

Discovering the link between nutrition and skin aging

Silke K. Schagen,^{1,†} Vasiliki A. Zampeli,^{1,2,†} Evgenia Makrantonaki^{1,2} and Christos C. Zouboulis^{1,*}

¹Departments of Dermatology, Venereology, Allergy 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

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.

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 research field not only for scientists but also a common field of interest for humans throughout the years, from ancient times to nowadays. Skin aging consists of two didactically independent, clinically and biologically, distinct processes.¹ The first is intrinsic skin aging, which represents chronological aging and affects skin in the same pattern it affects all internal organs.² The second is extrinsic skin aging, which we view as aged skin and is the result of external factors and environmental influence, mainly chronic sun exposure and ultraviolet (UV) irradiation but also smoking, pollution, sleep deprivation and poor nutrition.

Prevention is the best and most effective way to work against extrinsic skin aging effects. The best prevention strategy against the harmful action of free radicals is a well regulated lifestyle

(caloric restriction, body care and physical exercise for body), with low stress conditions and a balanced nutritional diet, including anti-oxidative rich food.

Frequently researched antioxidants such as carotenoids, tocopherols and flavonoids, as well as vitamins (A, C, D and E), essential omega-3-fatty acids, some proteins and lactobacilli have been referred as agents capable of promoting skin health and beauty.^{3,4} To find a proper balance, this review considers the beneficial “anti-aging” effects of increased reactive oxygen species (ROS) signaling recently.

The appropriate generation of ROS (for instance after physical exercise) has beneficial cell-protective and anti-aging effects. ROS activate via stimulation of STE-like 20 protein kinase 1 (MST1) and Jun N-terminus kinase (JNK) specific phosphorylations of forkhead box class O transcription factor (FoxO transcription factors), which thereafter translocate from the cytoplasm into the nucleus and thereby induce the expression of anti-oxidative enzymes like superoxide dismutase, catalase and others. The expression and upregulation of the cell’s own intrinsic anti-oxidative enzyme systems finally do the “job” and protect the cell against accumulating and harmful cellular levels of ROS.⁵ Remarkably, upregulation of nuclear FoxO levels suppresses cell proliferation and induces apoptosis.

The aim of this work is to review the existing literature and eventually to give an insight to the question whether diet actually influences the way our skin ages.

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.⁶ 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.⁷

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.⁸

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.^{6,9-11} 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.¹² 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.¹³

Nutricosmetic products with L-ascorbic acid work as free radical scavengers and repair the membrane bound oxidized vitamin E.¹⁴ 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.⁹ Another paper describes an 8-week study, which compared topical and systemic antioxidant treatment. Topical and systemic treatment both seemed to be good photoprotectants.¹⁵

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.¹⁶ These topical or oral products do not have the effects provided by L-ascorbic acid.

Tocopherols (vitamin E). The vitamin E complex is a group of 8 compounds called tocopherols. Tocopherol is a fat-soluble membrane bound antioxidant and consequently a free-radical scavenger especially of highly reactive singlet oxygen. Tocopherol is like vitamin C a naturally occurring endogenous non-enzymatic antioxidant.

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.^{17,18} 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.^{13,19} Vitamin E deficiency has been associated with a syndrome of edema with papular erythema or seborrheic changes, dryness and depigmentation in premature infants.²⁰

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.²¹ 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.²²

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.²³

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.²⁴

β -carotene is the most prominent member of the group of carotenoids, natural colorants that can be found in the human diet.²⁵ 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.²⁶ 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.²⁷

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.²⁸ β -carotene is an endogenous photoprotector, and its efficacy to prevent UV-induced erythema formation has been demonstrated in various studies.^{29,30} In healthy volunteers, a 12-week oral administration of β -carotene may result in a reduction of UV-induced erythema.³¹ Similar effects have been described in volunteers receiving a lycopene-rich diet.³²

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.^{31,33-35} With treatment periods of only 3–4 weeks, studies reported no protective effects.³⁶ Furthermore, β -carotene supplementation can significantly reduce the rate of mitochondrial mutation in human dermal fibroblasts after UV irradiation.³⁷

