake in 2010. The recommended dietary allowance (Table 1) represents a daily intake that is sufficient to maintain bone health and normal calcium metabolism in healthy people.66

Long-term intakes of vitamin D above the upper intake levels increase the risk of adverse health effects. Most reports suggest a toxicity threshold for vitamin D of 10,000 to 40,000 IU/day and serum 25(OH)D levels of 500–600 nmol/L (200–240 ng/mL).66

With daily intakes below 10,000 IU/day, toxicity symptoms are very unlikely. However, recent results from observational studies, national survey data and clinical trials have shown adverse health effects over time at much lower levels of vitamin D intakes and serum 25(OH)D. Since serum levels of approximately 75–120 nmol/L or 30–48 ng/mL have been associated with increased all-cause mortality, greater risk of cancer at some sites like the pancreas, greater risk of cardiovascular events as well as more falls and fractures with elderly subjects, the Food and Nutrition Board advises that serum 25(OH)D levels above 125–150 nmol/L (50–60 ng/mL) should be avoided and cites research results that link vitamin D intakes of 5,000 IU/day with a serum concentration at a maximum of 100–150 nmol/L (40–60 ng/mL).66

### Polyphenols

Polyphenols have drawn the attention of the anti-aging research community over the last decade, mainly because of their antioxidant properties, their great intake amount in our diet and the increasing studies showing their probable role in the prevention of various diseases associated with oxidative stress, such as cancer and cardiovascular and neurodegenerative diseases.67 Their total dietary intake could be as high as 1 g/d, which is much higher than that of all other classes of phytochemicals and known dietary antioxidants.68,69 They are mostly found in fruits and plant-derived beverages such as fruit juices, tea, coffee and red wine.

| Age          | Male          | Female        | Pregnancy    | Lactation    |
|--------------|---------------|---------------|--------------|--------------|
| 0–12 months*| 400 IU (10 mcg)| 400 IU (10 mcg)|              |              |
| 1–13 years  | 600 IU (15 mcg)| 600 IU (15 mcg)|              |              |
| 14–18 years | 600 IU (15 mcg)| 600 IU (15 mcg)| 600 IU (15 mcg)| 600 IU (15 mcg)|
| 19–50 years | 600 IU (15 mcg)| 600 IU (15 mcg)| 600 IU (15 mcg)| 600 IU (15 mcg)|
| 51–70 years | 600 IU (15 mcg)| 600 IU (15 mcg)|              |              |
| >70 years    | 800 IU (20 mcg)| 800 IU (20 mcg)|              |              |

*AI, adequate intake; IU, international unit; mcg, microgram; 40 IU = 1 mcg.
Vegetables, cereals, chocolate and dry legumes are also sources for the total polyphenol intake. Several thousand molecules having a polyphenol structure have been identified in plants being generally involved in defense against UV radiation or aggression by pathogens. Depending on the number of phenol rings and the way that these rings bind to one another, polyphenols can be divided into many different functional groups such as the phenolic acids, flavonoids, stilbenes, and lignans. Flavonoids are also further divided into flavones, flavonols, isoflavones, and flavanones, each with a slightly different chemical structure.

It has been reported that the polyphenolic content of foods can be easily affected or seriously reduced by methods of meal preparation and culinary traditions. For example, onions, which are a major source of phenolic acids and flavonoids, and tomatoes lose between 75% and 80% of their initial content when boiled over 15 min, 65% when cooked in a microwave oven and 30% when fried. In French fries or freeze-dried mashed potatoes no remaining phenolic acids were to be found.

Laboratory studies of different polyphenols such as, green tea polyphenols, grape seed proanthocyanidins, resveratrol, silymarin and genistein, conducted in animal models on UV-induced skin inflammation, oxidative stress and DNA damage, suggested that these polyphenols, combined with sunscreen protection, have the ability to protect the skin from the adverse effects of UV radiation, including the risk of skin cancers. The underlying mechanism of polyphenols actions has been a major discussion over the last decades. One of the most abundant theories is that the cells respond to polyphenols mainly through direct interactions with receptors or enzymes involved in signal transduction, which may result in modification of the redox status of the cell and may trigger a series of redox-dependent reactions. As antioxidants, polyphenols may improve cell survival; as prooxidants, they may induce apoptosis and prevent tumor growth. However, the biological effects of polyphenols may extend well beyond the modulation of oxidative stress.

Some interesting polyphenols, flavonoids and botanical antioxidants and their properties, which have drawn attention for their unique anti-aging effects are discussed next.

