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The Role of Functional Foods in Cutaneous Anti-aging

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Oral supplementation of micronutrients, or functional foods, to prevent aging has gained much attention and popularity as society ages and becomes more affluent, and as science reveals the pathological mechanisms of aging. Aging of the skin combines biologic aging and extrinsic aging caused predominantly by sunlight and other environmental toxins. Anti-aging functional foods exert their influence mostly through their anti-oxidant and anti-inflammatory effects, thereby abrogating collagen degradation and/or increasing procollagen synthesis. Clinical evidence supporting a role in preventing cutaneous aging is available for oral supplements such as carotenoids, polyphenols, chlorophyll, aloe vera, vitamins C and E, red ginseng, squalene, and omega-3 fatty acids. Collagen peptides and proteoglycans are claimed to provide building blocks of the dermal matrix. This review summarizes the current study findings of these functional foods.

Key Words: Functional foods, Photoaging, Anti-oxidant, Collagen

INTRODUCTION

Cutaneous aging is the composite sum of biologic aging and extrinsic aging due to environmental factors including sunlight, smoking, pollution, and inflammation. Regardless of etiology, the aging process essentially involves the generation of reactive oxygen species (ROS) with subsequent signal transduction and activation of transcription factors activator protein 1 (AP-1) and nuclear factor κB (NF-κB). AP-1 increases the secretion of matrix-degrading enzymes called matrix metalloproteinases (MMPs), which results in the degradation of the dermal matrix, including collagen [1]. Functional foods and 'nutraceuticals' include all kinds of food with health or medical effects. According to an international survey, about 69% of adults worldwide take vitamins, minerals, or food supplement products daily [2]. There is an ever increasing interest in anti-aging substances derived from food, and since the aging process inevitably involves the generation of reactive oxygen species, oral supplements with antioxidant properties are the most popular. These include botanicals with carotenoids or polyphenols, isoflavones, vitamins, coenzyme Q10, phytoestrogens, probiotics, and omega-3 fatty acids. In addition, collagen peptides and hyaluronic acid, which provide building blocks of the skin, are on the market.

Endogenous antioxidant defenses include non-enzymatic (e.g., uric acid, glutathione, bilirubin, thiols, albumin, and nutritional factors such as vitamins C and E, β-carotene, ubiquinone, and phenols) and enzymatic (e.g., superoxide dismutases, glutathione peroxidases, and catalase) components. Although nutritional antioxidants are all mainly free radical scavengers, they act through different mechanisms and in different compartments: 1) they directly neutralize free radicals, 2) they reduce peroxide concentrations and repair

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oxidized membranes, 3) they quench iron to decrease ROS production, and 4) they neutralize ROS via lipid metabolism, i.e., short-chain free fatty acids and cholesteryl esters [3].

In contrast to topically applied cosmeceuticals, the effects of dietary bioactive compounds are complicated by the fact that they must go through the gastrointestinal tract, cross the intestinal barrier, reach the blood circulation, and then be distributed to the target tissue, the skin [4].

CAROTENOIDS

Beta-carotene is a very lipophilic, plant-derived carotenoid that has provitamin A (retinol) ROS-quenching activity [5] and therefore has been used for the treatment of erythropoietic protoporphyria and to increase sunburn threshold. The maximum dosage recommended by the Food and Drug Administration is 300 mg/d [6]. In 30 photoaged female subjects, 90 days of 30 mg/d β-carotene supplementation improved facial wrinkles and elasticity, increased type I procollagen mRNA levels, decreased UV-induced thymine dimer staining, and reduced 8-hydroxy-2'-deoxyguanosine staining, hence demonstrating its anti-photoaging effects; however, 90 mg/d β-carotene decreased minimal erythema dose (MED) and tended to increase thymine dimer-staining cells after supplementation (Fig. 1) [7]. Since MED is a measure of cutaneous reactivity to UV irradiation, 90 mg/d of β-carotene seems to render the skin more susceptible to UV-induced erythema. In addition, UV-induced direct cutaneous DNA damage, as measured by thymine dimer staining, tended to increase, albeit non-significantly, in the high-dose group. Oxidative DNA damage, as measured by 8-OHdG stain, was not significantly affected by high-dose β-carotene. Taken together, the dosage of β-carotene matters: 30 mg/d has beneficial effects on cutaneous photoaging, but single 90 mg/d supplementation is not recommended.