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.³⁸ Therefore, astaxanthin has considerable potential and promising applications in human health and nutrition³⁹ 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 UVA-induced alterations in cellular superoxide dismutase activity and decrease in cellular glutathione content.⁴²

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.⁴³ 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 UVA-induced matrix-metalloproteinase-1 and skin fibroblast elastase/neutral endopeptidase expression.⁴⁴ 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.^{36,42,44}

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.⁴⁵

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.⁴⁶ Lycopene and tomato products are also mentioned for preventing cancer.^{47,48}

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.⁴⁹

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 $\mu\text{g/ml}$.^{50,51}

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.⁵² The topical retinoid treatments inhibit the UV-induced, MMP-mediated breakdown of collagen and protect against UV-induced decreases in procollagen expression.⁵³⁻⁵⁵

Endogenous retinoids cannot be linked to the pathogenesis of common skin diseases like acne and psoriasis. Oral treatment with retinol or retinal 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).⁵¹

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.⁵⁶ 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. Omenn's 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

Table 1. Recommended dietary allowances for vitamin D

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.

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.⁵¹ 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.¹³

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.⁶⁵

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).

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.

Vegetables, cereals, chocolate and dry legumes are also sources for the total polyphenol intake.⁶⁹ 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.⁶⁷ Flavonoids are also further divided into flavones, flavonols, isoflavones, and flavanones, each with a slightly different chemical structure.⁶

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.⁷⁰ In French fries or freeze-dried mashed potatoes no remaining phenolic acids were to be found.⁷¹

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.⁷² 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.^{73,74} As antioxidants, polyphenols may improve cell survival; as prooxidants, they may induce apoptosis and prevent tumor growth.^{69,75} However, the biological effects of polyphenols may extend well beyond the modulation of oxidative stress.⁶⁹

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. However, its anti-aging effects have only been reported in the last years. Investigations of the effects of phlorizin on lifespan of the yeast *Saccharomyces cerevisiae* showed an improvement of the viability of the yeast, which was dose-dependent under oxidative stress.⁷⁶ Further investigations on humans are needed.

Many other botanical extracts, which are not discussed in this review, have been described to have potent anti-oxidant properties. Among them silymarin,⁷⁷ apigenin⁷⁸ and genistein⁷⁹ have been demonstrated to have beneficial effects on skin aging parameters.

Botanical anti-oxidants. The nutrient-sensitive kinase mammalian target of rapamycin complex 1 (mTORC1) integrates nutrient signaling. This mTORC1 is the central hub regulating

protein and lipid synthesis, cell growth and cell proliferation and the process of autophagy and is thus intimately involved in central regulatory events associated with cell survival and cell aging. Intriguingly, all natural plant-derived polyphenols like EGCG, resveratrol, curcumin, genestin and others are natural inhibitors of mTORC1, recently described in this journal.⁸⁰ Natural polyphenols exert their major metabolic activity as mTORC1 inhibitors, a fundamental aspect relating calorie restriction and/or nutrient-derived mTORC1 attenuation to deceleration of aging. In fact, it has recently been demonstrated that mTORC1 inhibition by rapamycin extended life span in mice.⁸¹ These antioxidants from natural sources exhibit more crucial functions as “Botanical mTORC1 inhibitors” and attenuate mTORC1 signaling, a beneficial property which decelerates cell metabolism, energy expenditure, mitochondrial activity and thus total ROS generation and oxidative stress load of the cells.