Flavonoids. Phlorizin. Phlorizin belongs to the group of dihydrochalcones, a type of flavonoids and it is naturally occurring in some plants. It could be found in the bark of pear (Pyrus communis), apple, cherry and other fruit trees. It has been used as a pharmaceutical and tool for physiology research for over 150 y. Investigations of the effects of phlorizin on lifespan of the D. melanogaster flies were conducted by Giardina et al. reported in 2010 that in experiments in vitro with HaCaT cells to the nitric oxide free radical donor sodium nitroprusside. Furthermore, Giardina et al. reported in 2010 that in experiments in vitro with skin fibroblasts treated with resveratrol there was a dose-related increase in the rate of cell proliferation and in inhibition of collagenase activity. Steinberg showed that resveratrol oligomers hopeaphenol, epsilon-viniferin, R2-viniferin, ampelopsin inhibit the growth number of human tumor cell lines significantly stronger than resveratrol itself.

Curcumin. Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family (Zingiberaceae) and is frequently found in rice dishes to add yellow color to the otherwise white rice. Curcumin has been shown to protect against the deleterious effects of injury by attenuating oxidative stress and suppressing inflammation (reviewed in ref. 89). In human fibroblasts curcumin induced cellular stress responses through phosphatidylinositol 3-kinase/Akt pathway and redox
signaling, thus providing evidence that curcumin-induced hormetic stimulation of cellular antioxidant defenses can be a useful approach toward anti-aging intervention. Oral ingestion in rodents has produced correction of cystic fibrosis defects and inhibition of tumor proliferation, but human trials are lacking.6,90,92

**Green tea polyphenols.** Green tea polyphenols (GTPs) deriving from the leaves of the *Camellia sinensis* have been postulated to protect human skin from the cutaneous signs of photoaging. In animal models, UV-induced cutaneous edema and cyclooxygenase activity could be significantly inhibited by feeding the animals with GTPs.93 However, in a study in 2005, although participants treated with a combination regimen of topical and oral green tea showed histologic improvement in elastic tissue content, clinically significant changes could not be detected.94 Many laboratories have reported that topical treatment or oral consumption of green tea polyphenols inhibits chemical carcinogen- or UV radiation-induced skin tumorigenesis in different animal models. Studies have shown that green tea extract also possesses anti-inflammatory activity. These anti-inflammatory and anti-carcinogenic properties of green tea are due to their polyphenolic constituents present therein. The major and most chemopreventive constituent in green tea responsible for these biochemical or pharmacological effects is (-)-epigallocatechin-3-gallate (EGCG).95 EGCG can directly inhibit the expression of metalloproteinases such as MMP-2, MMP-9 and MMP-12,96 and is a potent inhibitor of leukocyte elastase,97 which is instrumental in tumor invasion and metastasis.

Topical application of green tea extract containing GTPs on C3H mice reduced UVB-induced inflammation.98 The researchers also found protection against UV-induced edema, erythema, and antioxidant depletion in the epidermis. This work further investigated the effects of GTPs after application to the back of humans 30 min before UV irradiation. A decrease of myeloperoxidase activity and infiltration of leukocytes compared with the untreated skin was documented.99

**Ubiquinol (Coenzyme Q10)**

Coenzyme Q10 (CoQ10) is a fat-soluble, endogenous (synthesized by the body), vitamin-like substance that is mainly stored in the fat tissues of our body. It is present in most eukaryotic cells, primarily in the mitochondria and plays an important role as a component of the electron transport chain in the aerobic cellular respiration, generating energy. Ubiquinol is also a well-known powerful antioxidant compound. In the skin, CoQ10 is mainly to be found in the epidermis where it acts in combination with other enzymic and non-enzymic substances as the initial barrier to oxidant assault.100 Primary dietary sources of CoQ10 include oily fish (such as salmon and tuna), organ meats (such as liver), and whole grains. The amount of CoQ10 needed in human organism can be gained through a balanced diet, however in the market CoQ10 is available in several forms as a supplement, including soft gel capsules, oral spray, hard shell capsules, and tablets. As a fat-soluble substance it is better absorbed when taken with fat rich meals. CoQ10 is also added to various cosmetics. It has been shown on rats that a CoQ supplementation elevates CoQ homologs in tissues and their mitochondria, thus causing a selective decrease in protein oxidative damage, and an increase in antioxidative potential.101 Furthermore, in a human study where 50 mg each of vitamin E, coenzyme Q10, and selenium were administered combined with the use of topical bio-cosmetics, an increase in stratum corneum CoQ10 was noted after 15 and 30 d of ingestion.102 In cases of primary CoQ10 deficiency in vitro experiments have shown that they should be treated with CoQ10 supplementation and that complementary administration of antioxidants with high bioavailability should be considered if oxidative stress is present.103 On the other hand, in experiments contacted on mice the supplemental intake of CoQ10 had no effect on the main antioxidant defense or pro-oxidant generation in most tissues, and had no impact on the life span of mice.104

**Pre- and Probiotics**

The term probiotic is defined as "living microorganisms, which, when consumed in adequate amounts, confer a health effect on the host."105,106

The most commonly used probiotics in humans and animals are enterococci, lactobacilli and bifidobacteria, which are natural residents of the intestinal tract.