Astaxanthin is a xanthophyll carotenoid widely distributed in marine organisms and is responsible for the red color of lobsters and shrimp. It has potent anti-oxidant and anti-inflammatory properties, with 10-fold greater anti-oxidant action than that of other carotenoids and 100-fold greater action than that of α-tocopherol [8]. Our group found that dietary astaxanthin (2 mg/d) combined with collagen (3 g/d) improves facial elasticity and skin barrier integrity, upregulates type I procollagen gene expression, and decreases MMP-1 and -12 expression in human subjects compared to placebo (unpublished data).

POLYPHENOLS AND ISOFLAVONES

Natural polyphenols or flavonoids are not only plant pig-

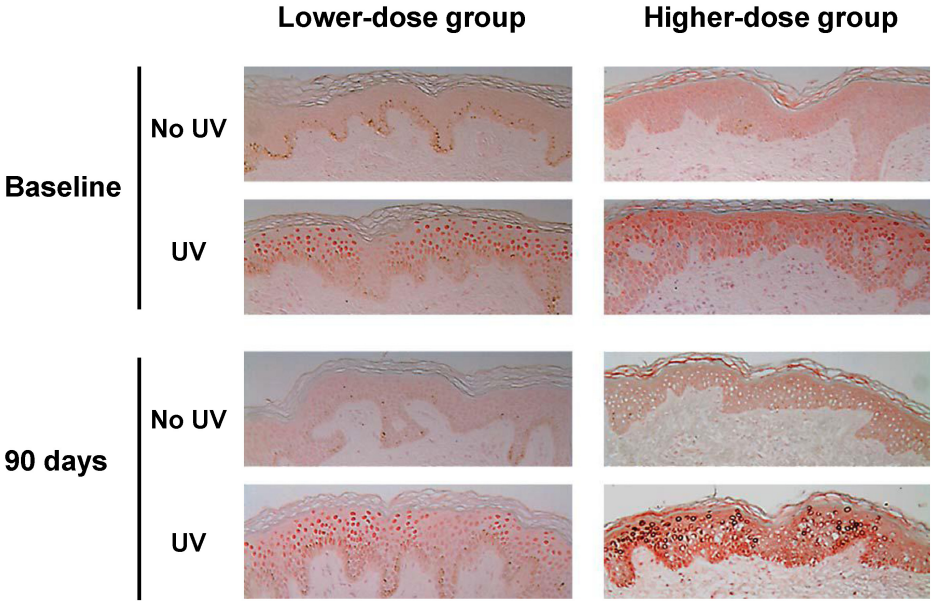

Fig. 1. Thymine dimer immunostaining demonstrating nuclear staining of thymine dimer in UV-irradiated buttock skin 24 hrs after 2 MED of UV irradiation, before and after β-carotene intake. The figures are representative of data from 6 subjects (original magnification ×400) (from ref. 7).

ments but also powerful antioxidants that protect plants from diseases. Flavonoids may be divided into 7 subclasses: flavones (apigenin, luteolin, etc.), flavonols (quercetin, etc.), flavanones (hesperitin, etc.), flavanonols (taxifolin), flavanols (catechin, epigallocatechin gallate, etc.), isoflavones (genistein, daidzein, etc.), anthocyanins, and anthocyanidins.