Resveratrol (Stilbenes). Resveratrol is an antioxidant, natural polyphenol, abundant in the skin of grapes (but not in the flesh). It has been the subject of intense interest in recent years due to a range of unique anti-aging properties. High concentrations of natural resveratrol and resveratrol oligomers are found in grape shoots from *Vitis Vinifera*. Resveratrol and its oligomers, trans-piceatannol, the dimers epsilon-viniferin, ampelopsin, isoeepsilon-viniferin, the trimers miyabenol C and the tetramers hopeaphenol, R-viniferin and R2-viniferin belong to the subgroup of stilbenes. Resveratrol works both as a chelating agent and as a radical scavenger and in addition it takes part in inflammation by inhibiting the production of IL-8 by LPS-induced MAPK phosphorylation and a block of NFκB activation.⁸² In 2002 Bhat et al. reported that resveratrol possesses cancer chemopreventive activities.⁸³ Cardiovascular benefits via increased nitric oxide production, downregulation of vasoactive peptides, lowered levels of oxidized low-density lipoprotein, and cyclooxygenase inhibition; possible benefits on Alzheimer disease by breakdown of β-amyloid and direct effects on neural tissues; phytohormonal actions; antimicrobial effects; and sirtuin activation, which is believed to be involved in the caloric restriction-longevity effect have also been reported.⁸⁴ As far as skin is concerned, resveratrol has been recently shown to possess a protective action in vitro against cell death after exposure of HaCaT cells to the nitric oxide free radical donor sodium nitroprusside.⁸⁵ 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.⁸⁶ 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.^{87,88}

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.⁹⁰ Oral ingestion in rodents has produced correction of cystic fibrosis defects and inhibition of tumor proliferation, but human trials are lacking.^{6,91,92}

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 leucocyte 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 conducted 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 prostaglandin 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.¹¹⁵ 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.¹¹⁶

EFAs can also be found as artificial supplements in the market. Fish oil supplements are usually made from mackerel, herring, tuna, halibut, salmon, cod liver, whale blubber, or seal blubber, are rich in omega-3 fatty acids and often contain small amounts of vitamin E. They might be also combined with calcium, iron, or vitamins A, B1, B2, B3, C or D.

Caloric Restriction

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 be not 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. Tzellos TG, Klagas I, Vahsevanos K, Triaridis S, Printza A, Kyrgidis A, et al. Extrinsic ageing 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. Ristow 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. Ristow M, Zarse K, Oberbach A, Klötting 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.001222>
6. Draeos ZD. Nutrition and enhancing youthful-appearing skin. *Clin Dermatol* 2010; 28:400-8; PMID:20620756; <http://dx.doi.org/10.1016/j.clindermatol.2010.03.019>
7. Ryan AS, Goldsmith LA. Nutrition and the skin. *Clin Dermatol* 1996; 14:389-406; PMID:8862916; [http://dx.doi.org/10.1016/0738-081X\(96\)00068-5](http://dx.doi.org/10.1016/0738-081X(96)00068-5)
8. Boyera 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. Placzek M, Gaube S, Kerkmann U, Gilbertz KP, Herzinger T, Haen E, et al. Ultraviolet 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.0022-202X.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/10.1067/mjd.2003.16>
11. Gasperlin M, Gosenca 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, Jung K. Ex vivo evaluation of radical sun protection factor in popular sunscreens with antioxidants. *J Am Acad Dermatol* 2011; 65:525-30; 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 Mech* 2008; 5:e153-62; <http://dx.doi.org/10.1016/j.ddmec.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 F, Cardillo A, Del Ciotto P, Valenzano F. Role of topical and nutritional supplement to modify the oxidative stress. *Int J Cosmet Sci* 2002; 24:331-9; PMID:18494887; <http://dx.doi.org/10.1046/j.1467-2494.2002.00159.x>
16. Kockaert M, Neumann M. Systemic and topical drugs for aging skin. *J Drugs Dermatol* 2003; 2:435-41; 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/j.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