A prebiotic is a non-viable food component that confers a health benefit on the host associated with modulation of the microbiota.107 Oligofructose and other oligosaccharides are prebiotic which have a significant effect on the population of luminal flora, in particular, stimulating bifidobacterial populations.

Currently, finding alternatives to antibiotics for skin treatment is receiving a lot of interest in research. It has been found that, similarly to the gut microflora, the skin’s microbiota plays a beneficial role. Thus, the possibility to modulate the microbiota more selectively is highly interesting.

UV exposure is known to negatively affect immune system functions.108 Clinical studies that used probiotic bacteria (*Lactobacillus johnsonii* NCC 533) to modulate the cutaneous immune homeostasis altered by solar-simulated UV exposure in humans suggest that certain probiotics can help preserve the skin homeostasis by modulating the skin immune system.109,110 According to Schouten et al., a prebiotic diet caused reduced acute allergic skin response in recipient mice.111

**Essential Fatty Acids (Vitamin F)**

Essential fatty acids (EFAs) are long-chain polyunsaturated fatty acids derived from linolenic, linoleic and oleic acids. They cannot be produced in the human body and they have to be consumed through our daily dietary intake. EFAs have also been known as vitamin F. Arachidonic acid is a semi-EFA, as it can be synthesized in the body from linoleic acid. The two families of EFAs are ω-3, derived from linolenic acid, and ω-6, derived from linoleic acid, with the number indicating the position of the first double bond continuing from the terminal methyl group on the molecule.6,112 They are present in multiple food sources such as fish and shellfish, flaxseed, hemp oil, soya oil, canola oil,
chia seeds, pumpkin seeds, sunflower seeds, leafy vegetables, walnuts, sesame seeds, avocados, salmon and albacore tuna. EFAs are essential for the synthesis of tissue lipids, play an important role in the regulation of cholesterol levels and are precursors of prostaglandins.113

The association between nutrient intakes and skin aging has been examined in 2008 in 4025 women (40–74 y), using data from the first National Health and Nutrition Examination Survey. Skin-aging appearance was defined as having a wrinkled appearance, senile dryness, and skin atrophy. Higher linoleic acid intakes were associated with a lower likelihood of senile dryness and skin atrophy.114 In a study where the effect of fish oil on UV (UV) B-induced prostat gland metabolism was examined, 13 patients with polymorphic light eruption received dietary supplements of fish oil rich in omega-3 polyunsaturated fatty acids for 3 mo. The authors managed to show a reduction in UV-induced inflammation, possibly due to lowered prostaglandin-E2 levels. Furthermore, oral administration of an antioxidant mixture containing vitamin C, vitamin E, pycnogenol and evening primrose oil significantly inhibited wrinkle formation caused by chronic UVB irradiation through significant inhibition of UVB-induced matrix metalloproteinase (MMP) activity accompanied by enhancement of collagen synthesis on hairless mouse skin.115

It is widely accepted that caloric restriction (CR), without malnutrition, delays the onset of aging and extends lifespan in diverse animal models including yeast, worms, flies, and laboratory rodents.117 Although the underlying mechanisms remain still unknown, some explanations such as alterations of hormone metabolism, hormone-related cellular signaling, oxidation status, DNA repair, apoptosis, and oncogene expression, have been postulated.118,119 In a histological study on Fischer 344 rats undergoing dietary CR, the histomorphological changes resulting from intrinsic aging were delayed or prevented by CR. Namely, a trend toward increased values for collagen and elastic fibers, fibroblasts, and capillaries and a prevention of age-related increase in the depth of the epidermis, dermis, and fat layer was observed in skin samples from CR rats.120 Furthermore, in skin tissues of mice with CR weight control a palette of genes showed a differential expression when compared with mice receiving normal diet. The authors concluded that dietary CR showed profound inhibitory impact on the expression of genes relevant to cancer risks.121 Studies evaluating CR in nonhuman primates and its effects on human health, and on the metabolic parameters are ongoing.

Conclusions

To conclude, nutrition and skin aging still remains a controversial and conflicting subject. A promising strategy for enhancing skin protection from oxidative stress is to support the endogenous antioxidant system, with antioxidants containing products that are normally present in the skin.11 However, this should not be confused with a permanent intake of non-physiological high dosages of isolated antioxidants. Fruit and vegetables consumption may represent the most healthy and safe method in order to maintain a balanced diet and youthful appearing skin.

 Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Triellis TG, Klagas I, Valvenyanos K, Triaridis S, Printza A, Kyrgidis A, et al. Extrinsic aging in the human skin is associated with alterations in the expression of hyaluronic acid and its metabolizing enzymes. Exp Dermatol 2009; 18:1028-35; PMID:19601984; http://dx.doi.org/10.1111/j.1600-0625.2009.00889.x
2. Makrantonaki E, Zouboulis CC; German National Genome Research Network 2. The skin as a mirror of the aging process in the human organism–state of the art and results of the aging research in the German National Genome Research Network 2 (NGFN-2). Exp Gerontol 2007; 42:879-86; PMID:17689905; http://dx.doi.org/10.1016/j.exger.2007.07.002
3. Ristrick M, Schmeisser S. Extending life span by increasing oxidative stress. Free Radic Biol Med 2011; 51:327-36; PMID:21619928; http://dx.doi.org/10.1016/j.freeradbiomed.2011.05.010
4. Ristrick M, Zarse K, Oberbach A, Kloting N, Birringer M, Kiehntopf M, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci U S A 2009; 106:8665-70; PMID:19433800; http://dx.doi.org/10.1073/pnas.0903485106
5. Huang H, Tindall DJ. Dynamic FoxO transcription factors. J Cell Sci 2007; 120:2479-87; PMID:17646672; http://dx.doi.org/10.1242/jcs.010222
6. Draelos ZD. Nutrition and enhancing youthful-appearing skin. Clin Dermatol 2010; 28:400-8; PMID:20620756; http://dx.doi.org/10.1016/j.clindermat.2010.03.019
7. Ryan AS, Goldsmith LA. Nutrition and the skin. Clin Dermatol 1996; 14:389-406; PMID:8862916; http://dx.doi.org/10.1016/0160-0561(96)00068-5
8. Boynton N, Galey I, Bernard BA. Effect of vitamin C and its derivatives on collagen synthesis and cross-linking by normal human fibroblasts. Int J Cosmet Sci 1998; 20:151-8; PMID:18505499; http://dx.doi.org/10.1046/j.1467-2494.1998.171747.x
9. Placek M, Gaube S, Kerkmann U, Gilbertz KP, Herzinger T, Haen E, et al. Ultrasviolet-B-induced DNA damage in human epidermis is modified by the antioxidants ascorbic acid and D-alpha-tocopherol. J Invest Dermatol 2005; 124:304-7; PMID:15675947; http://dx.doi.org/10.1111/j.1523-1747.2004.23560.x
10. Pinnell SR. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. J Am Acad Dermatol 2003; 48:1-19, quiz 20-2; PMID:12522365; http://dx.doi.org/10.1016/j.jaad.2003.05.017
11. Galperin M, Gosenka M. Main approaches for delivering antioxidant vitamins through the skin to prevent skin ageing. Expert Opin Drug Deliv 2011; 8:905-19; PMID:21599565; http://dx.doi.org/10.1517/17425247.2011.581657
12. Wang SQ, Osterwalder U, Jang K. Ex vivo evaluation of radical sun protection factor in popular sunscreens with antioxidants. J Am Acad Dermatol 2011; 65:252-30; PMID:21624700; http://dx.doi.org/10.1016/j.jaad.2010.07.009
13. Makrantonaki E, Zouboulis C. Skin alterations and diseases in advanced age. Drug Discov Today Dis Discov 2008; 5:e153-62; http://dx.doi.org/10.1016/j.dddt.2008.05.008
14. Chan AC. Partners in defense, vitamin E and vitamin C. Can J Physiol Pharmacol 1993; 71:725-31; PMID:8313238; http://dx.doi.org/10.1139/y93-109
15. Morganti P, Bruno C, Guarneri E, Cardillo A, Del Ciommo P, Valenzano F. Role of topical and nutritional supplement to modify the oxidative stress. Int J Cosmet Sci 2002; 24:351-9; PMID:18494887; http://dx.doi.org/10.1046/j.1467-2494.2002.00159.x
16. Koekuept M, Neumann M. Systemic and topical drugs for aging skin. J Drugs Dermatol 2003; 2:345-51; PMID:12884471
17. Fryer MJ. Evidence for the photoprotective effects of vitamin E. Photochem Photobiol 1993; 58:304-12; PMID:8415922; http://dx.doi.org/10.1111/1751-1097.1993.tb09566.x
18. Chan AC, Tran K, Raynor T, Ganz PR, Chow CK. Regeneration of vitamin E in human platelets. J Biol Chem 1991; 266:17290-5; PMID:1910041
Am J Clin Nutr 2001; 73:853-64; PMID:11333837