Resveratrol is a small polyphenol compound found in red grape skin, nuts, fruits, and red wine. Many studies have suggested that this compound has anti-carcinogenic effects that can be attributed to its free radical-scavenging ability [9] and anti-inflammatory effects [10]. It has been shown to protect against depletion of endogenous antioxidant defense enzymes, suppress H_2O_2 and NO production as well as lipid and protein oxidation, inhibit activation of mitogen-activated protein kinase (MAPK) and NF-κB, and inhibit apoptosis through activation of p53 activity [11]. It has poor bioavailability, and up to 5 g of resveratrol intake has been described as safe [12]; however, in a recent pilot study with 10 healthy volunteers, resveratrol was shown to possess cytokine-potentiating, pro-inflammatory properties with a significant increase in TNF-α and activation of alternative NF-κB signaling, suggesting enhanced immune surveillance as the mechanism behind its anti-carcinogenic effects [13].

Green tea polyphenols have been shown to prevent UVB-induced protein oxidation and MMP expression in mouse skin [14]. Epigallocatechin gallate (EGCG) comprises 59% of total catechins and is responsible for most of the biological activity of tea, and oral EGCG supplementation has been shown to increase MED, skin barrier function, and to reduce UVB-induced skin damage in rats [15]. However, similar studies in human beings have not demonstrated such effects [16,17], presumably because the human dermis forms a stronger barrier to absorption from the vasculature [18], warranting further clinical studies with high methodological quality.

Soybean isoflavone, a well-known anti-aging agent, is also referred to as a phytoestrogen because it has a chemical structure similar to estrogen [19]. In hairless mouse models, dietary soy isoflavones cause less skin wrinkling in UV-irradiated skin than in controls, with a concomitant increase in collagen deposition, which is partly due to the inhibitory effects on UV-induced MMP expression and subsequent collagen degradation [20]. In human subjects, facial fine wrinkles are decreased after 12 weeks of isoflavone aglycone supplementation [21]; however, more robust clinical studies are necessary to substantiate these initial findings.

OTHER BOTANICALS

We reported that chlorophyll improves facial wrinkles and elasticity in female volunteers over the age of 45 who received two different doses of chlorophyll extract supplement for 90 days. Compared to baseline, type I procollagen synthesis was increased, with a substantial reduction in UV-induced thymine dimer staining and UV-induced apoptosis of keratinocytes in a dose-dependent manner [22]. Considering the pivotal role of ROS in photoaging, chlorophyll's anti-oxidant properties are speculated to play a role in reducing wrinkles, epidermal DNA damage, and apoptosis.

Aloe vera gel is obtained from the pulp of a tropical cactus that belongs to the lily family with purported anti-inflammatory, healing, moisturizing, antibacterial, antifungal, and antiviral properties. Dietary aloe vera gel supplementation (low dose, 1,200 mg/d; high dose, 3,600 mg/d) in 30 photoaged female volunteers for 90 days resulted in improvements in facial wrinkles and elasticity, an increase in type I procollagen mRNA levels, and a reduction in MMP-1 mRNA levels at both doses. Compared to baseline, type I procollagen immunostaining increases throughout the dermis in both groups (Fig. 2) [23]. No dose-response relationship has been found in the tested doses. The known therapeutic effect of aloe vera is due to its immunostimulatory properties attributed to the presence of polysaccharides; the polysaccharides have no significant anti-oxidant activity [24]. An acetylated glucomannan, acemannan, is the biologically active, dominant polysaccharide that has been shown to increase collagen biosynthesis, probably through macrophage immunostimulation [25].