19. McVean M, Liebler DC. Prevention of DNA photodamage by vitamin E compounds and sunscreens: roles of ultraviolet absorbance and cellular uptake. *Mol Carcinog* 1999; 24:169-76; PMID:10204801; [http://dx.doi.org/10.1002/\(SICI\)1098-2744\(199903\)24:3<169::AID-MC3>3.0.CO;2-A](http://dx.doi.org/10.1002/(SICI)1098-2744(199903)24:3<169::AID-MC3>3.0.CO;2-A)
20. Passi S, Morrone A, De Luca C, Picardo M, Ippolito F. Blood levels of vitamin E, polyunsaturated fatty acids of phospholipids, lipoperoxides and glutathione peroxidase in patients affected with seborrheic dermatitis. *J Dermatol Sci* 1991; 2:171-8; PMID:1831657; [http://dx.doi.org/10.1016/0923-1811\(91\)90064-5](http://dx.doi.org/10.1016/0923-1811(91)90064-5)
21. Boelsma E, Hendriks HF, Roza L. Nutritional skin care: health effects of micronutrients and fatty acids. *Am J Clin Nutr* 2001; 73:853-64; PMID:11333837
22. Ekanayake-Mudiyanselage S, Thiele J. [Sebaceous glands as transporters of vitamin E]. *Hautarzt* 2006; 57:291-6; PMID:16477469; <http://dx.doi.org/10.1007/s00105-005-1090-7>
23. Eberlein-König B, Ring J. Relevance of vitamins C and E in cutaneous photoprotection. *J Cosmet Dermatol* 2005; 4:4-9; PMID:17134414; <http://dx.doi.org/10.1111/j.1473-2165.2005.00151.x>
24. Scarmo S, Cartmel B, Lin H, Leffell DJ, Welch E, Bhosale P, et al. Significant correlations of dermal total carotenoids and dermal lycopene with their respective plasma levels in healthy adults. *Arch Biochem Biophys* 2010; 504:34-9; PMID:20637178; <http://dx.doi.org/10.1016/j.abb.2010.07.004>
25. Britton G, Liaen-Jensen S, Pfander H. Carotenoids. Basel: Birkhäuser 2008
26. Grune T, Lietz G, Palou A, Ross AC, Stahl W, Tang G, et al. Beta-carotene is an important vitamin A source for humans. *J Nutr* 2010; 140:2268S-85S; PMID:20980645; <http://dx.doi.org/10.3945/jn.109.119024>
27. Lindqvist A, Andersson S. Cell type-specific expression of beta-carotene 15,15'-mono-oxygenase in human tissues. *J Histochem Cytochem* 2004; 52:491-9; PMID:15034000; <http://dx.doi.org/10.1177/002215540405200407>
28. Alaluf S, Heinrich U, Stahl W, Tronnier H, Wiseman S. Dietary carotenoids contribute to normal human skin color and UV photosensitivity. *J Nutr* 2002; 132:399-403; PMID:11880562
29. Köpcke W, Krutmann J. Protection from sunburn with beta-Carotene—a meta-analysis. *Photochem Photobiol* 2008; 84:284-8; PMID:18086246; <http://dx.doi.org/10.1111/j.1751-1097.2007.00253.x>
30. Sies H, Stahl W. Nutritional protection against skin damage from sunlight. *Annu Rev Nutr* 2004; 24:173-200; PMID:15189118; <http://dx.doi.org/10.1146/annurev.nutr.24.012003.132320>
31. Stahl W, Heinrich U, Jungmann H, Sies H, Tronnier H. Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. *Am J Clin Nutr* 2000; 71:795-8; PMID:10702175