Blood levels of vitamin E, polyunsaturated fatty acids against ultraviolet light-induced erythema in humans. J Dermatol Sci 1991; 2:171-8; PMID:1831657; http://dx.doi.org/10.1016/0165-4848(91)90089-5

Eicker J, Kürten V, Wild S, Riss G, Goralczyk R, Kruttman J, et al. Beta-carotene supplementation protects from photoaging-associated mitochondrial DNA mutation. Photochem Photobiol Sci 2003; 2:655-9; PMID:12859149; http://dx.doi.org/10.1016/j.photobiology.2003.03.001

Lorenz RT, Cyweski GR. Commercial potential for Haematococcus microalgae as a natural source of astaxanthin. Trends Biotechnol 2000; 18:160-7; PMID:10764262; http://dx.doi.org/10.1016/s0167-7718(00)01443-5

Hussein G, Goto H, Oda S, Sankawa U, Matsumoto K, Watanabe H. Antihypertensive potential and mechanism of action of astaxanthin. III: Antioxidant and histopathological effects in spontaneously hypertensive rats. Biol Pharm Bull 2006; 29:684-8; PMID:16595899; http://dx.doi.org/10.1248/bpb.29.684

Yuan JP, Peng J, Yin K, Wang JH. Potential health-promoting effects of astaxanthin: a high-value carotenoid of marine microalgae. Med Nutr Food Res 2011; 55:150-65; PMID:21207751; http://dx.doi.org/10.1002/mnf.201000414

Higuera-Ciapara I, Félix-Valenzuela L, Goycoolea FM, Astaxanthin: a review of its chemistry and bioactivity. Photochem Photobiol B 2005; 78:141-8; PMID:15664501; http://dx.doi.org/10.1016/j.photobiology.2005.06.003

Lyons NM, O’Brien NM. Modulatory effects of an algal extract containing astaxanthin on UVA-irradiated cells in culture. J Dermatol Sci 2002; 30:73-84; PMID:12354422; http://dx.doi.org/10.1016/s0923-2181(02)00063-4

Camera E, Mastrofrancesco A, Fabbrini C, Daubrawa F, Picardo M, Sies H, et al. Astaxanthin, canthaxanthin and beta-carotene differently affect UVA-induced oxidative damage and expression of oxidative-stress responsive enzymes. Exp Dermatol 2009; 18:222-31; PMID:18803658; http://dx.doi.org/10.1111/j.1600-0625.2008.00799.x

Sagunuma K, Nakajima H, Ohtosu M, Imokawa G. Astaxanthin attenuates the UVA-induced up-regulation of matrix-metalloproteinase-1 and skin fibroblast elastase in human dermal fibroblasts. J Dermatol Sci 2010; 58:136-42; PMID:20219323; http://dx.doi.org/10.1016/j.jdermsci.2010.02.009

Stahl W, Heinrich U, Ungermann H, Sies H, Tronnier H, Sies H. Lycopene-rich products and dietary photoprotection. Photobiomodulation Photomed Laser Surg 2006; 2:52-8; PMID:16465309; http://dx.doi.org/10.1039/b505312a

Rihaya-Mercado JD, Garmyn M, Gilchrist BA, Russell RM. Skin lycopene is destroyed preferentially over beta-carotene during ultraviolet irradiation in humans. J Nutr 1995; 125:1854-9; PMID:7616301

Emtman M, Takkosiche B, Caamato-Isoerna E. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev 2004; 13:340-5; PMID:15060906

Pihok KS, Gong MC, Bahmann R, Miller EC, Clinton SK. Tomatoes, lycopene and prostate cancer: a clinician’s guide to counseling those at risk for prostate cancer. World J Urol 2003; 21:9-14; PMID:12754488

Zouboulis CC, Schagen S, Aleset A. The sebocyte culture: a model to study the pathophysiology of the sebaceous gland in sebostasis, seborrhoea and acne. Arch Dermatol Res 2008; 300:397-413; PMID:18694676; http://dx.doi.org/10.1007/s00423-008-0879-5

Safavi K. Serum vitamin A levels in postmenopausal women: Results from the first national health and nutrition examination survey. Arch Dermatol 1992; 128:1130-1; PMID:1497375; http://dx.doi.org/10.1001/archderm.1992.016001801262x

Reichl J, Schönheit S, Caizberg G, Varani J. Zouboulis CC. Vitamins as hormones. Horm Metab Res 2007; 39:17-84; PMID:17362003; http://dx.doi.org/10.1055/s-2007-958715