VITAMINS C AND E

Vitamin C (ascorbic acid) is the major water-soluble endogenous antioxidant; it is a powerful inhibitor of lipid peroxidation, regenerates vitamin E in lipoproteins and mem-

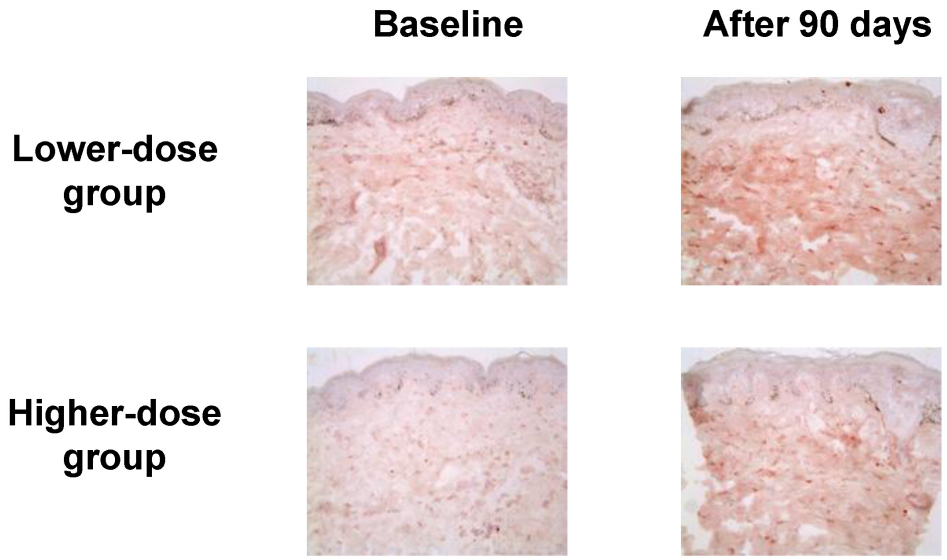

Fig. 2. Type I procollagen immunostaining in the buttock skin before and after aloe vera intake (original magnification ×200). The results are representative of 6 biopsied subjects in each group (from ref. 23).

branes, and is essential for the production of collagen. It has been shown to provide a wide variety of benefits including lowering blood pressure and decreasing infectious episodes in daily doses of 500 mg to 6 g [26]; however, no benefit has been reported regarding skin aging. Vitamin E (α-tocopherol) is a lipid-soluble anti-oxidant vitamin found in cell membranes and circulating lipoproteins. Vitamin E can also enhance immune function, reducing infection rates in elderly subjects [27]. For a systemic photoprotective effect, several hundred mg/d is required, and doses up to 800 mg/d have been taken for years without harm. Vitamin C and vitamin E act synergistically [28]. Simultaneous oral intake of these two vitamins has been shown to reduce UV-induced skin inflammation, in contrast to either vitamin alone, which has shown no protective effects [29]. Several controlled clinical studies have demonstrated that the two vitamins act synergistically to reduce sunburn reaction and increase MED [30]. Unfortunately, oral supplementation of vitamin C and E has proven insufficient in preventing skin aging owing to their poor solubility, inefficient skin permeability, or instability during storage [31]. Chemical modification of the molecules or new delivery systems would make optimized delivery of these molecules to the skin possible in the future. On the other hand, there are some promising reports regarding mixtures of antioxidants: an antioxidant combination containing vitamins C and E, carotenoids, selenium, and proanthocyanidins decrease MMP-1 compared to placebo in humans [32], and a combination of vitamins C and E, pycnogenol, and evening primrose oil also decrease wrinkles and MMP while increasing collagen synthesis in hairless mice [33]. Both studies imply that antioxidants are effective when they work together.

RED GINSENG

The roots of *Panax ginseng* have been used as a general tonic in Oriental medicine for several thousand years. Red ginseng is prepared by steaming and air-drying *P. ginseng*, and reportedly has more bioactivity than white ginseng, which is the peeled and air-dried form [34]. Red ginseng contains various ginsenosides that have antioxidant, immunostimulatory, and anti-aging activity. Our group performed the first controlled human study on 82 female volunteers to assess red ginseng's effects on photoaged skin. Compared to placebo, the group that took 3 g/d of a red ginseng extract-containing herbal mixture for 24 weeks had decreased facial wrinkles with concomitant increases in type I procollagen synthesis (Fig. 3) and fibrillin-1 fiber length (Fig. 4). Therefore, objective evidence of a reduction in facial wrinkles by long-term ingestion of red ginseng was provided for the first time; the clinical improvement was substantiated by biochemical and histological evidence of increased collagen and elastic fiber synthesis in the dermis [35]. The clinical improvement may be due to the activation