32. Stahl W, Sies H. Carotenoids and protection against solar UV radiation. *Skin Pharmacol Appl Skin Physiol* 2002; 15:291-6; PMID:12239422; <http://dx.doi.org/10.1159/000064532>
33. Mathews-Roth MM, Pathak MA, Parrish J, Fitzpatrick TB, Kass EH, Toda K, et al. A clinical trial of the effects of oral beta-carotene on the responses of human skin to solar radiation. *J Invest Dermatol* 1972; 59:349-53; PMID:4569104; <http://dx.doi.org/10.1111/1523-1747.ep12627408>
34. Lee J, Jiang S, Levine N, Watson RR. Carotenoid supplementation reduces erythema in human skin after simulated solar radiation exposure. *Proc Soc Exp Biol Med* 2000; 223:170-4; PMID:10654620; <http://dx.doi.org/10.1046/j.1525-1373.2000.22323.x>
35. Heinrich U, Gärtner C, Wiebusch M, Eichler O, Sies H, Tronnier H, et al. Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. *J Nutr* 2003; 133:98-101; PMID:12514275
36. Wolf C, Steiner A, Hönigsmann H. Do oral carotenoids protect human skin against ultraviolet erythema, psoralen phototoxicity, and ultraviolet-induced DNA damage? *J Invest Dermatol* 1988; 90:55-7; PMID:3335790; <http://dx.doi.org/10.1111/1523-1747.ep12462564>
37. Eicker J, Kürten V, Wild S, Riss G, Goralczyk R, Krutmann 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/10.1039/b300808h>
38. Lorenz RT, Cysewski GR. Commercial potential for Haematococcus microalgae as a natural source of astaxanthin. *Trends Biotechnol* 2000; 18:160-7; PMID:10740262; [http://dx.doi.org/10.1016/S0167-7799\(00\)01433-5](http://dx.doi.org/10.1016/S0167-7799(00)01433-5)
39. 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>
40. Yuan JP, Peng J, Yin K, Wang JH. Potential health-promoting effects of astaxanthin: a high-value carotenoid mostly from microalgae. *Mol Nutr Food Res* 2011; 55:150-65; PMID:21207519; <http://dx.doi.org/10.1002/mnfr.201000414>
41. Higuera-Ciampara I, Félix-Valenzuela L, Goycoolea FM. Astaxanthin: a review of its chemistry and applications. *Crit Rev Food Sci Nutr* 2006; 46:185-96; PMID:16431409; <http://dx.doi.org/10.1080/10408690509057188>
42. 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/S0923-1811\(02\)00063-4](http://dx.doi.org/10.1016/S0923-1811(02)00063-4)
43. Camera E, Mastrofrancesco A, Fabbri 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.1600-0625.2008.00790.x>
44. Suganuma K, Nakajima H, Ohtsuki 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>
45. Stahl W, Heinrich U, Aust O, Tronnier H, Sies H. Lycopene-rich products and dietary photoprotection. *Photochem Photobiol Sci* 2006; 5:238-42; PMID:16465309; <http://dx.doi.org/10.1039/b505312a>
46. Ribaya-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
47. Ertninan M, Takkouche B, Caamaño-Isorna F. 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:15006906