Bayerl C. [Topical treatment of skin aging]. Hautarzt 2007; 58:328-30; 356-9; PMID:17550677; http://dx.doi.org/10.1007/s00105-009-0990-6

Fischer G, Wang ZQ, Datta SC, Varani J, Kang S. Voorhees JJ. Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med 1997; 337:1419-28; PMID:9388139; http://dx.doi.org/10.1056/NEJM199711133357003

Lee SJ, Cho SA, An SS, Na YJ, Park NH, Kim HS, et al. Alstonia scholaris R. Br. Significantly Inhibits Retinoid-Induced Skin Irritation In Vitro and In Vivo. Evid Based Complement Alternat Med 2012; 2012:99370; PMID:22912567; http://dx.doi.org/10.1155/2012/99370

De Haas P, Garmyn M, Degrefe H, Vantieghem C, Bouillon R, Segaert S. 1,25-Dihydroxyvitamin D3 inhibits ultraviolet B-induced apoptosis, Jun kinase activation, and interleukin-6 production in primary human keratinocytes. J Cell Biochem 2003; 89:663-73; PMID:12858333; http://dx.doi.org/10.1002/jcb.10540

Ommen GS, Goodman GE, Thorneqvist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996; 334:1150-5; PMID:8602180; http://dx.doi.org/10.1056/NEJM199605303431402

De Haas P, Garmyn M, Vervaart A, De Clercq P, Vandewalle M, Degrefe H, et al. 1,25-Dihydroxyvitamin D3 and analogues protect primary human keratinocytes against UVB-induced DNA damage. J Photochem Photobiol B 2005; 78:141-8; PMID:15664501; http://dx.doi.org/10.1016/j.jpb.2005.07.006

Dixon KM, Deo SS, Wong G, Slater M, Norman AW, Bishop JE, et al. Skin cancer prevention: a possible role of 1,25-dihydroxyvitamin D3 and its analogs. J Steroid Biochem Mol Biol 2005; 97:137-43; PMID:16039116; http://dx.doi.org/10.1016/j.jsbmb.2005.06.006

Weber G, Herllorn JD, Chamorro Jimenez CJ, Hammarjo A, Törmi H, Stahle M. Vitamin D induces the antimicrobial protein ICAP18 in human skin. J Invest Dermatol 2005; 124:1080-2; PMID:15854055; http://dx.doi.org/10.1097/00002227-200505000-00006

MacLaughlin J, Holick ME. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 1985; 76:1536-8; PMID:2997282; http://dx.doi.org/10.1172/JCI112134

Chang AL, Fu T, Amor O, Tang YF. Association of facial skin aging with vitamin D in mid-aged white women. Cancer Causes Control 2010; 21:235-6; PMID:20882333; http://dx.doi.org/10.1007/s10555-009-9664-3

Glossmann H, Vitamin D. Vitamin D, UV, and skin cancer in the elderly: to expose or not to expose? Gerontology 2011; 57:350-5; PMID:21219670; http://dx.doi.org/10.1159/000332521

Lehmam B. Role of the vitamin D3 pathway in healthy and diseased skin—facts, contradictions and hypotheses. Exp Dermatol 2009; 18:97-108; PMID:19146880; http://dx.doi.org/10.1111/j.1600-0625.2008.00180.x