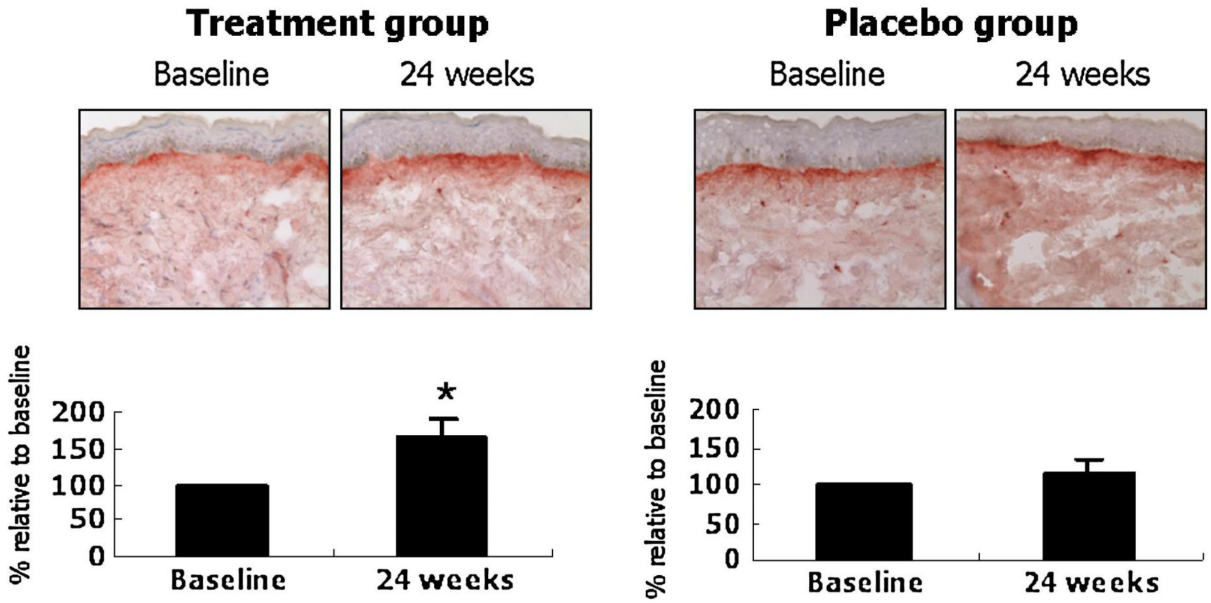

FIG. 3. Ginseng mixture treatment increases type I procollagen immunostaining in human facial skin. Immunohistochemistry for SP1.D8 was performed from punch-biopsied skin samples, and the degree of staining was visually graded by five dermatologists. Data are mean ± SE values (n = 6, treatment group; n = 7, placebo group). *p < 05 by Wilcoxon signed rank test, compared with baseline (from ref. 35).