48. Pohar KS, Gong MC, Bahnson R, Miller EC, Clinton SK. Tomatoes, lycopene and prostate cancer: a clinician's guide for counseling those at risk for prostate cancer. *World J Urol* 2003; 21:9-14; PMID:12756488
49. Zouboulis CC, Schagen S, Aletas T. The sebocyte culture: a model to study the pathophysiology of the sebaceous gland in seborrhea, seborrhea and acne. *Arch Dermatol Res* 2008; 300:397-413; PMID:18690467; <http://dx.doi.org/10.1007/s00403-008-0879-5>
50. Safavi K. Serum vitamin A levels in psoriasis: 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.1992.01680180126023>
51. Reichrath J, Lehmann B, Carlberg C, Varani J, Zouboulis CC. Vitamins as hormones. *Horm Metab Res* 2007; 39:71-84; PMID:17326003; <http://dx.doi.org/10.1055/s-2007-958715>
52. Bayerl C. [Topical treatment of skin aging]. *Hautarzt* 2005; 56:328, 330-4, 336-9; PMID:15750677; <http://dx.doi.org/10.1007/s00105-005-0909-6>
53. Fisher GJ, 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:9358139; <http://dx.doi.org/10.1056/NEJM199711133372003>
54. 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; 2012:190370; PMID:21912567; <http://dx.doi.org/10.1155/2012/190370>
55. Fisher GJ, Datta S, Wang Z, Li XY, Quan T, Chung JH, et al. c-Jun-dependent inhibition of cutaneous procollagen transcription following ultraviolet irradiation is reversed by all-trans retinoic acid. *J Clin Invest* 2000; 106:663-70; PMID:10974019; <http://dx.doi.org/10.1172/JCI9362>
56. Omenn GS, Goodman GE, Thornquist 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/NEJM199605023341802>
57. De Haes P, Garmyn M, Degreef H, Vantieghem K, 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>
58. De Haes P, Garmyn M, Verstuyf A, De Clercq P, Vandewalle M, Degreef 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.jphotobiol.2004.09.010>
59. 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.jsmb.2005.06.006>
60. Weber G, Heilborn JD, Chamorro Jimenez CI, Hammarsjö A, Törmä H, Stähle M. Vitamin D induces the antimicrobial protein hCAP18 in human skin. *J Invest Dermatol* 2005; 124:1080-2; PMID:15854055; <http://dx.doi.org/10.1111/j.0022-202X.2005.23687.x>
61. MacLaughlin J, Holick MF. 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>
62. Chang AL, Fu T, Amir O, Tang JY. Association of facial skin aging and vitamin D levels in middle-aged white women. *Cancer Causes Control* 2010; 21:2315-6; PMID:20882333; <http://dx.doi.org/10.1007/s10552-010-9646-y>
63. Glossmann H, Vitamin D. Vitamin D, UV, and skin cancer in the elderly: to expose or not to expose? *Gerontology* 2011; 57:350-3; PMID:21196703; <http://dx.doi.org/10.1159/000322521>
64. Lehmann B. Role of the vitamin D3 pathway in healthy and diseased skin—facts, contradictions and hypotheses. *Exp Dermatol* 2009; 18:97-108; PMID:19146580; <http://dx.doi.org/10.1111/j.1600-0625.2008.00810.x>
65. AAD. Position Statement on Vitamin D. www.aad.org 2009