AAD. Position Statement on Vitamin D. www.aad.org 2009
68. Franco R, Calvaneso M, Muniru P, Manzo R, Guida C, Di Gennaro D, et al. Skin toxicity from external beam radiation therapy in breast cancer patients: protective effects of Resveratrol, Lycopene, Vitamin C and thiamin (B1). Radiat Oncol 2012; 7;12: http://dx.doi.org/10.1186/1747-717X-7-12
69. Kaur S, Deshpande CA, Agarwal R, Mukhtar H. Protection against ultraviolet-B radiation-induced local and systemic suppression of contact hypersensitivity and edema responses in C3H/HeN mice by green tea polyphenols. Photochem Photobiol 1995; 62:855-61; PMID:8570723; http://dx.doi.org/10.1111/j.1751-1058.1995.tb09147.x
70. Elmets C, Singh D, Tubbing K, Matsui M, Katiyar S, Mukhtar H. Green tea polyphenols as chemopreventive agents against cutaneous photodamage. J Am Acad Dermatol 2001; 44:425-32; PMID:1129910; http://dx.doi.org/10.1016/s0146-8175(01)80264-5
71. Crozier A, Lean M, McDonald M, Black C. Quantitative analysis of the flavonoid content of commercial tomatoes, onions, lettuce, and celery. J Agric Food Chem 1997; 45:590-5; http://dx.doi.org/10.1021/jf980339y
72. Nichols JA, Katiyar SK. Skin photoprotection by natural polyphenols: anti-inflammatory, antioxidant and DNA repair mechanisms. Arch Dermatol Res 2010; 302:71-83; PMID:19898857; http://dx.doi.org/10.1007/s00403-009-0970-1
73. Hallwell B, Rafer J, Jenner A. Health promotion by flavonoids, tocopherols, tocotrienols, and other phenols: direct or indirect effects? Antioxidant or not? Am J Clin Nutr 2005; 81(Suppl):268S-76S; PMID:16104483
74. Baxer RA. Anti-aging properties of resveratrol: review and report of a potent new antioxidant skin care formulation. J Cosmet Dermatol 2008; 7:2-7; PMID:18254804; http://dx.doi.org/10.1111/j.1473-2068.2008.0034x.x
75. Bastianetto S, Dumont Y, Darouesar A, Veracatren F, Breton L, Quirit R. Protective action of resveratrol in human skin: possible involvement of specific receptor binding sites. PLoS One 2010; 5:e1295; http://dx.doi.org/10.1371/journal.pone.0012935
76. Giardina S, Michelotti A, Zavattini G, Finzi S, Ghisalberti C, Marraticco F. Efficacy in study: assessment of the properties of resveratrol and resveratrol + N-acetyl-cysteine on proliferation and inhibition of collagen synthesis. Minerove Ginecola Vino 2010; 62:195-201; PMID:20595544
77. Muller C, Ullmann K, Steinberg P. The grapevine-shoot extract Vinetrol30 inhibits the chemically induced malignant transformation of BALB/c-3T3 cells. J Med Food 2011; 14:34-9; PMID:21128830; http://dx.doi.org/10.1089/jmf.2010.0022
78. Steinberg P. Special: Resveratrol-Oligomer - Eine neue Klasse von krebserregten Stoffen? Ernährung Umschau 2011; 566
79. Heng MC. Curcumin targeted signaling pathways: basis for anti-angiogenic and anti-carcinogenic therapy. Int J Dermatol 2010; 49:608-22; PMID:20618466; http://dx.doi.org/10.1111/j.1365-4632.2010.04468.x
80. Lima CF, Pereira-Wilson C, Rattan SI. Curcumin induces heme oxygenase-1 in normal human skin fibroblasts through redox signaling: relevance for anti-aging intervention. Mol Nutr Food Res 2011; 55:430-42; PMID:20938978; http://dx.doi.org/10.1002/mnfr.201001221
81. Kunnunmakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of cancer cells through interactions with multiple cell signaling proteins. Cancer Lett 2008; 269:199-225; PMID:18479807; http://dx.doi.org/10.1016/j.clet.2008.03.009
82. Egan ME, Pearson M, Weiner SA, Rajendran V, Ruben D, Gherini P, et al. Curcumin, a major plant constituent of turmeric, corrects cystic fibrosis defects. Science 2004; 304:600-2; PMID:15105504; http://dx.doi.org/10.1126/science.1096941
83. Agarwal R, Katiyar SK, Khan SG, Mukhtar H. Protection against ultraviolet B radiation-induced effects in the skin of SKH-1 hairless mice by a polyphenolic fraction isolated from green tea. Photochem Photobiol 1993; 58:695-705; PMID:28824325; http://dx.doi.org/10.1111/j.1751-1075.1993.tb09545.x
84. Chiu AE, Chen JH, LG D, Sekhar RS, Kim HL, et al. Cancer chemopreventive agents against cutaneous photodamage. J Am Acad Dermatol 2001; 45:1447-58; PMID:11644617; http://dx.doi.org/10.1016/S0146-8175(01)80264-5
85. R. Matrix metalloproteinase inhibition by green tea polyphenols. J Biol Med 2002; 33:627-38; PMID:12208349; http://dx.doi.org/10.1111/j.1473-2014.2002.tb12744.x
86. Talmon I, Kaufman D, Gavish G, Kornfeld R, Gutterman D, et al. Anti-aging effects of phloridzin, an apple polyphenol, absorbed and metabolized in the small intestine of healthy volunteers. Nutr Biomed 2007; 5:16-29; PMID:14695946; http://dx.doi.org/10.1016/j.nbb.2007.05.0023
87. Lopez LC, Quinzi CM, Area E, Naini A, Rahman S, Schaeule M, et al. Treatment of CoQ10 deficient fibroblasts with ubiquinone, CoQ analogs, and vitamin C time- and compound-dependent effects. PLoS One 2010; 5:e11897; PMID:20685959; http://dx.doi.org/10.1371/journal.pone.0011897
88. Sohal RS, Kamzalov S, Sumien N, Ferguson M, Rehrin I, Heinrich KR, et al. Effect of coenzyme Q10 intake on endogenous coenzyme Q10 content, mitochondrial electron transport chain, antioxidant defenses, and life span of mice. Free Radic Biol Med 2006; 40:480-7; PMID:16443163; http://dx.doi.org/10.1016/j.freeradbiomed.2005.08.037
89. FAO/WHO. Joint expert consultation on evaluation of health and nutritional properties of probiotics in food including powdered milk with live lactic acid bacteria. 2001. www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf
90. Fuller P. Probiotics in man and animals. J Appl Bacteriol 1989; 66:365-78; PMID:2666378; http://dx.doi.org/10.1111/j.1365-2672.1989.tb06105.x
91. Pineiro M, Asp NG, Brunor O, Macfarlane S, Morelli L, Reed G, et al. FAO Technical Meeting on PREBIOTICS. http://www.fao.org/ag/agl/env/agn/lives/PREBIOTICS_Tech_Meeting_Report2007.pdf
92. Knutsson J. Pre- and probiotics for human skin. Clin Plast Surg 2012; 39:59-64; PMID:22099848; http://dx.doi.org/10.1016/j.cps.2011.09.009
93. Güeniche A, Philippe D, Bastien P, Blum S, Buyukpamukcu E, Castel-Gigounez L, I. Probiotics for photoprotection. Dermatolendocrinol 2009; 1:275-9; PMID:20808516; http://dx.doi.org/10.4161/derm.1.5.9849
94. Güeniche A. Benyacoub J, Bueter TM, Smola H, Blum S. Supplementation with oral probiotic bacteria maintains cutaneous homeostasis after UV exposure. Eur J Dermatol 2006; 16:511-7; PMID:17101471
95. Schouten B, Van Esch BC, Kormelink TG, Moro GE, Anlagalu S, Boehm G, et al. Non-digestible oligosaccharides reduce immune cell infiltration and free light-chain concentrations in infants at risk for allergy. Pediatr Allergy Immunol 2011; 22:537-42; PMID:2177085; http://dx.doi.org/10.1111/j.1399-3080.2010.0132x..
112. Horrobin DF. Essential fatty acids in clinical dermatology. J Am Acad Dermatol 1989; 20:1045-53; PMID:2526823; http://dx.doi.org/10.1016/S0190-9622(89)70130-4

113. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr 2002; 21:495-505; PMID:12480795

114. Cosgrove MC, Franco OH, Granger SP, Murray PG, Mayes AE. Dietary nutrient intakes and skin-aging appearance among middle-aged American women. Am J Clin Nutr 2007; 86:1225-31; PMID:17921406

115. Rhodes LE, Durham BH, Fraser WD, Friedmann PS. Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. J Invest Dermatol 1995; 105:532-5; PMID:7561154; http://dx.doi.org/10.1111/1523-1747.ep12383389

116. Cho HS, Lee MH, Lee JW, No KO, Park SK, Lee HS, et al. Anti-wrinkling effects of the mixture of vitamin C, vitamin E, pycnogenol and evening primrose oil, and molecular mechanisms on hairless mouse skin caused by chronic ultraviolet B irradiation. Photodermatol Photoimmunol Photomed 2007; 23:155-62; PMID:17803593; http://dx.doi.org/10.1111/j.1600-0781.2007.00298.x

117. Anderson RM, Shanmuganayagam D, Weindruch R. Caloric restriction and aging: studies in mice and monkeys. Toxicol Pathol 2009; 37:47-53; PMID:19075044; http://dx.doi.org/10.1177/0192623308329476

118. Zhu Z, Jiang W, Thompson HJ. Mechanisms by which energy restriction inhibits rat mammary carcinogenesis: in vivo effects of corticosterone on cell cycle machinery in mammary carcinomas. Carcinogenesis 2003; 24:1225-31; PMID:12807724; http://dx.doi.org/10.1093/carcin/bgg077

119. Rogers AE, Zeisel SH, Groopman J. Diet and carcinogenesis. Carcinogenesis 1993; 14:2205-17; PMID:8242845; http://dx.doi.org/10.1093/carcin/14.11.2205

120. Bhattacharyya TK, Merz M, Thomas JR. Modulation of cutaneous aging with calorie restriction in Fischer 344 rats: a histological study. Arch Facial Plast Surg 2005; 7:12-6; PMID:15655168; http://dx.doi.org/10.1001/archfaci.7.1.12

121. Lu J, Xie L, Sylvester J, Wang J, Bai J, Baybutt R, et al. Different gene expression of skin tissues between mice with weight controlled by either calorie restriction or physical exercise. Exp Biol Med (Maywood) 2007; 232:473-80; PMID:17392482