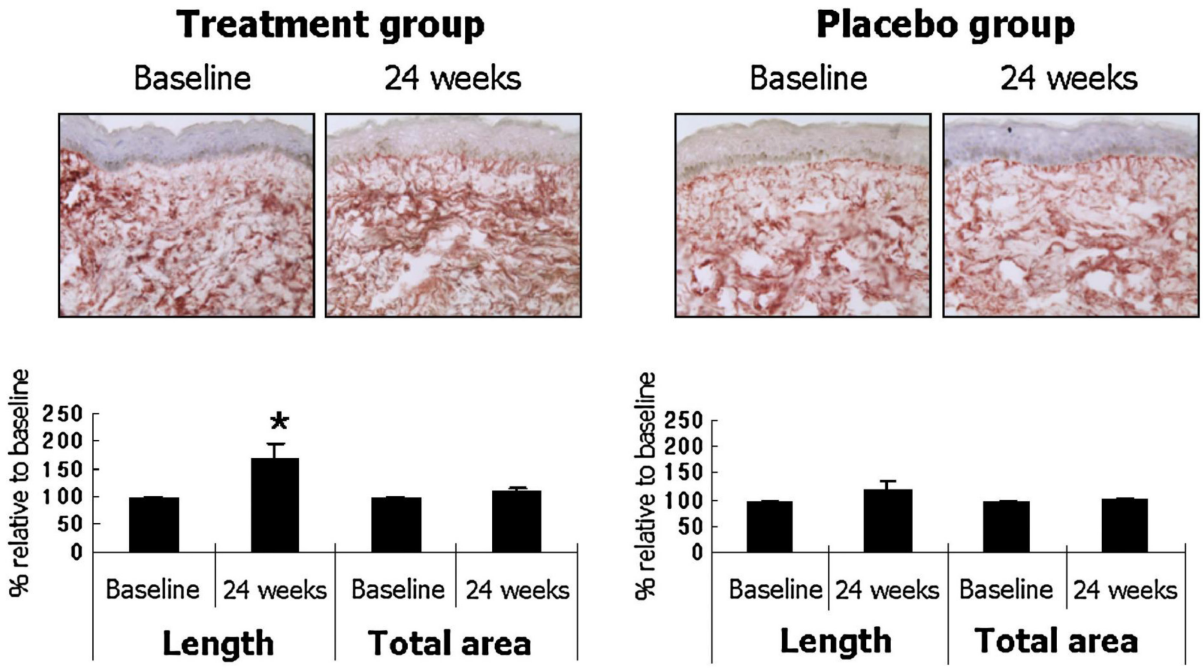

FIG. 4. Ginseng mixture treatment increases fibrillin-1 fiber length in the papillary dermis. Total percentage area and fiber length of fibrillin-1 were measured from the dermo-epidermal junction to 15 μm downward. The photographs are representative of six subjects in the ginseng group and seven subjects in the placebo group. Data are mean ± SE values. *p < 05 by Wilcoxon signed rank test, compared with baseline (from ref. 35).

of COL1A2 promoter and Smad signaling [36], through ginseng's estrogen-like activity [37], and/or additionally through increased hyaluronan levels by a metabolite of ginsenosides [38].

SQUALENE AND OTHER LIPIDS

Squalene is a polyunsaturated aliphatic hydrocarbon that is abundant in shark liver oil. Our group previously reported that 27 g/day (high dose) oral squalene supplementation for 90 days decreased facial wrinkles, while 13.5 g/day (low dose) increased type I procollagen mRNA levels and MED [39]. Both dosage groups had a significant decrease in facial erythema. Both dosages of squalene protected against UV-induced keratinocytic damage, as shown by reduced thymine dimer-staining cells and apoptotic cells in the skin. The antioxidant action of squalene may be implicated in all these phenomena. However, transient loose stool was experienced by 35% of subjects in the low-dose group and 55% in the high-dose group, making high-dose squalene supplementation unsuitable for the treatment of skin aging.

Lipid compounds from honeybee royal jelly extracts, which are composed of mostly medium-chain aliphatic fatty acids, have been shown to possess *in vitro* collagen production-promoting effects. 10-hydroxy-2-decenoic acid, a characteristic constituent of lipids in royal jelly, stimulate normal human dermal fibroblast cell lines and produce transforming growth factor(TGF) β1, a cytokine that induces collagen synthesis [40,41]; however, these results are yet to be confirmed in controlled clinical trials.