66. Ross A, Taylor CL, Yaktine A, Valle HD, et al. Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press (US) 2011
67. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr* 2004; 79:727-47; PMID:15113710
68. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. *J Nutr* 2000; 130(Suppl):2073S-85S; PMID:10917926
69. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. *Am J Clin Nutr* 2005; 81(Suppl):215S-7S; PMID:15640483
70. 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/jf960339y>
71. Clifford M. Chlorogenic acids and other cinnamates-nature, occurrence, dietary burden, absorption and metabolism. *J Sci Food Agric* 2000; 80:1033-43; [http://dx.doi.org/10.1002/\(SICI\)1097-0010\(20000515\)80:7<1033::AID-JSFA595>3.0.CO;2-T](http://dx.doi.org/10.1002/(SICI)1097-0010(20000515)80:7<1033::AID-JSFA595>3.0.CO;2-T)
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/s00403-009-1001-3>
73. Halliwell B, Rafter 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:15640490
74. Moskaug JO, Carlsen H, Myhrstad MC, Blomhoff R. Polyphenols and glutathione synthesis regulation. *Am J Clin Nutr* 2005; 81(Suppl):277S-83S; PMID:15640491
75. Lambert JD, Hong J, Yang GY, Liao J, Yang CS. Inhibition of carcinogenesis by polyphenols: evidence from laboratory investigations. *Am J Clin Nutr* 2005; 81(Suppl):284S-91S; PMID:15640492
76. Xiang L, Sun K, Lu J, Weng Y, Taoka A, Sakagami Y, et al. Anti-aging effects of phloridzin, an apple polyphenol, on yeast via the SOD and Sir2 genes. *Biosci Biotechnol Biochem* 2011; 75:854-8; PMID:21597195; <http://dx.doi.org/10.1271/bbb.100774>
77. Katiyar SK. Treatment of silymarin, a plant flavonoid, prevents ultraviolet light-induced immune suppression and oxidative stress in mouse skin. *Int J Oncol* 2002; 21:1213-22; PMID:12429970
78. Sim GS, Lee BC, Cho HS, Lee JW, Kim JH, Lee DH, et al. Structure activity relationship of antioxidative property of flavonoids and inhibitory effect on matrix metalloproteinase activity in UVA-irradiated human dermal fibroblast. *Arch Pharm Res* 2007; 30:290-8; PMID:17424933; <http://dx.doi.org/10.1007/BF02977608>
79. Moore JO, Wang Y, Stebbins WG, Gao D, Zhou X, Phelps R, et al. Photoprotective effect of isoflavone genistein on ultraviolet B-induced pyrimidine dimer formation and PCNA expression in human reconstituted skin and its implications in dermatology and prevention of cutaneous carcinogenesis. *Carcinogenesis* 2006; 27:1627-35; PMID:16522663; <http://dx.doi.org/10.1093/carcin/bgi367>
80. Melnik B. Dietary intervention in acne: Attenuation of increased mTORC1 signaling promoted by Western diet. *Dermatoendocrinol* 2012; 4:20-32; PMID:22870349; <http://dx.doi.org/10.4161/derm.19828>
81. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 2009; 460:392-5; PMID:19587680
82. Di Franco R, Calvanese M, Murino 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 anthocianin (Ixor®). *Radiat Oncol* 2012; 7:12; PMID:22289566; <http://dx.doi.org/10.1186/1748-717X-7-12>
83. Bhat KP, Pezzuto JM. Cancer chemopreventive activity of resveratrol. *Ann N Y Acad Sci* 2002; 957:210-29; PMID:12074974; <http://dx.doi.org/10.1111/j.1749-6632.2002.tb02918.x>
84. Baxter 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:218254804; <http://dx.doi.org/10.1111/j.1473-2165.2008.00354.x>
85. Bastianetto S, Dumont Y, Duranton A, Vercauteren F, Breton L, Quirion R. Protective action of resveratrol in human skin: possible involvement of specific receptor binding sites. *PLoS One* 2010; 5:e12935; PMID:20886076; <http://dx.doi.org/10.1371/journal.pone.0012935>
86. Giardina S, Michelotti A, Zavattini G, Finzi S, Ghisalbetti C, Marzatico F. [Efficacy study in vitro: assessment of the properties of resveratrol and resveratrol + N-acetyl-cysteine on proliferation and inhibition of collagen activity]. *Minerva Ginecol* 2010; 62:195-201; PMID:20595944
87. Müller C, Ullmann K, Steinberg P. The grapevine-shoot extract Vincetrol30 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>
88. Steinberg P. Special: Resveratrol-Oligomere - Eine neue Klasse von krebspräventiven Naturstoffen? *Ernährungs Umschau* 2011:366
89. Heng MC. Curcumin targeted signaling pathways: basis for anti-photoaging and anti-carcinogenic therapy. *Int J Dermatol* 2010; 49:608-22; PMID:20618464; <http://dx.doi.org/10.1111/j.1365-4632.2010.04468.x>
90. 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:20938987; <http://dx.doi.org/10.1002/mnfr.201000221>
91. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett* 2008; 269:199-225; PMID:18479807; <http://dx.doi.org/10.1016/j.canlet.2008.03.009>
92. Egan ME, Pearson M, Weiner SA, Rajendran V, Rubin D, Glöckner-Pagel J, et al. Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. *Science* 2004; 304:600-2; PMID:15105504; <http://dx.doi.org/10.1126/science.1093941>
93. 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; 58:695-700; PMID:8284325; <http://dx.doi.org/10.1111/j.1751-1097.1993.tb04954.x>
94. Chiu AE, Chan JL, Kern DG, Kohler S, Rehms WE, Kimball AB. Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin. *Dermatol Surg* 2005; 31:855-60, discussion 860; PMID:16029678; <http://dx.doi.org/10.1111/j.1524-4725.2005.31731>
95. Katiyar SK, Elmets CA. Green tea polyphenolic antioxidants and skin photoprotection (Review). *[Review]. Int J Oncol* 2001; 18:1307-13; PMID:11351267
96. Demeule M, Brossard M, Pagé M, Gingras D, Bédiveau R. Matrix metalloproteinase inhibition by green tea catechins. *Biochim Biophys Acta* 2000; 1478:51-60; PMID:10719174; [http://dx.doi.org/10.1016/S0167-4838\(00\)00009-1](http://dx.doi.org/10.1016/S0167-4838(00)00009-1)
97. Sartor L, Pezzato E, Garbisa S. (-)Epigallocatechin-3-gallate inhibits leukocyte elastase: potential of the phyto-factor in hindering inflammation, emphysema, and invasion. *J Leukoc Biol* 2002; 71:73-9; PMID:11781382
98. Katiyar SK, Elmets 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.1751-1097.1995.tb09147.x>
99. Elmets C, Singh D, Tubesing 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:11209110; <http://dx.doi.org/10.1067/mjd.2001.112919>
100. Shindo Y, Witt E, Han D, Epstein W, Packer L. Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. *J Invest Dermatol* 1994; 102:122-4; PMID:8288904; <http://dx.doi.org/10.1111/1523-1747.ep12371744>
101. Kwong LK, Kamzalov S, Rebrin I, Bayne AC, Jana CK, Morris P, et al. Effects of coenzyme Q(10) administration on its tissue concentrations, mitochondrial oxidant generation, and oxidative stress in the rat. *Free Radic Biol Med* 2002; 33:627-38; PMID:12208349; [http://dx.doi.org/10.1016/S0891-5849\(02\)00916-4](http://dx.doi.org/10.1016/S0891-5849(02)00916-4)
102. Passi SDO, De Pittà O, Grandinetti M, Simotti C, Littarru GP. The combined use of oral and topical lipophilic antioxidants increases their levels both in sebum and stratum corneum. *Biofactors* 2003; 18:289-97; PMID:14695946; <http://dx.doi.org/10.1002/biof.5520180233>
103. López LC, Quinón CM, Area E, Naini A, Rahman S, Schuelke M, et al. Treatment of CoQ(10) deficient fibroblasts with ubiquinone, CoQ analogs, and vitamin C: time- and compound-dependent effects. *PLoS One* 2010; 5:e11897; PMID:20689595; <http://dx.doi.org/10.1371/journal.pone.0011897>
104. Sohal RS, Kamzalov S, Sumien N, Ferguson M, Rebrin I, Heinrich KR, et al. Effect of coenzyme Q10 intake on endogenous coenzyme Q content, mitochondrial electron transport chain, antioxidative 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>
105. 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
106. Fuller R. Probiotics in man and animals. *J Appl Bacteriol* 1989; 66:365-78; PMID:2666378; <http://dx.doi.org/10.1111/j.1365-2672.1989.tb05105.x>
107. Pineiro M, Asp NG, Brunser O, Macfarlane S, Morelli L, Reid G, et al. FAO Technical Meeting on PREBIOTICS. http://www.fao.org/ag/agn/agns/files/Prebiotics_Tech_Meeting_Report.pdf 2007
108. Krutmann 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>
109. Guéniche A, Philippe D, Bastien P, Blum S, Buyukpamukcu E, Castiel-Higounenc I. Probiotics for photoprotection. *Dermatoendocrinol* 2009; 1:275-9; PMID:20808516; <http://dx.doi.org/10.4161/derm.1.5.9849>
110. Guéniche A, Benyacoub J, Buetler TM, Smola H, Blum S. Supplementation with oral probiotic bacteria maintains cutaneous immune homeostasis after UV exposure. *Eur J Dermatol* 2006; 16:511-7; PMID:17101471
111. Schouten B, Van Esch BC, Kormelink TG, Moro GE, Arslanoglu S, Boehm G, et al. Non-digestible oligosaccharides reduce immunoglobulin free light-chain concentrations in infants at risk for allergy. *Pediatr Allergy Immunol* 2011; 22:537-42; PMID:21771085; <http://dx.doi.org/10.1111/j.1399-3038.2010.01132.x>

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](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 SB, 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.ep12323389>
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; 37:47-51; 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