When consumed in high amounts ranging from 4 to 10 g/d, eicosapentaenoic acid (EPA) and other omega-3 fatty acids reduce levels of pro-inflammatory and immunosuppressive mediators, including PGE2, IL-6, IL-8, and TNF-α, while decreasing UV-induced p53 upregulation in the skin, reducing DNA strand breaks, and increasing sunburn threshold, hence conferring protection against UV-induced cutaneous damage [42,43].

COLLAGEN PEPTIDES

In a study by Proksch et al., oral supplementation of collagen hydrolysate composed of specific collagen peptides (2.5 g/d or 5.0 g/d for 8 weeks) increased skin elasticity in middle-aged women after 4 weeks of supplementation, and a skin moisturizing effect was observed in women over 50 years of age. The supplement had a long-lasting effect, especially in women over 50 years of age [44]. Prior studies have demonstrated that collagen hydrolysate is absorbed in the digestive tract, appears in human blood partly in a small peptide form, and is deposited in the skin for up to 96 hrs [45]. Food-derived collagen peptides in human blood are chemotactic for dermal fibroblasts [46], and they increase the migration and growth of mouse skin fibroblasts [47]. One controlled study found that type I and IV collagen increases while MMP-2 decreases, implying that the effect of collagen is protein-specific [48], and providing evidence for the improved cutaneous elasticity. In animal studies, oral administration of collagen peptide induced an increase in fibroblast density and formation of dermal collagen fibrils in piglet skin [49], and suppressed UVB-induced decreases in skin hydration, epidermal hypertrophy, and soluble type I collagen in mouse skin [50].

PROTEOGLYCANS

Proteoglycans (PG) are a family of complex macromolecules consisting of a core protein with covalently attached glycosaminoglycan chains. In hairless mice, oral administration of high molecular weight PG from salmon nasal cartilage inhibited UVB-induced skin aging, i.e., increased erythema and transepidermal water loss, and decreased hydration, in a molecular weight-dependent manner [51]. From decreased serum and dorsal skin inflammatory cytokine levels, it is speculated that PG acts on gut immunity and improves skin condition by inhibiting surplus inflammatory cytokine production induced by UVB irradiation. Aggrecan, the most abundant PG in cartilage, was shown to bind to hyaluronic acid *in vivo* [52]; in contrast, chondroitin sulfate, a degradation product of salmon nasal cartilage PG, did not show any beneficial anti-photoaging effects [53]. Therefore, the cutaneous anti-aging effects of PG are molecular weight-dependent [51].

CONCLUSION

The advantage of functional foods is that once they go through systemic circulation in active forms, they can then be distributed to all skin compartments--including the epidermis, dermis, subcutaneous fat, and sebum [4]--of the entire body, which is much more convenient and efficient than applying cosmetics topically. Many manufacturers have already begun to launch strategic combinations of nutraceuticals and cosmeceuticals. Functional foods with some evidence of cutaneous anti-aging properties include carotenoids, polyphenols, other botanicals, vitamins C and E, red ginseng, squalene, omega-3 fatty acids, collagen peptides, and proteoglycans. However, since effective governmental regulation of anti-aging interventions is lacking, consumers may be misled by the manufacturers' claims. Moreover, long-term supplementation of a single micronutrient in higher doses might lead to "flooding" of the organism and be even harmful. In addition, some studies in humans suggest that anti-oxidant supplementation can blunt the beneficial effects of exercise in humans, probably by abrogating beneficial ROS signaling that stimulates mitochondrial biogenesis and expression of oxidant defense biomolecules [54,55]. Manufacturers are therefore presently at work to achieve "nutritargeting", which means accumulating certain micronutrients selectively in specific target tissues by means of nanocolloids, microemulsions, and other means. The ball is in the court of dermatologists: they should be diligent in testing the scientific veracity of the manufacturers' claims regarding the health benefits of numerous anti-aging substances, for the good of all consumers and patients. At the same time, physicians should keep educating patients on the importance and superior efficacy of topical sunscreen and retinoid use, compared to functional foods, in preventing cutaneous aging.

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